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Original Article

Cause-specific mortality beyond prostate cancer in young men: a population-based study of second malignancies and non-tumor causes

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Abstract: Objectives: To investigate the cause-specific mortality patterns in young people (<50 years) diagnosed with prostate cancer (PCa). Methods: Using the Surveillance, Epidemiology, and End Results (SEER) database, we identified young PCa patients diagnosed between 2000 and 2018. Causes of death were analyzed, and standardized mortality ratios (SMRs) were calculated. An independent clinical cohort (n=200) was used for external validation. Results: Among 19,352 patients with localized PCa, 1,177 deaths were observed, of which 21.4% were due to pCAs, 22.9% to site-specific malignancies (SMTs), and 55.7% to other non-tumor causes. Colorectal cancer exhibited a significantly reduced mortality risk among SMTs (SMR: 0.67) compared to the general population. Heart disease (SMR: 0.67) was the leading non-cancer cause of death. In 4,445 individuals with regional PCa, 540 deaths were observed, with PCa-specific causes accounting for 54.6%. Lung cancer mortality was significantly reduced (SMR: 0.51). Among 1,070 patients with metastatic PCa, 769 deaths were recorded, with 87.6% attributed to PCa. This stage-specific mortality pattern was consistently validated in the independent clinical cohort. Conclusions: Cause-specific mortality among young PCa patients varies substantially by disease stage at diagnosis. Non-PCa causes predominate in patients with localized disease, whereas PCa remains the principal cause of death in metastatic cases.

Keywords: Prostate cancer, young patients, causes of death, second malignant tumors, SMR, SEER

Introduction

Prostate cancer (PCa) is the most commonly diagnosed malignancy in men, with more than 288,300 new cases annually in the United States [1]. Although PCa usually follows an indolent clinical course, it remains the second leading cause of cancer-related death in men [2]. Following the introduction of prostate-specific antigen (PSA) screening and the popularization of radical prostatectomy (RP), the incidence of fatal prostate cancer (death within 10 years of diagnosis) has substantially declined [3]. The survival of metastatic PCa (mPCa) has significantly improved due to the advances in therapeutic strategies [4, 5]. With the prolonged period of survival, other causes of deaths besides PCa are becoming more threatening for patients' lives. In the PLCO (Prostate, Lung, Colorectal, and Ovarian Cancer) Cancer Screening Trial cohort including 10,859 PCa patients, 81% of the 3,318 deaths were attributable to non-PCa causes [6].

Young PCa patients, usually defined as a male diagnosed under the age of 50 years, account for more than 10% of new diagnoses [7]. This population differs greatly from older PCa patients. Tumors in younger men tend to be more aggressive, while patients usually have better physical condition, fewer comorbidities, stronger family companionship, and longer life expectancy [8-10]. Therefore, the survival outcomes in young PCa patients deserve particular attention. Although many studies have evaluated the prognosis in this population, most have focused on tumor-related outcomes and PCa-specific mortality. In contrast, deaths caused by other factors, such as second malignant tumors (SMTs) and non-tumor diseases, have been insufficiently investigated [11]. These causes constitute a considerable portion of overall

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mortality and are especially relevant for patients who had not entered the metastatic stage at diagnosis.

This study aims to comprehensively evaluate all-cause mortality among young PCa patients, and to calculate a standardized mortality ratio (SMR) for each cause of death in comparison with the general US population.

Methods

Sources of information

Data for this study was sourced from the Surveillance, Epidemiology, and End Results (SEER) program database, which offers population-based cancer incidence and survival data covering roughly 28% of the U.S. population. Mortality data for the general population were acquired from the National Center for Health Statistics (NCHS). This publicly available data was freely accessed using the SEER*Stat software version 8.4.0.1.

Study population and variables

Young patients (<50 years) diagnosed with PCa between 2000 and 2018 were identified from the SEER database. All patients had definite staging information (localized, regional, or metastatic) based on SEER Summary Stage 2000. Only cases in which PCa was the primary cancer or the initial malignancy among multiple primary cancers were included. Cases identified solely through death certificates or autopsy were excluded. Additionally, patients with unknown follow-up time and unclear reasons of death were excluded. Mortality data for the general population, stratified by causes of deaths, were obtained from the NCHS and served as the reference population.

Eligible patients were firstly stratified by disease stage (localized, regional, or metastatic). The following demographic and clinical variables were collected: year of diagnosis (2000-2006, 2007-2012, and 2013-2018), race (White, Black, and Others), tumor grade (well differentiated, moderately differentiated, poorly differentiated, and undifferentiated), PSA level (≤20.0 ng/ml, >20.0 ng/ml, and unknown), Gleason score (≤7, 8-10, and unknown), surgical treatment (no surgery, radical surgery, local surgery, and unknown), vital status (alive or deceased) and all causes of death. The final follow-up date was December 31, 2018.

