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The impact of pre-existing cancer on survival of prostate cancer patients
A population-based study

Yuan Zhou, MS[a,b], Han Guan, MD[b,c], Yong Fu, MS[a,b], Likai Mao, MS[a,b], Jiyue Ge, MS[a,b], Lutan Liu, MS[a,b], Lei Cheng, MD[d,e], Chao Guan, MS[a,b,*]

Abstract

Prostate cancer (PCa) is the second most common malignant tumors for male patients worldwide. However, whether a history of pre-existing cancer cases may affect the survival of prostate cancer patients is still not fully understood.

We identified patients diagnosed with PCa between 2000 and 2014 from the Surveillance, Epidemiology, and End Results (SEER) linked database. We further made propensity score matching and then compared all-cause and cancer-specific survival between patients with and those without a pre-existing cancer. Cox proportional hazards models and Kaplan–Meier analysis were used for survival comparison.

A total of 153,255 patients with PCa were included for analysis, of whom 5939 had a history of pre-existing cancer, including hematologic and lymph (11%), intestine (19%), urinary system (36%), head and neck (9%), lung (5%), skin (12%), and others (8%). Patients with a pre-existing cancer had a worse prognosis compared with those without a pre-existing cancer [all-cause death: hazard ratio (HR) = 2.74, $P < .001$; cancer-special death: HR = 3.98, $P < .001$]. Importantly, cancers in urinary bladder prior to PCa had a most adverse impact on all-cause (HR = 5.00, $P < .001$) and cancer-specific death risk (HR = 10.45, $P < .001$). Time between the pre-existing cancer and PCa had a dose-dependent effect on survival of PCa patients, with a decreased death risk as the increase of the interval time.

Pre-existing cancer has a negative impact on the prognosis of patients with PCa, which is most evident in the presence of a pre-existing urinary bladder cancer. Our results provide epidemiologic evidence with low between-group bias, large sample size, and long-term follow-up, highlighting the need for site-, and interval-time-based clinical management for patients with PCa who had a pre-existing cancer.

Abbreviations: CI = confidence interval, HR = hazard ratio, PCa = prostate cancer, PSA = prostate-specific antigen, PSM = propensity score matching, RP/Ur/UB = renal pelvis, ureter, or urinary bladder, SEER = Surveillance Epidemiology and End Results, SPM = second primary malignance.

Keywords: bladder cancer, prostate cancer, second primary cancer, SEER, survival

[a] Department of Urology Surgery, The Second Affiliated Hospital of Bengbu Medical College, [b] Bengbu Medical College, [c] Department of Urology Surgery, The Frist Affiliated Hospital of Bengbu Medical College, Longzi, Bengbu, [d] Cancer Institute, Collaborative Innovation Center for Cancer Medicine, Fudan University Shanghai Cancer Center, [e] Department of Oncology, Shanghai Medical College, Fudan University, Xuhui, Shanghai, China.

[*] Correspondence: Chao Guan, Department of Urology Surgery, The Second Affiliated Hospital of Bengbu Medical College, 220 Hongye Road, Longzi, Bengbu, 233000, China (e-mail: chao_guan60@163.com).

1. Introduction

Prostate cancer (PCa) is the second most common cancer worldwide, and the fifth leading cause of cancer-related deaths in men worldwide.[1] There is a notable difference in PCa incidence among different regions and races, with a highest incidence in the United States and a lowest incidence in Asia.[2] From 1980s, extensive prostate specific antigen (PSA) detection largely facilitate the screening of prostate cancer.[3] Because of a high rate of over diagnosis induced by PSA screening,[4,5] PSA density of transition zone, free/total PSA ratio, p2PSA and Prostate Health Index as well as prostate-specific membrane antigen have also been tried to be introduced into clinical management to improve PCa screening.[6–9] At the same time, PCa patients were greatly benefited from the development of drug therapy and radiotherapy.[10–12] With the advances in both the screening and therapy, the 5-year relative survival rate reached almost 100% for PCa patients with localized disease and 28% for those harboring a distant disease.[13]

