Comparison of prostate cancer diagnosis in patients receiving unrelated urological and non-urological cancer care

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Objective

- To evaluate prostate cancer diagnosis rates and survival outcomes in patients receiving unrelated (non-prostate) urological care with those in patients receiving non-urological care.

Materials and Methods

- We conducted a population-based study using the Surveillance Epidemiology and End Results (SEER) database to identify men who underwent surgical treatment of renal cell carcinoma (RCC; $n = 18\,188$) and colorectal carcinoma (CRC; $n = 45\,093$) between 1992 and 2008.
- Using SEER*stat software to estimate standardized incidence ratios (SIRs), we investigated rates of prostate cancer diagnosis in patients with RCC and patients with CRC.
- Adjusting for patient age, race and year of diagnosis on multivariate analysis, we used Cox and Fine and Gray proportional hazards regressions to evaluate overall and disease-specific survival endpoints.

Results

- The observed incidence of prostate cancer was higher in both the patients with RCC and those with CRC: SIR = 1.36 (95% confidence interval [CI] 1.27–1.46) vs 1.06 (95% CI 1.02–1.11). Adjusted prostate cancer SIRs were 30% higher ($P < 0.001$) in patients with RCC.
- Overall (hazard ratio = 1.13, $P < 0.001$) and primary cancer-adjusted mortalities (sub-distribution Hazard Ratio (sHR) = 1.17, $P < 0.001$) were higher in patients with RCC with no significant difference in prostate cancer-specific mortality (sHR = 0.827, $P = 0.391$).

Conclusion

- Rates of prostate cancer diagnosis were higher in patients with RCC (a cohort with unrelated urological cancer care) than in those with CRC. Despite higher overall mortality in patients with RCC, prostate cancer-specific survival was similar in both groups.
- Opportunities may exist to better target prostate cancer screening in patients who receive non-prostate-related urological care. Furthermore, urologists should not feel obligated to perform prostate-specific antigen screening for all patients receiving non-prostate-related urological care.

Keywords

prostate carcinoma, screening, PSA, urological care, overdiagnosis

Introduction

The survival benefit of mass screening for prostate cancer with serum PSA testing is controversial and has significant health policy implications. Among the trials investigating the impact of screening on survival, the two largest and highest quality studies have reported conflicting outcomes [1,2]. As a result of this uncertainty, there is considerable variation between the screening recommendations of key national organizations [3–6], which affect provider decisions regarding the value of PSA screening [7]. While the National Cancer Collaborative Network, AUA and American Cancer Society endorse a targeted approach to PSA screening, several professional organizations do not support, and some even recommend against, routine PSA screening [8]. This is largely attributable to concerns that the improvements in long-term survival are not sufficient to justify mass screening or the potential for treatment

morbidity. Most recently, the US Preventive Services Task Force finalized a revision to a draft statement on PSA screening with a grade 'D' recommendation, concluding with 'moderate certainty' that the harms of PSA-based detection and early intervention exceed the potential benefits regardless of age, racial or ethnic group, or family history [3].

Although prostate cancer screening by urologists has remained nearly ubiquitous since the introduction of PSA testing, the lack of consensus regarding PSA screening is evidenced by the heterogeneity of practice patterns by primary care physicians [7]. Yet, the impact of patient exposure to routine urological care on prostate cancer diagnosis rates and on prostate cancer-specific outcomes is poorly studied. We hypothesized that exposure to a urologist for non-prostate-related diagnoses significantly increases the likelihood of prostate cancer detection and sought to understand whether any improvement in cancer detection improves long-term survival in these individuals. We compared the incidence of new prostate cancer diagnoses and survival outcomes for those with either of two unrelated incident cancers, RCC and colorectal carcinoma (CRC). Whereas localized RCC is a disease uniformly treated and followed by urologists in the USA, patients with localized CRC are not routinely exposed to urological care. Given the lack of known overlapping environmental or genetic risk factors between RCC, CRC and prostate cancer, a differential rate of prostate cancer diagnosis between patients with localized RCC and CRC would most probably be attributable to differences in exposure to prostate cancer screening.