Outcome evaluations

Cause of death was identified based on the mortality codes in the SEER. Causes of death after PCa diagnosis were classified as malignant tumor-related deaths (e.g., prostate cancer, lung cancer, and others) and non-tumor deaths (e.g., heart disease, chronic liver disease, cirrhosis, and suicide and self-inflicted injury). The primary outcomes of this study were cause-specific mortality and the corresponding SMR with 95% confidence intervals (CIs).

Retrospective clinical cases

To further validate the results, we obtained further data using the SEER database, from a retrospective medical study conducted on 200 young PCa patients (aged <50 years) who were treated at the Suining Central Hospital between January 2010 and December 2020. Inclusion criteria: (1) A diagnosis of PCa before the age of 50 years; (2) Complete medical records, including cause of death; (3) Clearly documented disease stage (localized, regional, or metastatic), and (4) Follow-up data available until death or December 2020.

Clinical information were extracted from electronic medical records, including demographic features, disease severity, medical history, and cause of death. Death causes were categorized as prostate cancer, SMTs, or other non-tumor causes, consistent with the SEER classification. SMRs were calculated using the same method as applied in the SEER analysis, and the general Chinese male population aged <50 years served as the reference population. This independent clinical cohort was used for external validation of the SEER-based findings and to enhance the generalizability of the results in a real-world clinical setting.

This study was approved by the Ethics Committee of Suining Central Hospital. Given the retrospective nature of the study and the use of anonymized data, the requirement for informed consent was waived.

Data analysis

Descriptive statistics were employed to summarize baseline characteristics of the study population. Categorical variables were presented as counts and proportions (n, %), whereas

Table 1. Baseline characteristics of included patients

Characteristic	Localized PCa		Regional PCa		mPCa	
	All	Dead	All	Dead	All	Dead
N	19,352	1,177	4,445	540	1070	769
Race, n (%)						
White	13248 (68.5)	701 (59.6)	3106 (69.9)	377 (69.8)	360 (33.6)	315 (41)
Black	5556 (28.7)	458 (38.9)	1210 (27.2)	148 (27.4)	347 (32.4)	291 (37.8)
Other	548 (2.8)	18 (1.5)	129 (2.9)	15 (2.8)	363 (33.9)	163 (21.2)
Year, n (%)						
2000-2006	7713 (39.9)	797 (67.7)	1937 (43.6)	359 (66.5)	720 (67.3)	521 (67.8)
2007-2012	7882 (40.7)	327 (27.8)	1681 (37.8)	160 (29.6)	295 (27.6)	216 (28.1)
2013-2018	3757 (19.4)	53 (4.5)	827 (18.6)	21 (3.9)	55 (5.1)	32 (4.2)
Grade, n (%)						
Well differentiated	1556 (8)	30 (2.5)	53 (1.2)	2 (0.4)	6 (0.6)	1 (0.1)
Moderately differentiated	12052 (62.3)	694 (59)	1776 (40)	129 (23.9)	87 (8.1)	53 (6.9)
Poorly differentiated	5257 (27.2)	411 (34.9)	2546 (57.3)	391 (72.4)	630 (58.9)	488 (63.5)
Undifferentiated	19 (0.1)	2 (0.2)	13 (0.3)	6 (1.1)	13 (1.2)	12 (1.6)
Unknown	468 (2.4)	40 (3.4)	57 (1.3)	12 (2.2)	334 (31.2)	215 (28)
PSA, n (%)						
≤20 ng/ml	13142 (67.9)	482 (41)	2598 (58.4)	186 (34.4)	164 (15.3)	103 (13.4)
>20 ng/ml	480 (2.5)	80 (6.8)	517 (11.6)	102 (18.9)	252 (23.6)	177 (23)
unclear	5730 (29.6)	615 (52.3)	1330 (29.9)	252 (46.7)	94 (8.8)	57 (7.4)
Gleason score, n (%)					144 (13.5)	103 (13.4)
≤7	6968 (36)	384 (32.6)	1357 (30.5)	103 (19.1)	416 (38.9)	329 (42.8)
8-10	247 (1.3)	59 (5)	335 (7.5)	120 (22.2)		
Unclear	12137 (62.7)	734 (62.4)	2753 (61.9)	317 (58.7)	360 (33.6)	235 (30.6)
Surgical therapy, n (%)	6778 (35)	624 (53)	260 (5.8)	99 (18.3)	356 (33.3)	240 (31.2)
No surgery	12094 (62.5)	505 (42.9)	4131 (92.9)	421 (78)	1 (0.1)	1 (0.1)
Radical surgery	394 (2)	35 (3)	51 (1.1)	19 (3.5)	0 (0)	0 (0)
Local surgery	86 (0.4)	13 (1.1)	3 (0.1)	1 (0.2)	353 (33)	293 (38.1)
Unknown	13248 (68.5)	701 (59.6)	3106 (69.9)	377 (69.8)		

Abbreviations: PSA, prostate-specific antigen; NOS, Not otherwise specified.