With frequent early diagnosis and advances in cancer treatments in recent years, about 15.1 million cancer survivors lived in the United States in 2016 and the number are expected to increase to 20.3 million by 2026.[13] Survivors of cancer patients are at

high risk of developing a second primary cancer (SPM).[14] SPM as a serious long-term complication, largely increased the death risk of cancer patients.[15] According to follow-up analysis, about 8% cancer patients developed a SPM in patients with first incident cancers.[15,16] In patients with only one primary cancer, the cancer mortality rate was approximately 52%.[15] Among those who carried a SPM, 13% died of the initial, and 55%, however, died of the SPM,[15] indicating that SPMs had a synergistically fatal impact on the patients. For all types of SPMs, lung cancer was recognized as the most common and deadliest cancer, and survivors of bladder cancer showed the highest incidence of SPMs.[15] According to a study in France, males have more than twice the risk of SPM compared with females.[17] Regional differences can also lead to different incidence of SPMs, likely due to differences in dietary habits and genetic factors. In addition, tobacco and alcohol were recognized as the 2 major factors that accounted for the increased risk of SPM.[17]

As reported by analysis of SPM incidence from Surveillance, Epidemiology, and End Results (SEER) database, survivors of colorectal cancer, lung cancer, kidney cancer and melanoma patients had a relatively high risk of carrying PCa as a SPM,[15] indicating a high incidence of suffering cancers prior to PCa. However, to our best knowledge, the impact of pre-existing cancers on survival of PCa patients is still unclear. Therefore, it is necessary to assess the prevalence of cancers prior to PCa and their role in mediating survival of PCa patients, in the light of the widely accessed and worldwide epidemiological data provided by SEER database.

2. Materials and methods

2.1. Data acquisition

Data used for analysis in the present study were obtained from SEER database [SEER 18 Regs Research Data, (1973–2014 varing); Version 8.3.4]. The SEER database published the population-based incidence and survival data of cancer patients, covering about 28% of cancer registries from the United States.[18] Clinical information provided by the SEER database largely facilitates clinical cancer research.

2.2. Study population

This study included patients diagnosed with PCa between year of 2000 and 2014. All cancer patients had pathologically confirmed diagnosis, and we included only PCa patients with the most common pathological subtype, adenocarcinoma, to minimize the pathological bias. The available information on race, age, stage, surgery, PSA, Gleason score, tumor size, grade, and marital status were prerequisites for the inclusion of the patients. We excluded the patients with blank information above mentioned. PCa was defined as the first primary cancer if no primary cancer were detected for patients as indicated by SEER database. Patients were deemed as to have suffered a pre-existing cancer, if there was one type of cancer out of prostate that prior to the diagnosis of PCa.

2.3. Statistical analysis

The prevalence and stage of pre-existing cancer, site of pre-existing cancer, and interval time between prostate and pre-existing cancer were reported in the present study.

To balance the clinical variables and reduce the statistical bias as more as possible, we made a propensity score matching (PSM) between patients who had a pre-existing cancer and those who did not. The information on race, age, stage, surgery, PSA, Gleason score, tumor size, grade and marital status were propensity matched. Then, the matched data were used for survival comparison. We used PSM-adjusted Kaplan–Meier analysis to compare survival between patients with and without a pre-existing cancer. All-cause and cancer-specific deaths were primary end-points in the presents study. For all-cause survival analysis, alive patients were considered as censored data. For cancer-specific survival analysis, alive patients and those who died for the reasons unrelated to cancer were considered as censored data during survival analysis. Cox proportional hazards regression models were used for the comparison of all-cause cancer death risk and cancer-specific death risk among patients. We also made subgroup survival analysis by pathological type of pre-existing lung and bladder cancer, to reveal its impact on survival of PCa patients.

All statistical analyses were achieved by R software (Version 3.4.0, R Foundation, Vienna). Two-tailed P value <.05 was considered as statistical significance.

Ethical approval: All data in our study were obtained from SEER database with the aims of research, thus this study does not contain any human participants or animals collected by any of the authors.