Patients and Methods

The Surveillance, Epidemiology and End Results (SEER) programme of the National Cancer Institute was used to identify our study population [9]. The SEER programme collects data on all individuals diagnosed with cancer residing in several geographically defined regions of the USA [10]. Male patients with clinically localized RCC and CRC who underwent surgical treatment of their localized primary kidney or colon tumour between 1992 and 2008 were identified from the SEER database, which relies on 13 cancer registries and covers ~14% of the population. We chose the 13 registries from which data were available for all years of interest. We did not include newer registries so as to reduce the potential for confounding by geography over time. The 13 SEER registries included the San Francisco-Oakland, Detroit, Seattle Puget Sound, Atlanta, San Jose Monterey, Los Angeles, rural Georgia and the Alaska Native Tumor Registry, as well as the states of Connecticut, Hawaii, Iowa, New Mexico and Utah.

To measure the relative risk for prostate cancer in patients surgically treated for localized RCC or CRC compared with the general SEER registry population, we calculated a standardized incidence ratio (SIR) of prostate cancer diagnosis (i.e. observed/expected incidence) for patients with CRC and RCC, along with an exact 95% CI. The SEER*Stat Multiple Primary-SIR program (version 7.0.4) was used to calculate the SIRs [9,11]. SIR estimates reflect the increase in the incidence of tumours compared with what we would expect in the general population after adjusting for age, race and year of diagnosis. The SIR estimates were obtained by using the MP-SIR macro in SEER*Stat. SIRs > 1 indicated that those who underwent resection for CRC or RCC were at increased risk of developing prostate cancer as compared with the general population, while SIRs < 1 suggested that those who underwent resection for CRC or RCC were at a decreased risk of developing another type of cancer as compared with the general population. To assess the generalizability of our findings, additional cancer sites (localized disease only) were added as control groups. These included skin (excluding basal and squamous), oropharynx, thyroid, lung and bladder cancers.

To better reflect the incidence of *de novo* prostate cancer diagnoses in the post-treatment period, only patients who were diagnosed with prostate cancer > 2 months after the diagnosis of a primary malignancy (RCC or CRC) were included in this study. Person-years at risk in the cohort were accumulated by age groups (35–49, 50–59, 60–69, 70–79 and >80 years) and also analysed according to follow-up interval (2–5, 6–11, 12– 59, 60–119 and >120 months) to identify potential differences in screening patterns.

We estimated cumulative incidence functions using propensity score-based weighting to adjust for measured confounders [12]. The cumulative incidence functions [13] provide estimates of adjusted disease-specific mortality. We used Cox proportional hazards regressions to investigate the variables associated with overall survival and Fine and Gray proportional hazards regressions [14] to investigate variables associated with disease-specific survival.

Differences in demographic data between groups were compared using chi-squared and *t*-tests. Survival analyses and demographic comparisons were implemented using STATA version 12 (STATA Corp, College Station, TX, USA); *P* values < 0.05 were considered statistically significant for all analyses.

Results

Between 1992 and 2008, 19 188 patients undergoing surgical treatment for localized RCC and 45 093 patients undergoing surgical treatment for localized CRC were identified from the SEER database. Of these, 4.3% (a total of 2793 patients; 2031 and 762 patients from the CRC and

Table 1 Patient follow-up interval stratified by duration.

Duration of follow-up	No. of patients alive	Mortality from primary cancer	Mortality from prostate cancer	Other-cause mortality	Total no. of patients
0–4.99 years	19 000	4249	55	7 187	30 491
5–9.99 years	13 461	1614	79	4 698	19 852
>10 years	10 530	362	38	2 008	12 938
Total no. of patients	42 991	6225	172	13 893	63 281

Table 2 Descriptive statistics and clinical characteristics of the study cohort.