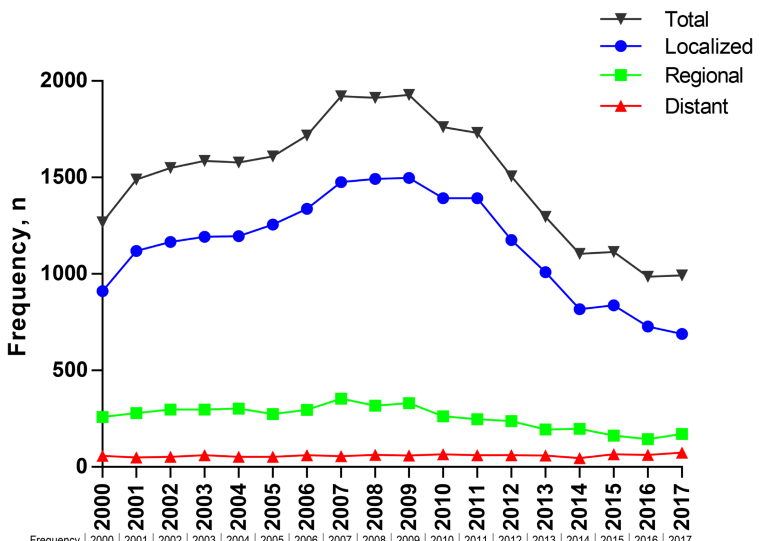
continuous variables were expressed as mean ± standard deviation or median with interquartile range, as appropriate.

For each disease stage (localized, regional, and metastatic), SMRs and their 95% CIs were calculated for each cause of death. The SMR was defined as the ratio of the observed number of deaths among young PCa patients to the expected number of deaths, which were estimated based on the total person-years accumulated by the young PCa cohort and the cause-specific mortality rates of the general population. A 95% CI for SMRs was calculated under the assumption that the observed number of deaths followed a Poisson distribution. Statistical significance was inferred when the 95% CI did not include 1. Subgroup analyses were further performed by calculating SMRs for each cause of death across different follow-up periods after diagnosis (<1 year, 1-5 years, 5-10 years, >10 years). All SMR calculations and statistical analyses were conducted using SEER*Stat software (version 8.4.0.1). A two-sided *P* value <0.05 was deemed statistically significant.

Results

Demographic and clinical characteristics

In total, 19,352 young patients with localized PCa and 4,445 with regional PCa were identified. During follow-up, 1,177 deaths occurred in patients with localized disease and 540 among patients with regional disease. Detailed demographic and clinical characteristics of included patients are shown in **Table 1**.



Frequency	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Total	1268	1489	1549	1586	1578	1609	1717	1920	1913	1927	1760	1731	1506	1296	1104	1114	985	992
Localized	911	1119	1165	1192	1195	1256	1337	1476	1493	1497	1392	1392	1176	1009	818	838	727	689
Regional	259	279	298	297	303	274	295	354	317	331	263	248	237	194	197	162	144	170
Distant	58	49	53	60	53	53	60	56	62	59	66	60	61	59	46	66	63	74

Figure 1. The number of newly diagnosed young prostate cancer patients from 2000 to 2017.

Temporal trends in the incidence of newly diagnosed young patients with localized, regional, and metastatic PCa are shown in **Figure 1**.

Causes of death in young patients with localized PCa

Among patients with localized PCa, PCa-specific mortality accounted for 21.4% of all deaths, death due to SMTs accounted for 22.9%, and deaths from non-neoplastic causes accounted for 55.7%.

The most frequent SMTs were identified based on the highest observed case numbers, including lung and bronchus cancer [n=79, SMR: 0.81 (0.64-1.01)], colorectal cancer [n=25, SMR: 0.67 (0.43-0.98)], and pancreatic cancer [n=28, SMR: 1.07 (0.71-1.54)]. Compared with the general population, mortality from colorectal cancer was significantly decreased, while no statistically significant differences were observed for lung and bronchus cancer or pancreatic cancer. Mortality from liver cancer was also significantly lower [SMR: 0.44, 95% CI: 0.23-0.77].

Among the non-neoplastic causes of death, heart diseases were the primary contributor [n=236, SMR: 0.67 (0.59-0.76)]. Other major non-neoplastic mortality causes included accidents and adverse effects [n=61, SMR: 0.46 (0.35-0.6)], chronic liver disease and cirrhosis [n=37, SMR: 0.61 (0.43-0.85)], cerebrovascular diseases [n=23, SMR: 0.47 (0.3-0.7)], chronic obstructive pulmonary disease (COPD) and allied conditions [n=26, SMR: 0.65 (0.42-0.95)], and diabetes mellitus [n=26, SMR: 0.47 (0.31-0.69)]. For suicide and self-inflicted injury [n=39, SMR: 0.79 (0.56-1.08)], the risk was not statistically different from the general population. All results are presented in **Table 2**.