3. Results

A total of 153,255 PCa patients diagnosed between 2000 and 2014 were included in the present study. Among these patients, 5939 PCa patients had a history of pre-existing cancer. The type of pre-existing cancer contained hematologic and lymph (11%), intestine (19%), urinary system (36%), head and neck (9%), lung (5%), skin (12%) and others (8%). 61% (n=3650) of pre-existing cancers were staged as localized or in situ, and only 7% (n=443) were distant disease. 86% (n=5107) of pre-existing cancers were diagnosed within 5 years prior to PCa. The average time between the pre-existing cancer and PCa was about 3 years. About 5% PCa patients (n=7,329) with one primary PCa and 16% PCa patients (n=925) who had a pre-existing cancer, were died of cancer-specific reasons, respectively. Table 1 listed the available information for all patients and those with a pre-existing cancer on race, age, sex, stage, surgery, PSA, Gleason score, tumor size, grade and marry status. Distribution of all variables did not differ between groups after adjustment for propensity matching (P>.05 for all).

In PSM-adjusted K-M curves, PCa patients with a pre-existing cancer had a worse all-cause (5-year survival, 72.65% vs 91.67%, P<.001 for all) and cancer-special survival (5-year survival, 86.73% vs 97.41%, P<.001 for all) in comparison with those with only one primary PCa (Figure 1). In K-M analysis stratified by the type of pre-existing cancer, cancers in urinary bladder prior to PCa had a most adverse impact on survival of PCa patients (For pre-existing cancer in urinary bladder cancer, 5-year all-cause survival: 61.79% vs 92.36%; 5-year cancer-specific survival: 77.26% vs 97.92%, P<.001 for all, Figure 2).

We further made comparisons of all-cause death risk and cancer-specific death risk between groups by PSM-adjusted Cox regression models. We found that a pre-existing cancer increased the all-cause death risk and cancer-specific death risk by 174% [hazard ratio (HR)=2.74, 95% confidence interval (CI)=2.63–2.87, P<.001] and 298% (HR=3.98, 95%CI=3.70–4.27, P<.001), respectively, for PCa patients (Table 2). Interestingly, time between the pre-existing cancer and PCa had a dose-

Table 1

Baseline characteristics of PCa patients included from SEER data cohort (N = 153,255) and between-group comparisons (No pre-existing cancer vs pre-existing cancer).

| Patient characteristics	No. of total patients	No. of patients with pre-existing cancer	Unadjusted P value	PSM-adjusted P value[*]
Age, years			<.001	.9750
Age< 60	42,391	983		
60<=Age< 80	100,860	4250		
Age>=80	10,004	706		
Race			<.001	.9776
White	121,880	5074		
Black	22,794	615		
Other	8581	250		
Marriage status			<.001	.8771
Married	117,822	4567		
Sep/Div/Wid	19,414	833		
Single	16,019	539		
PSA			<.001	.8339
PSA<=10	2016	162		
10< PSA< 50	44,434	1456		
PSA>=50	106,805	4321		
Gleason			<.001	.7873
Gleason< 5	907	67		
5<=Gleason< 8	132,210	5064		
Gleason>=8	20,138	808		
Tumor size, mm			<.001	.3516
Size< 4	82,840	3456		
4<=Size	70,415	2483		
Grade			<.001	.8531
Well	994	73		
Moderately	73361	3009		
Poor	78,525	2841		
Undifferentiated	375	16		
Stage			<.001	.9581
Localized	127,486	5149		
Regional	22,699	651		
Distant	3070	139		
Surgery			.0151	.8544
Yes	77,447	2909		
No	75,808	3030		
Death status			<.001	
Alive	128,758	3624		
Death	24,497	2315		
Cause of death			<.001	
By cancer	7329	925		
Other cause or alive	145,926	5014		
Total				
	153,255	5939		

[*] Comparisons between groups after adjustment for propensity matching score.