	CRC, *N* = 45 093	RCC, *N* = 18 188	*P*
Age (continuous)			**<0.001**
Mean (SD)	66.5 (12.4)	58.9 (14.0)	
Median	68	60	
Age (categorical), *n* (%)			**<0.001**
<35 years	455 (1.0)	644 (3.5)	
35–49 years	3 639 (8.1)	3 586 (19.7)	
50–59 years	8 678 (19.2)	4 799 (26.4)	
60–69 years	12 472 (27.7)	4 871 (26.8)	
70–79 years	13 176 (29.2)	3 344 (18.4)	
>80 years	6 673 (14.8)	944 (5.2)	
Race, *n* (%)			**<0.001**
White	36 237 (80.0)	14 801 (81.3)	
African-American	3 654 (8.5)	1 901 (10.4)	
Other	5 202 (11.5)	1 486 (8.1)	
Primary tumour grade, *n* (%)			**<0.001**
Well differentiated	6 288 (13.9)	2 360 (13.0)	
Moderately differentiated	27 063 (60.0)	7 171 (39.4)	
Poor differentiated	3 659 (8.1)	2 980 (16.4)	
Undifferentiated	166 (0.4)	465 (2.6)	

RCC cohorts, respectively) were diagnosed with prostate cancer. Follow-up data (Table 1) showed a large number of patients (12 938) who afforded data for ≥10 years of follow-up. There were no significant differences observed in prostate cancer tumour stage between the CRC and RCC cohorts ($P = 0.205$). In general, patients with RCC were younger (median age 60 vs 68 years; $P < 0.001$) and were more often African-American (10.4 vs 8.5%; $P < 0.001$) than patients with CRC (Table 2). Patients with CRC had well or moderately differentiated primary cancer more often than patients with RCC (73.9 vs 42.4%; $P < 0.001$).

The observed incidence of prostate cancer was higher than the expected incidence in both the RCC and CRC cohorts, which were adjusted for age, race and year of diagnosis in the SEER*stat analysis (Table 3, SIR = 1.36 [95% CI 1.27–1.46] vs. 1.06 [95% CI 1.02–1.11]). The difference in observed risk of prostate cancer diagnosis was ~30% higher for patients with RCC than for those with CRC ($P < 0.001$). This increase in prostate cancer diagnosis was observed when comparing the RCC cohort with other control patient cohorts (skin, oropharynx and lung cancers; Table 3, all $P < 0.01$). In patients with localized bladder cancer, another urological malignancy, a statistically similar elevation in the rate of prostate cancer diagnosis as in patients with kidney cancer was observed ($P < 0.01$). Interestingly, patients with thyroid cancers, a cancer with high rates of overdiagnosis [15], also displayed unusually high rates of newly diagnosed prostate cancer (Table 3).

Differences in the patterns of prostate cancer diagnosis were observed when RCC and CRC groups were stratified by follow-up interval (Table 4) and age at diagnosis (Table 5). At a follow-up interval of 2–5 months, the observed prostate cancer diagnosis was significantly higher than expected in both the CRC and RCC cohorts, while only patients with RCC had a higher than expected observed prostate cancer diagnosis at 6–11, 12–59 and >120 months of follow-up. Observed prostate cancer diagnoses were higher than expected values in both the CRC and RCC cohorts in the 70–79 years age group. In comparison, in patients aged 50– 70 years, only patients with RCC had a higher than expected observed incidence of prostate cancer.

Multivariable analyses were performed to evaluate overall and disease-specific survival endpoints. Adjusting for age, race and year of diagnosis, no significant difference in prostate cancer-specific survival was observed between the RCC and CRC cohorts (sHR = 0.83, $P = 0.39$). A subanalysis of patients with at least 10 years (1992–1998) of expected follow-up ($n = 23\,369$) also failed to show a difference in prostate cancer-specific survival (sHR = 0.78,

Table 3 Standardized incidence ratios of prostate cancer diagnosis in patients diagnosed with cancers of the skin, head and neck, thorax and abdomen.