Causes of death in young patients with regional PCa

Among deaths in young patients with regional PCa, prostate cancer (n=295) was the leading cause, accounting for 54.6% of all fatalities. Death due to SMTs accounted for 15.8%, and non-neoplastic causes accounted for 29.6%.

The primary SMTs included cancers of lung and bronchus [n=12, SMR: 0.51 (0.26-0.89)], liver [n=10, SMR: 1.53 (0.73-2.81)], and pancreas [n=8, SMR: 1.28 (0.55-2.52)]. Compared with the general population, mortality from lung and bronchus cancers was significantly decreased, whereas no significant differences were observed for liver or pancreatic cancer.

Among non-neoplastic causes of death, heart disease [n=49, SMR: 0.59 (0.43-0.78)] showed a significantly reduced mortality risk. Mortality from cerebrovascular diseases [n=14, SMR: 1.21 (0.66-2.03)] exhibited no statistical difference from that of the general population. Results are presented in **Table 3**.

Causes of death in young patients with mPCa

Among deaths in young mPCa patients, prostate cancer (n=647) was the predominant contributor, accounting for 87.6% of all deaths. SMTs accounted for 7.3% and non-neoplastic causes accounted for 5.2%. Soft tissue sarcoma, including heart sarcoma, was the main SMT and was associated with an obviously increased mortality risk compared with the

Table 2. Cause-specific mortality in young patients with localized prostate cancer

Causes of deaths	Total			<1 year			1-5 years			5-10 years			>10 years		
	Observed	Expected	SMR (95% CI)	Observed	Expected	SMR (95% CI)	Observed	Expected	SMR (95% CI)	Observed	Expected	SMR (95% CI)	Observed	Expected	SMR (95% CI)
All Causes of Death	1,177	1,443.60	0.82# (0.77-0.86)	46	75.24	0.61# (0.45-0.82)	319	399.2	0.80# (0.71-0.89)	405	510.83	0.79# (0.72-0.87)	407	458.32	0.89# (0.8-0.98)
All Malignant Cancers	521	357.47	1.46# (1.33-1.59)	12	14.01	0.86 (0.44-1.5)	140	84.74	1.65# (1.39-1.95)	183	128.24	1.43# (1.23-1.65)	186	130.48	1.43# (1.23-1.65)
Male Genital System	253	14.12	17.92# (15.78-20.27)	11	0.3	36.74# (18.34-65.73)	76	2.18	34.80# (27.42-43.56)	101	4.63	21.82# (17.77-26.52)	65	7.01	9.28# (7.16-11.82)
Prostate	252	13.18	19.12# (16.83-21.63)	11	0.23	48.40# (24.16-86.6)	76	1.86	40.76# (32.11-51.02)	100	4.31	23.19# (18.87-28.21)	65	6.78	9.59# (7.4-12.22)
Urinary System	15	18.3	0.82 (0.46-1.35)	0	0.69	0 (0-5.32)	3	4.23	0.71 (0.15-2.07)	5	6.54	0.76 (0.25-1.78)	7	6.85	1.02 (0.41-2.11)
Urinary Bladder	8	6.43	1.24 (0.54-2.45)	0	0.19	0 (0-19.01)	2	1.27	1.57 (0.19-5.69)	3	2.25	1.33 (0.27-3.89)	3	2.71	1.11 (0.23-3.23)
Kidney and Renal Pelvis	6	11.58	0.52 (0.19-1.13)	0	0.49	0 (0-7.55)	1	2.89	0.35 (0.01-1.93)	2	4.19	0.48 (0.06-1.72)	3	4.02	0.75 (0.15-2.18)
Respiratory System	81	103.03	0.79# (0.62-0.98)	0	3.77	0.00# (0-0.98)	19	23.73	0.8 (0.48-1.25)	22	37.23	0.59# (0.37-0.89)	40	38.3	1.04 (0.75-1.42)
Lung and Bronchus	79	97.14	0.81 (0.64-1.01)	0	3.54	0 (0-1.04)	19	22.32	0.85 (0.51-1.33)	22	35.08	0.63# (0.39-0.95)	38	36.2	1.05 (0.74-1.44)
Digestive System	89	125.72	0.71# (0.57-0.87)	1	4.79	0.21 (0.01-1.16)	20	29.68	0.67 (0.41-1.04)	30	45.63	0.66# (0.44-0.94)	38	45.62	0.83 (0.59-1.14)
Pancreas	28	26.22	1.07 (0.71-1.54)	1	0.91	1.09 (0.03-6.1)	5	5.85	0.85 (0.28-1.99)	10	9.4	1.06 (0.51-1.96)	12	10.05	1.19 (0.62-2.09)
Colon and Rectum	25	37.57	0.67# (0.43-0.98)	0	1.65	0 (0-2.24)	6	9.78	0.61 (0.23-1.34)	11	13.67	0.8 (0.4-1.44)	8	12.47	0.64 (0.28-1.26)
Liver and Intrahepatic Bile Duct	16	30.8	0.52# (0.3-0.84)	0	0.92	0 (0-4)	4	6.33	0.63 (0.17-1.62)	3	11.33	0.26# (0.05-0.77)	9	12.22	0.74 (0.34-1.4)
Liver	12	27.18	0.44# (0.23-0.77)	0	0.81	0 (0-4.56)	2	5.58	0.36 (0.04-1.29)	3	10.04	0.30# (0.06-0.87)	7	10.75	0.65 (0.26-1.34)
Esophagus	12	16.9	0.71 (0.37-1.24)	0	0.65	0 (0-5.71)	3	4	0.75 (0.15-2.19)	4	6.14	0.65 (0.18-1.67)	5	6.12	0.82 (0.27-1.91)
Stomach	6	9.76	0.61 (0.23-1.34)	0	0.48	0 (0-7.76)	1	2.67	0.38 (0.01-2.09)	2	3.5	0.57 (0.07-2.06)	3	3.12	0.96 (0.2-2.81)
Brain and Other Nervous System	15	13.4	1.12 (0.63-1.85)	0	0.69	0 (0-5.32)	7	3.69	1.89 (0.76-3.9)	5	4.8	1.04 (0.34-2.43)	3	4.21	0.71 (0.15-2.08)
Lymphoma	9	11.51	0.78 (0.36-1.48)	0	0.6	0 (0-6.13)	1	3.15	0.32 (0.01-1.77)	2	4.01	0.5 (0.06-1.8)	6	3.76	1.6 (0.59-3.47)
Myeloma	4	6.49	0.62 (0.17-1.58)	0	0.24	0 (0-15.29)	2	1.51	1.32 (0.16-4.78)	0	2.3	0 (0-1.61)	2	2.44	0.82 (0.1-2.97)
Leukemia	6	10.13	0.59 (0.22-1.29)	0	0.49	0 (0-7.58)	2	2.59	0.77 (0.09-2.79)	2	3.47	0.58 (0.07-2.08)	2	3.58	0.56 (0.07-2.02)