PCa = prostate cancer, Sep/Div/Wid = separated, divorced, or widowed.
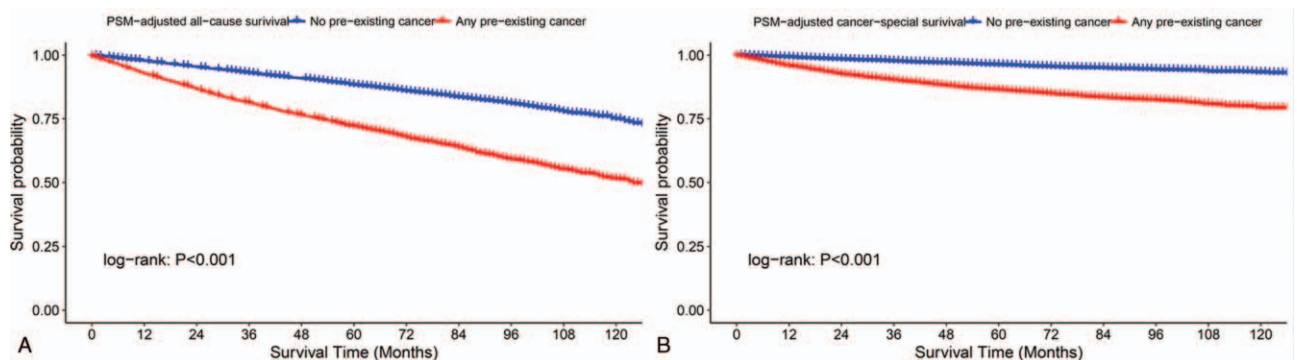
Figure 1. PSM-adjusted comparison for all-cause (A) and cancer-specific survival (B) between PCa patients with and without a pre-existing cancer. PCa = prostate cancer, PSM = propensity score matching.
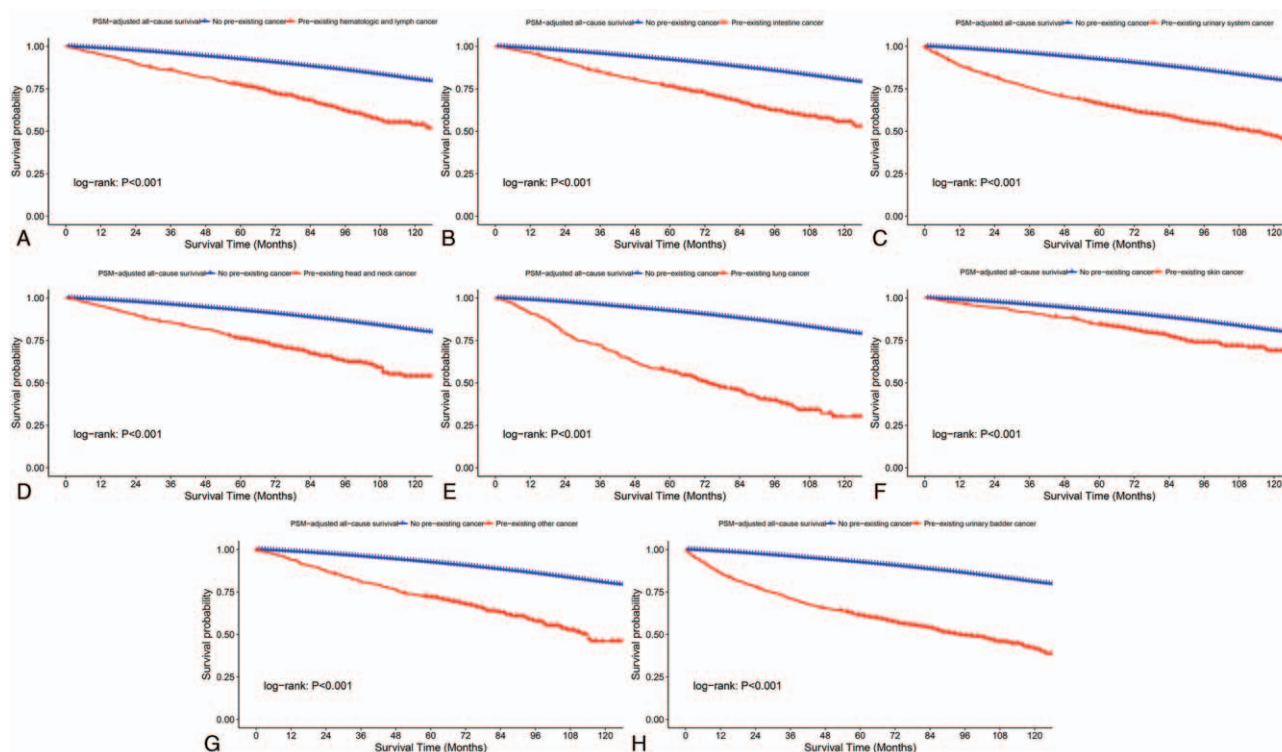
Figure 2. The comparison of all-cause survival between PCa patients with and without a pre-existing cancer, adjusted by PSM score and stratified by the pre-existing cancer type. (A) No pre-existing cancer vs pre-existing hematologic and lymph cancer; (B) No pre-existing cancer vs pre-existing intestine cancer; (C) No pre-existing cancer vs pre-existing urinary system cancer; (D) No pre-existing cancer vs pre-existing head and neck cancer; (E) No pre-existing cancer vs pre-existing lung cancer; (F) No pre-existing cancer vs pre-existing skin cancer; (G) No pre-existing cancer vs pre-existing other cancer; (H) No pre-existing cancer vs pre-existing urinary bladder cancer. PCa = prostate cancer, PSM = propensity score matching.