Site	Median age, years	Unadjusted median survival, years	Number observed prostate cancer diagnoses (% of cohort)	Number expected prostate cancer diagnoses (% of cohort)	No. of deaths from prostate cancer (% of cohort)	SIR of prostate cancer diagnosis (95% CI)	*P*-value SIR
Non-visceral							
Skin excluding basal and squamous, $n = 40\,553$	66	16.9	1445 (3.6)	1214 (3.0)	78 (0.19)	1.19 (1.13–1.25)	<0.01
Head and neck							
Oral cavity and pharynx, $n = 8860$	67	16.5	328 (3.7)	308 (3.5)	27 (0.3)	1.07 (0.95–1.19)	NS
Thyroid, $n = 5199$	63	16.7	139 (2.7)	103 (2.0)	8 (0.2)	1.34 (1.13–1.59)	<0.01
Thorax							
Lung and bronchus, $n = 13\,654$	67	10.8	549 (4.0)	483 (3.5)	35 (0.3)	1.14 (1.04–1.24)	<0.01
Abdominal							
CRC $n = 45\,093$	68	11.6	2031 (4.5)	1911 (4.2)	186 (0.41)	1.06 (1.02–1.11)	<0.01
RCC $n = 18\,188$	60	14.2	762 (4.2)	559 (3.0)	30 (0.16)	1.36 (1.27–1.46)	<0.01
Bladder $n = 49\,020$	70	12.3	2760 (5.6)	2081 (4.2)	141 (0.3)	1.33 (1.28–1.38)	<0.01

$P = 0.34$). Furthermore, compared with CRC, those with RCC had higher primary cancer mortality (sHR = 1.17, $P < 0.001$) and overall mortality (hazard ratio = 1.13, $P < 0.001$) in adjusted models. Figure 1 shows cumulative incidence curves estimated by propensity score-based weighting. The curves show that patients with RCC were more likely than those with CRC to incur mortality from their primary cancer and from other causes, while exhibiting similar prostate cancer-specific mortality (despite 30% higher rates of prostate cancer diagnosis). Results did not significantly change when multivariable analysis controlled for available grade and stage data (data not shown).

Discussion

In the context of the ongoing debate over the merits of PSA-based screening, it is imperative to better understand the key factors that affect the diagnosis of patients with prostate cancer. One factor that has received little attention appears to be exposure to urological care. Our study shows an increased rate of prostate cancer diagnoses in both patients with localized CRC and those with RCC than in individuals with no previously identified cancers; however, after adjusting for age, race and year of diagnosis, we observed a 30% higher rate of prostate cancer diagnosis in patients with localized RCC than in those with localized CRC. In the absence of any known genetic or environmental factors causing patients with RCC to be more likely to develop prostate cancer than matched patients with CRC, these results suggest a differential probability of prostate cancer detection that is most probably attributable to the screening practices of the specialist caring for the patient's primary malignancy. This higher-than-expected probability of prostate cancer diagnoses among patients with RCC held across all age groups > 50 years. Interestingly, prostate cancer diagnosis rates were higher than expected in both RCC and CRC cohorts in patients aged 70–79 years. This finding is notable, as elderly patients have been identified as the group that appear least likely to benefit from prostate cancer screening using both population level [16] and prospective [17] data. Additionally, our identified RCC population was more likely to die from unrelated causes when compared with patients with CRC in a competing-risks analysis, suggesting the relative increase in prostate cancer diagnoses among patients with RCC was not a result of differences in anticipated life expectancy. Incorporating available grade and stage data to multivariate survival analysis has limitations related to missing data and inconsistencies in stage reporting over time in SEER; however, an additional analysis comparing RCC and CRC cohorts, when incorporating available grade and stage data, did not alter the results for prostate cancer-specific survival and overall survival.

To assess whether patterns of prostate cancer diagnosis seen in CRC and RCC cohorts were generalizable to patients with other malignancies, rates of prostate cancer diagnosis in patients who were first diagnosed with skin, oropharynx, thyroid, lung and bladder cancer were obtained (Table 3). As observed for patients with CRC, patients diagnosed with skin, oropharynx and lung cancer were much less likely to be diagnosed with prostate cancer than patients with RCC. Rates of prostate cancer diagnosis in patients with bladder cancer – another malignancy primarily treated by urologists – were similar to those seen in patients with RCC; however, these results may be confounded by incidental diagnoses of prostate cancer at cystoprostatectomy. Interestingly, there was a significant increase in prostate cancer diagnosis in patients diagnosed