Miscellaneous Malignant Cancer	30	27.16	1.1 (0.75-1.58)	0	1.12	0 (0-3.3)	6	6.59	0.91 (0.33-1.98)	9	9.72	0.93 (0.42-1.76)	15	9.74	1.54 (0.86-2.54)
Non-tumor causes															
Diseases of Heart	236	353.06	0.67# (0.59-0.76)	12	17.2	0.7 (0.36-1.22)	69	95.48	0.72# (0.56-0.91)	83	125.82	0.66# (0.53-0.82)	72	114.56	0.63# (0.49-0.79)
Accidents and Adverse Effects	61	131.61	0.46# (0.35-0.6)	4	10.12	0.4 (0.11-1.01)	14	46.3	0.30# (0.17-0.51)	21	46.18	0.45# (0.28-0.7)	22	29.02	0.76 (0.48-1.15)
Suicide and Self-Inflicted Injury	39	49.53	0.79 (0.56-1.08)	5	3.91	1.28 (0.42-2.98)	12	17.9	0.67 (0.35-1.17)	12	17.51	0.69 (0.35-1.2)	10	10.22	0.98 (0.47-1.8)
Chronic Liver Disease and Cirrhosis	37	60.34	0.61# (0.43-0.85)	1	3.27	0.31 (0.01-1.7)	15	17.96	0.84 (0.47-1.38)	9	22.36	0.40# (0.18-0.76)	12	16.75	0.72 (0.37-1.25)
Cerebrovascular Diseases	23	49.02	0.47# (0.3-0.7)	2	2.42	0.83 (0.1-2.99)	9	13.21	0.68 (0.31-1.29)	4	17.14	0.23# (0.06-0.6)	8	16.26	0.49# (0.21-0.97)
COPD and Allied Cond	26	40.09	0.65# (0.42-0.95)	1	1.09	0.91 (0.02-5.09)	4	7.3	0.55 (0.15-1.4)	7	13.53	0.52 (0.21-1.07)	14	18.17	0.77 (0.42-1.29)
Diabetes Mellitus	26	54.87	0.47# (0.31-0.69)	1	2.44	0.41 (0.01-2.28)	4	13.9	0.29# (0.08-0.74)	11	19.58	0.56 (0.28-1.01)	10	18.95	0.53# (0.25-0.97)
Other Infectious and Parasitic Diseases including HIV	19	49.56	0.38# (0.23-0.6)	1	4.22	0.24 (0.01-1.32)	7	18.23	0.38# (0.15-0.79)	6	16.8	0.36# (0.13-0.78)	5	10.3	0.49 (0.16-1.13)
Hypertension without Heart Disease	16	15.4	1.04 (0.59-1.69)	0	0.66	0 (0-5.55)	6	3.86	1.56 (0.57-3.39)	5	5.49	0.91 (0.3-2.12)	5	5.39	0.93 (0.3-2.17)
Nephritis, Nephrotic Syndrome and Nephrosis	17	21.72	0.78 (0.46-1.25)	0	0.98	0 (0-3.77)	3	5.49	0.55 (0.11-1.6)	5	7.6	0.66 (0.21-1.54)	9	7.66	1.18 (0.54-2.23)
Pneumonia and Influenza	13	17.66	0.74 (0.39-1.26)	1	0.86	1.17 (0.03-6.5)	2	4.63	0.43 (0.05-1.56)	3	6.14	0.49 (0.1-1.43)	7	6.03	1.16 (0.47-2.39)
Septicemia	7	19.93	0.35# (0.14-0.72)	0	0.9	0 (0-4.1)	3	5.1	0.59 (0.12-1.72)	3	7.06	0.42 (0.09-1.24)	1	6.87	0.15# (0-0.81)
Homicide and Legal Intervention	5	17.93	0.28# (0.09-0.65)	0	1.95	0 (0-1.9)	1	7.55	0.13# (0-0.74)	4	5.75	0.7 (0.19-1.78)	0	2.68	0 (0-1.38)
Other Cause of Death	96	163.9	0.59# (0.47-0.72)	5	8.7	0.57 (0.19-1.34)	18	45.53	0.40# (0.23-0.62)	38	57.51	0.66# (0.47-0.91)	35	52.15	0.67# (0.47-0.93)