Table 2

The comparison of all-cause death risk and all cancer-specific death risk between PCa patients with and without a pre-existing cancer.

Pre-existing cancer diagnosis (vs None)	All-cause HR (95% CI)	P value	Cancer-specific HR (95% CI)	P value
Site of pre-existing cancer				
All site	2.74 (2.63–2.87)	<.001	3.98 (3.70–4.27)	<.001
Hematologic/lymph	2.44 (2.14–2.79)	<.001	3.84 (3.12–4.73)	<.001
Intestine	1.86 (1.69–2.06)	<.001	1.82 (1.51–2.20)	.001
Urinary system	4.15 (3.88–4.43)	<.001	8.15 (7.39–9.02)	<.001
Kidney	2.17 (1.83–2.59)	<.001	3.02 (2.22–4.10)	<.001
RP/Ur/UB	4.88 (4.55–5.24)	<.001	10.16 (9.14–11.29)	<.001
Renal pelvis	2.31 (1.15–4.62)	.018	1.64 (0.23–11.67)	.622
Ureter	2.20 (0.99–4.63)	.054	1.99 (0.28–11.20)	.493
Urinary bladder	5.00 (4.65–5.37)	<.001	10.45 (9.40–11.62)	<.001
Head/Neck	2.57 (2.23–2.97)	<.001	2.91 (2.27–3.74)	<.001
Lung	4.23 (3.64–4.91)	<.001	6.68 (5.37–8.31)	<.001
Skin	1.52 (1.31–1.77)	<.001	1.18 (0.86–1.61)	<.001
Other	2.82 (2.45–3.26)	<.001	4.59 (3.72–5.65)	<.001
Stage of pre-existing cancer				
Unknown	2.36 (2.08–2.67)	<.001	2.97 (2.42–3.64)	<.001
In situ	2.18 (1.90–2.51)	<.001	1.94 (1.45–2.60)	<.001
Localized	2.27 (2.13–2.42)	<.001	2.68 (2.40–3.00)	<.001
Regional	4.67 (4.31–5.08)	<.001	9.18 (8.17–10.32)	<.001
Distant	4.15 (3.62–4.74)	<.001	8.96 (7.54–10.66)	<.001
Interval time of pre-existing cancer				
< 1 year	6.27 (5.73–6.88)	<.001	14.98 (13.21–16.99)	<.001
1–3 years	2.68 (2.53–2.84)	<.001	4.10 (3.73–4.50)	<.001
3–5 years	2.03 (1.84–2.24)	<.001	2.03 (1.70–2.43)	<.001
>5 years	2.01 (1.77–2.29)	<.001	1.64 (1.27–2.11)	<.001

Note: Cox regression was used for the death risk comparison according to site and stage of the pre-existing cancers, as well as the interval time between the pre-existing cancer and PCa. All comparisons were adjusted for propensity matching score.
CI = confidence interval, HR = hazard ratio, RP/Ur/UB = renal pelvis, ureter, or urinary bladder.