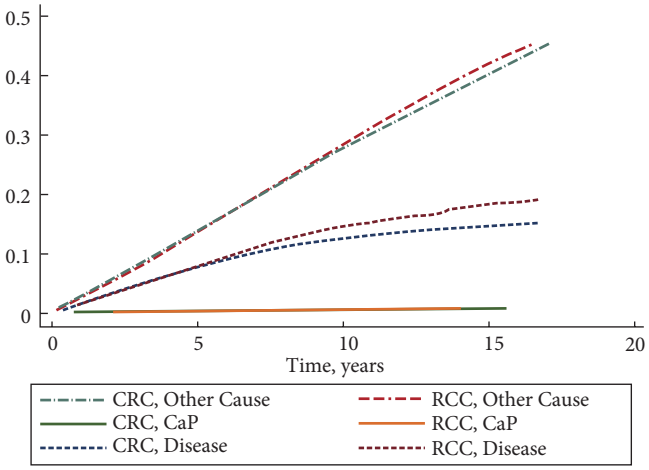
Table 4 Standardized incidence ratios of prostate cancer diagnosis in patients diagnosed with localized CRC or RCC, stratified by follow-up intervals after diagnosis of primary malignancy.

	Time after diagnosis of primary malignancy									
	2–5 months		6–11 months		12–59 months		60–119 months		>120 months	
	Observed/ expected	SIR (95% CI)	Observed/ expected	SIR (95% CI)	Observed/ expected	SIR (95% CI)	Observed/ expected	SIR (95% CI)	Observed/ expected	SIR (95% CI)
CRC, $n = 45\,093$	175/104	1.68 (1.44–1.95)	149/149	1 (0.85–1.18)	932/903	1.03 (0.97–1.1)	579/567	1.02 (0.94–1.11)	196/188	1.04 (0.9–1.2)
RCC, $n = 18\,188$	59/31	1.92 (1.46–2.47)	70/44	1.59 (1.24-2.02)	377/264	1.43 (1.29–1.58)	182/164	1.11 (0.96–1.29)	74/57	1.2 (1.03–1.63)
P (CRC vs RCC)		NS		*<0.05*		*<0.001*		NS		NS

Table 5 Standardized incidence ratios of prostate cancer diagnosis in patients diagnosed with localized CRC or RCC, stratified by age at initial cancer diagnosis (CRC or RCC).

Age range	35 to 49 years		50 to 59 years		60 to 69 years		70 to 79 years	
	Observed/ Expected	SIR (95% CI)	Observed/ Expected	SIR (95% CI)	Observed/ Expected	SIR (95% CI)	Observed/ Expected	SIR (95% CI)
CRC, $n = 45\,093$	37/30	1.24 (0.87–1.7)	278/267	1.04 (0.92–1.17)	722/726	0.99 (0.92–1.07)	758/682	1.11 (1.03–1.19)
RCC, $n = 18\,188$	40/26	1.53 (1.09–2.08)	182/126	1.45 (1.24–1.67)	308/226	1.36 (1.22–1.53)	199/154	1.29 (1.12–1.48)
P (CRC vs. RCC)		NS		*<0.05*		*<0.001*		NS

Fig. 1 Adjusted cumulative incidence curves controlling for age, race and year of diagnosis. No significant difference in prostate cancer-specific survival was observed between the RCC and CRC groups (sHR = 0.827, $P = 0.391$). CaP, prostate cancer.



with thyroid cancer. This association was not seen in a cohort from Sweden where systematic prostate cancer screening has not been adopted [18]. As such, this relationship may be explained by the fact that screening for thyroid and prostate cancer – arguably the two most overdiagnosed malignancies [15] – may be coupled in the USA.

Another key finding in our study was the absence of any differences in prostate cancer-specific mortality between the RCC and CRC cohorts, even in the large subgroup of patients ($n = 12\,938$) with >10 years of follow-up (Fig. 1). Thus, increased detection of prostate cancer in this highly select group of patients with another malignancy did not appear to translate into improved prostate cancer-specific outcomes. Nevertheless, as has been demonstrated in prospective randomized screening trials, longer follow-up may uncover differences between cohorts that may not have been evident in the current analysis [2].