Abbreviations: SMR, standardized mortality ratio; CI, confidence interval; COPD, Chronic Obstructive Pulmonary Disease. #P<0.05.

Table 3. Cause-specific mortality in young patients with regional prostate cancer

Causes of deaths	Total			<1 year			1-5 years			5-10 years			>10 years		
	Observed	Expected	SMR (95% CI)	Observed	Expected	SMR (95% CI)	Observed	Expected	SMR (95% CI)	Observed	Expected	SMR (95% CI)	Observed	Expected	SMR (95% CI)
All Causes of Death	540	340.81	1.58# (1.45-1.72)	12	17.49	0.69 (0.35-1.2)	142	92.66	1.53# (1.29-1.81)	232	118.12	1.96# (1.72-2.23)	154	112.53	1.37# (1.16-1.6)
All Malignant Cancers	380	85.56	4.44# (4.01-4.91)	10	3.31	3.03# (1.45-5.56)	107	19.94	5.37# (4.4-6.49)	170	30.05	5.66# (4.84-6.57)	93	32.26	2.88# (2.33-3.53)
Male Genital System	295	3.41	86.42# (76.84-96.87)	6	0.07	86.07# (31.59-187.35)	88	0.51	172.98# (138.74-213.12)	141	1.08	130.52# (109.86-153.92)	60	1.75	34.19# (26.09-44.01)
Prostate	295	3.2	92.31# (82.07-103.47)	6	0.05	113.11# (41.51-246.19)	88	0.44	201.97# (161.98-248.83)	141	1.01	139.89# (117.75-164.98)	60	1.7	35.31# (26.95-45.45)
Urinary System	9	4.39	2.05 (0.94-3.89)	1	0.16	6.11 (0.15-34.03)	2	1	2.01 (0.24-7.26)	3	1.53	1.96 (0.4-5.72)	3	1.7	1.77 (0.36-5.17)
Urinary Bladder	4	1.55	2.58 (0.7-6.6)	0	0.05	0 (0-80.4)	1	0.3	3.34 (0.08-18.63)	0	0.53	0 (0-6.96)	3	0.68	4.44 (0.92-12.97)
Kidney and Renal Pelvis	5	2.77	1.81 (0.59-4.22)	1	0.12	8.67 (0.22-48.3)	1	0.68	1.47 (0.04-8.18)	3	0.98	3.06 (0.63-8.94)	0	0.99	0 (0-3.73)
Respiratory System	13	24.85	0.52# (0.28-0.89)	0	0.9	0 (0-4.1)	2	5.64	0.35 (0.04-1.28)	5	8.8	0.57 (0.18-1.33)	6	9.5	0.63 (0.23-1.37)
Lung and Bronchus	12	23.44	0.51# (0.26-0.89)	0	0.85	0 (0-4.36)	2	5.31	0.38 (0.05-1.36)	5	8.3	0.6 (0.2-1.41)	5	8.99	0.56 (0.18-1.3)
Digestive System	25	29.94	0.84 (0.54-1.23)	1	1.12	0.89 (0.02-4.97)	5	6.94	0.72 (0.23-1.68)	5	10.64	0.47 (0.15-1.1)	14	11.24	1.25 (0.68-2.09)
Pancreas	8	6.26	1.28 (0.55-2.52)	1	0.21	4.67 (0.12-26.01)	1	1.37	0.73 (0.02-4.07)	1	2.19	0.46 (0.01-2.54)	5	2.49	2.01 (0.65-4.69)
Colon and Rectum	4	8.87	0.45 (0.12-1.15)	0	0.38	0 (0-9.64)	1	2.26	0.44 (0.01-2.46)	1	3.16	0.32 (0.01-1.76)	2	3.06	0.65 (0.08-2.36)
Liver and Intrahepatic Bile Duct	11	7.39	1.49 (0.74-2.66)	0	0.22	0 (0-16.9)	3	1.5	2 (0.41-5.85)	3	2.66	1.13 (0.23-3.29)	5	3.01	1.66 (0.54-3.87)
Liver	10	6.54	1.53 (0.73-2.81)	0	0.19	0 (0-19.21)	3	1.32	2.26 (0.47-6.62)	2	2.37	0.84 (0.1-3.05)	5	2.65	1.88 (0.61-4.4)
Esophagus	1	4.05	0.25 (0.01-1.37)	0	0.15	0 (0-24.1)	0	0.94	0 (0-3.9)	0	1.45	0 (0-2.55)	1	1.51	0.66 (0.02-3.69)
Stomach	1	2.3	0.43 (0.01-2.42)	0	0.11	0 (0-33.32)	0	0.62	0 (0-5.95)	0	0.81	0 (0-4.56)	1	0.76	1.31 (0.03-7.3)
Soft Tissue Sarcoma (including Heart)	4	0.76	5.28# (1.44-13.51)	0	0.04	0 (0-85.91)	1	0.22	4.59 (0.12-25.55)	3	0.26	11.42# (2.36-33.37)	0	0.23	0 (0-15.72)
Brain and Other Nervous System	5	3.17	1.58 (0.51-3.68)	0	0.16	0 (0-22.6)	1	0.86	1.16 (0.03-6.45)	1	1.12	0.9 (0.02-5)	3	1.03	2.91 (0.6-8.51)
Lymphoma	1	2.75	0.36 (0.01-2.03)	0	0.14	0 (0-25.98)	0	0.74	0 (0-4.98)	1	0.94	1.07 (0.03-5.93)	0	0.93	0 (0-3.97)
Myeloma	4	1.55	2.58 (0.7-6.61)	0	0.06	0 (0-65.39)	1	0.35	2.83 (0.07-15.76)	2	0.54	3.73 (0.45-13.49)	1	0.6	1.65 (0.04-9.21)
Leukemia	1	2.42	0.41 (0.01-2.3)	0	0.11	0 (0-32.39)	0	0.61	0 (0-6.09)	1	0.81	1.23 (0.03-6.85)	0	0.89	0 (0-4.15)