dependent effect on death risk of PCa patients, with a decreased all-cause death and cancer-specific death risks as the increase of the interval time (Table 2). In line with the trend toward poorest survival in the univariate Kaplan–Meier test, pre-existing cancers in urinary bladder cancers was also a most unfavorable factor for all-cause and cancer-specific death risk which was increased by 4.00-fold (HR = 5.00, 95%CI = 4.65–5.37, $P < .001$) and 9.45-fold (HR = 10.45, 95%CI = 9.40–11.62, $P < .001$), respectively, and followed by lung cancer, with death risk increased by 3.23-fold (HR = 4.23, 95%CI = 3.64–4.91, $P < .001$) and 5.68-fold (HR = 6.68, 95%CI = 5.37–8.31, $P < .001$), respectively (Table 2). However, renal pelvis and ureter cancers as the 2 other types of urinary system cancers prior to PCa, seemed to be unable to affect the cancer-specific death risk of PCa patients ($P > .05$ for all), despite a slight increased all-cause death risk was observed in presence of pre-existing renal pelvis cancer (HR = 2.31, 95%CI = 1.15–4.62, $P = 0.018$, Table 2). In subgroup analysis by pathological type of pre-existing cancer, we found that a pre-existing nontransitional bladder cancer had a most adverse impact on death risk of prostate cancer, followed by the pre-existing cancer of squamous cell lung carcinoma, in terms of either all-cause (for pre-existing nontransitional bladder cancer, HR = 6.83, 95%CI = 4.39–9.46; $P < .001$ and squamous cell lung carcinoma, HR = 5.15, 95%CI = 3.90–6.80; $P < .001$) or cancer-specific survival (for pre-existing non-transitional bladder cancer, HR = 20.24, 95%CI = 12.91–31.71; $P < .001$ and squamous cell lung carcinoma, HR = 8.74, 95%CI = 6.04–12.64; $P < .001$). However, because of the number of patients with specialize pathological type cancers was limited (e.g., for pre-existing nontransitional bladder cancer, n = 66; and squamous cell lung carcinoma, n = 73), further larger studies are warranted to validate our subgroup findings.

4. Discussion

For PCa patients, our study revealed that a pre-existing cancer increased the all-cause death risk and cancer-specific death risk by 1.74-fold and 2.98-fold, respectively. Importantly, the urinary bladder cancer and lung cancer were found in the present study as 2 leading types of pre-existing cancer responsible for poor survival, compared with other types of pre-existing cancer, that mostly contribute to the overall death risk increased by 4.00 and 3.23, respectively. However, pre-existing skin cancer had a minimum impact on cancer related death risk, and only a slight increase of death risk was observed in presence of the pre-existing kidney cancer for PCa patients. These results have important implications on the involvement of pre-existing cancer in clinical management of prostate cancer patients in a site-dependent manner.

In the present study, we combined the pre-existing renal pelvis cancer, ureter cancer, and urinary bladder cancer as the RP/Ur/UB, in order to analysis the collective effect of these 3 types of pre-existing cancers on survival analysis and death risk for PCa patients. The single survival impact of pre-existing renal pelvis cancer, ureter cancer, and urinary bladder cancer, respectively, were also analyzed, and the HR for both all-cause and cancer-specific deaths was lower or with an insignificant trend for both the PCa patients with renal pelvis and those with ureter pre-existing cancer types, but became much higher and significant in the presence of a pre-existing urinary bladder cancer. Also recognized, transitional cell carcinoma is the shared major pathological type in renal pelvis cancer, ureter caner, and urinary bladder cancer, which is a symbol of a similar genetic background

for these 3 types of cancer. Therefore, it is more biological plausible if the prognosis was similar to each other among the 3 types of pre-existing cancer carrier patients. However, the prominent adverse effect on prognosis induced by the pre-existing urinary bladder, not the renal pelvis cancer and ureter cancer, suggested that the coexistence of urinary bladder and PCa was the deadest factor that contributes to the poor survival of the patients. The potential mechanism underlying this observation needs further investigation.