The finding that patients with RCC, who are nearly uniformly exposed to urological care, have higher rates of prostate cancer diagnoses is not surprising. Albeit, to our knowledge, no recent studies have examined PSA screening patterns among urologists, routine PSA testing by urologists in men aged < 70 years has historically exceeded 97%, while up to 88% of men aged 70–74 years have had a PSA test performed [19]. Reasons for such practice patterns are multifactorial and probably a result of recommendations from the AUA, strong medico-legal disincentives for missing a potentially lethal urological diagnosis, and possibly financial and practice-based incentives [20]. Importantly, patients with CRC were found to have higher rates of prostate cancer diagnosis only in the first 2–6 months after identification of their initial cancer. This may be partially attributable to the results of DREs that are performed routinely as a part of the colorectal evaluation process. Meanwhile, patients treated for localized RCC were found to have higher than expected rates of prostate cancer diagnosis at all follow-up time points (Table 4).

Our findings lend support to the growing body of evidence for risk-based prostate cancer screening and treatment [8,21]. For instance, obtaining a baseline PSA level is emerging as a useful tool for assessing the risks of developing prostate cancer and can guide future PSA screening [8]. Specifically, the National Comprehensive Cancer Network guidelines on prostate cancer screening are now recommending that men obtain a baseline PSA at age 40 years. Only men with a baseline PSA ≥ 1 ng/mL are then advised to undergo annual PSA screening [7]. Moreover, how the context of a patient's overall health informs prostate cancer screening decisions is coming into better focus. Prognostication of life expectancy, quantification of competing risks of death, and better understanding of risk factors for developing high-risk prostate cancer must be balanced and integrated into a decision to initiate prostate cancer screening [8,21–23]. Furthermore, novel biomarkers for identification of high-risk malignancy, such as the PCA3 assay, hold significant promise [24–26]. As such, future efforts must continue to focus on helping physicians to better calibrate prostate cancer screening/treatment policies and practices, while developing improved clinical algorithms that minimize overtreatment, but do not hinder effective intervention for patients who are destined to succumb to prostate cancer [22,27]. Indeed, the urologist's role in appropriately contextualizing the screening, diagnosis and impact of treatment for prostate cancer to his/her patients cannot be overstated.

As with any study using an administrative dataset, our work has limitations. We recognize that the current analysis is limited by the treatment effects (type of prostate cancer treatment) that can be examined using the SEER database and by its retrospective nature. Also, SEER lacks data on comorbidities, and inferences based on the SIR estimates might be subject to a healthy survivor effect. Thus, those patients with RCC or CRC who live long enough to be diagnosed with prostate cancer may be inherently different from those who die before prostate cancer is detected. Furthermore, biological and epidemiological associations between RCC, CRC and prostate cancer may confound our results; however, no strong evidence to support such a link exists. In fact, epidemiological data estimating the prevalence and cumulative incidence of different cancers before prostate cancer diagnosis between matched cohorts suggest that cancer of the bladder, colon and

non-melanoma of the skin are the three most frequently observed malignancies before prostate cancer diagnosis [18]. When interpreted in the context of our study, these data strengthen our findings. This study is further strengthened by a large patient population, extensive long-term follow-up in a large subset of patients, and an analysis that incorporates SIR and multivariable methodologies.

In summary, in a cohort identified using SEER data, rates of prostate cancer diagnoses were significantly higher in patients with localized surgically treated RCC than in those with localized CRC. This finding is most probably related to increased exposure to urological care and suggests that urologists are closely attuned to the detection of prostate cancer even when caring for patients with non-prostate-related diagnoses. Meanwhile, prostate cancer-specific survival did not differ between the groups, even in an analysis restricted to patients with >10 years of follow-up. Furthermore, these data reveal that opportunities for better-targeted prostate cancer screening in patients who receive non-prostate-related urological care appear to exist. We believe the present study contributes to a growing body of literature that liberates urologists from being obligated to perform PSA screening for patients receiving non-prostate-related care and underscores the need for better-targeted prostate cancer screening.

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Conflict of Interest

None declared.

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Abbreviations: SEER, Surveillance Epidemiology and End Results; CRC, colorectal carcinoma; SIR, standardized incidence ratio; HR, hazard ratio; sHR, sub-distribution Hazard Ratio.