Miscellaneous Malignant Cancer	20	6.51	3.07# (1.88-4.75)	2	0.26	7.56 (0.92-27.32)	7	1.55	4.50# (1.81-9.28)	6	2.28	2.63 (0.97-5.72)	5	2.41	2.08 (0.67-4.84)
Non-tumor causes															
Diseases of Heart	49	83.54	0.59# (0.43-0.78)	1	4.01	0.25 (0.01-1.39)	9	22.23	0.40# (0.19-0.77)	18	29.14	0.62# (0.37-0.98)	21	28.17	0.75 (0.46-1.14)
Accidents and Adverse Effects	13	30.19	0.43# (0.23-0.74)	1	2.32	0.43 (0.01-2.4)	3	10.53	0.28# (0.06-0.83)	6	10.4	0.58 (0.21-1.26)	3	6.93	0.43 (0.09-1.26)
Suicide and Self-Inflicted Injury	11	11.44	0.96 (0.48-1.72)	0	0.9	0 (0-4.09)	6	4.1	1.46 (0.54-3.18)	4	4	1 (0.27-2.56)	1	2.43	0.41 (0.01-2.29)
Chronic Liver Disease and Cirrhosis	8	14.19	0.56 (0.24-1.11)	0	0.77	0 (0-4.79)	1	4.2	0.24 (0.01-1.33)	2	5.17	0.39 (0.05-1.4)	5	4.05	1.23 (0.4-2.88)
Cerebrovascular Diseases	14	11.59	1.21 (0.66-2.03)	0	0.56	0 (0-6.6)	1	3.06	0.33 (0.01-1.82)	6	3.96	1.51 (0.56-3.3)	7	4.01	1.75 (0.7-3.6)
COPD and Allied Cond	9	9.66	0.93 (0.43-1.77)	0	0.26	0 (0-14.4)	0	1.71	0 (0-2.16)	3	3.17	0.95 (0.2-2.77)	6	4.53	1.33 (0.49-2.88)
Diabetes Mellitus	5	12.92	0.39# (0.13-0.9)	0	0.56	0 (0-6.57)	2	3.2	0.63 (0.08-2.26)	1	4.5	0.22 (0.01-1.24)	2	4.66	0.43 (0.05-1.55)
Other Infectious and Parasitic Diseases including HIV	7	11.71	0.6 (0.24-1.23)	0	0.99	0 (0-3.72)	2	4.28	0.47 (0.06-1.69)	3	3.92	0.76 (0.16-2.23)	2	2.51	0.8 (0.1-2.87)
Hypertension without Heart Disease	3	3.6	0.83 (0.17-2.43)	0	0.15	0 (0-24.59)	1	0.88	1.14 (0.03-6.35)	2	1.25	1.6 (0.19-5.77)	0	1.32	0 (0-2.79)
Nephritis, Nephrotic Syndrome and Nephrosis	2	5.12	0.39 (0.05-1.41)	0	0.22	0 (0-16.46)	0	1.26	0 (0-2.93)	2	1.75	1.14 (0.14-4.13)	0	1.89	0 (0-1.95)
Septicemia	8	4.7	1.7 (0.73-3.35)	0	0.21	0 (0-17.82)	3	1.18	2.55 (0.53-7.45)	3	1.63	1.84 (0.38-5.39)	2	1.69	1.18 (0.14-4.27)
Other Cause of Death	19	38.54	0.49# (0.3-0.77)	0	2.02	0 (0-1.83)	3	10.52	0.29# (0.06-0.83)	9	13.22	0.68 (0.31-1.29)	7	12.78	0.55 (0.22-1.13)