Bladder cancer was found to be the most common cancer, with a prevalence of 28% (n = 1642), prior to PCa in the present study, similar to previous study which reported a high frequency of double primary cancers of the bladder and prostate.[19] Moreover, only 1% (n = 22) of patients with a pre-existing urinary bladder cancer had the same pathological type as prostate cancer. According to the age-adjusted incidence, bladder cancer patients had 18 times greater rate to suffer PCa, and PCa patients had 19 times greater risk to carry bladder cancer, when compared with the absolute PCa and bladder cancer incidence in the general population, respectively.[19] Moreover, the incidence of prostate cancer followed by invasive bladder cancer was reported by another report to be as high as 70%.[20] The coexistence of bladder cancer and PCa was of high presence, importantly, might result in a poor prognosis,[21] which was in accordance with our study in which we observed a prominent adverse impact of bladder cancer on survival of PCa patients. As we known, PCa and bladder cancer may share a similar carcinogenic process in the genetic and protein level, such as P53, nRb, and UROC28 protein over-expression,[22–25] underlying our observation that a pre-existing bladder cancer might synergistically with PCa to have increased the death risk of patients. Another molecular epidemiological evidence revealed that genetic variants of genes involved in DNA repair and N-acetyltransferase were shared causes of increased risk of both cancers.[26] Therefore, according to these results, we recommended a close surveillance of bladder cancer prior to PCa to advance the treatment decision for PCa patients.

In our study, next to bladder cancer, pre-existing lung cancer had the second most adverse impact on survival in PCa patients. Lung cancer is characterized by particularly lethal, with 5-year survival rate about 55%, 27% and 4% for localized, regional and distant disease, respectively.[13] However, according to cancer statistics, PCa was recognized as the most common SPM for lung cancer patients.[27] The high incidence of second primary PCa may be caused by its high prevalence in men, because the annual excess risk and observed annual risk for second primary PCa was lower than the average for SPM in lung cancer patients,[27] indicating that lung cancer and PCa might have no direct relationship like that between bladder cancer and PCa. Moreover, unlike PCa and bladder cancer that shared similar genetic background in cancer etiology,[22–25] few literature reported that there was a specific link between lung cancer and PCa. Collectively, in our study, the poor prognosis in patients with lung cancer prior to PCa might be only a reflection of poor survival and prognosis of lung cancer patients.

Interestingly, based on the results of the present study, the dose-dependent effect of interval time between pre-existing cancer and PCa on death risk of the patients, with a trend toward better prognosis with the increase of the interval time, post a necessary to set a time-dependent model to make reasonable clinical management for PCa patents who suffered a pre-existing cancer.

There are some limitations in this study. First, the treatment of pre-existing cancer such as radiation and chemotherapy may affect the risk of occurrence and survival of SPM,[28] and the smoking history of patients may affect the survival of patients, but the missing information on treatment and smoking history may introduce bias to the present study. Second, the number of patients in some specified sites or pathological type of the pre-existing cancer were limited, leading to the deficient in calculating the specified effect of some pre-existing cancers on survival of PCa cancer patients. Lastly, although a strict matching method was adopted to avoid between-group bias, because of the retrospective design in nature of the present study, large prospective studies are warranted to validate our results.

5. Conclusions

In conclusion, pre-existing cancer has an adverse impact on survival of PCa patients, and this adverse impact is more evident in presence of pre-existing cancers of urinary bladder. Interval time between pre-existing cancer and PCa had a dose-dependent effect with a trend toward favorable prognosis of PCa patients as the increase of the interval time. Our results provide efficient evidence on the role the pre-existing cancer may play in mediating the survival of PCa patents, raising the necessary for the site- and interval-time-depended individualized clinical management for PCa patients with a pre-existing cancer.

Author contributions

Conceptualization: Chao Guan, Lei Cheng.
Data curation: Yuan Zhou, Han Guan.
Formal analysis: Yuan Zhou, Lei Cheng.
Funding acquisition: Chao Guan.
Methodology: Yuan zhou, Han Guan.
Supervision: Chao Guan, Lei Cheng.
Validation: Yong Fu, Likai Mao, Gi-Yue Ge, Lutan Liu.
Writing – original draft: Yuan Zhou, Han Guan.
Writing – review & editing: Chao Guan, Lei Cheng.

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