Abbreviations: SMR, standardized mortality ratio; CI, confidence interval; COPD, Chronic Obstructive Pulmonary Disease. #P<0.05.

Table 4. Cause-specific mortality in young patients with metastatic prostate cancer

Causes of deaths	Total			<1 year			1-5 years			5-10 years			>10 years		
	Observed	Expected	SMR (95% CI)	Observed	Expected	SMR (95% CI)	Observed	Expected	SMR (95% CI)	Observed	Expected	SMR (95% CI)	Observed	Expected	SMR (95% CI)
All Causes of Death	741	21.81	33.97# (31.57-36.51)	124	3.53	35.09# (29.19-41.84)	515	9.59	53.73# (49.19-58.58)	81	5.08	15.95# (12.67-19.82)	21	3.62	5.81# (3.59-8.88)
All Malignant Cancers	701	4.9	143.05# (132.66-154.05)	116	0.64	181.38# (149.88-217.55)	490	1.97	248.11# (226.63-271.08)	75	1.28	58.72# (46.19-73.61)	20	1.01	19.83# (12.11-30.62)
Male Genital System	647	0.17	3,703.85# (3423.91-4000.58)	101	0.01	7,286.72# (5935.16-8854.03)	455	0.05	9,053.60# (8240.72-9924.98)	72	0.05	1,560.34# (1220.87-1965)	19	0.06	294.93# (177.57-460.57)
Prostate	647	0.16	4,083.00# (3774.41-4410.1)	101	0.01	9,698.75# (7899.79-11784.86)	455	0.04	10,754.60# (9788.99-11789.7)	72	0.04	1,672.40# (1308.55-2106.11)	19	0.06	303.09# (182.48-473.31)
Urinary System	4	0.24	16.45# (4.48-42.11)	1	0.03	31.82 (0.81-177.31)	3	0.1	30.47# (6.28-89.05)	0	0.06	0 (0-57.5)	0	0.05	0 (0-75.02)
Urinary Bladder	4	0.08	50.54# (13.77-129.41)	1	0.01	115.38# (2.92-642.87)	3	0.03	103.38# (21.32-302.12)	0	0.02	0 (0-167.58)	0	0.02	0 (0-189.72)
Digestive System	5	1.73	2.9 (0.94-6.76)	1	0.22	4.5 (0.11-25.09)	1	0.7	1.44 (0.04-8)	2	0.45	4.41 (0.53-15.94)	1	0.35	2.82 (0.07-15.7)
Colon and Rectum	2	0.54	3.68 (0.45-13.3)	1	0.08	12.88 (0.33-71.78)	0	0.23	0 (0-15.9)	1	0.14	7.4 (0.19-41.25)	0	0.1	0 (0-37.47)
Liver and Intrahepatic Bile Duct	1	0.4	2.5 (0.06-13.94)	0	0.04	0 (0-87.43)	0	0.15	0 (0-25.34)	0	0.11	0 (0-32.23)	1	0.1	10.27 (0.26-57.2)
Pancreas	2	0.35	5.74 (0.7-20.75)	0	0.04	0 (0-87.65)	1	0.14	7.32 (0.19-40.79)	1	0.09	10.84 (0.27-60.38)	0	0.08	0 (0-47.74)
Respiratory System	3	1.38	2.17 (0.45-6.34)	1	0.17	5.96 (0.15-33.22)	2	0.54	3.69 (0.45-13.34)	0	0.38	0 (0-9.84)	0	0.3	0 (0-12.35)
Larynx	1	0.07	14.22 (0.36-79.23)	0	0.01	0 (0-433.31)	1	0.03	35.93 (0.91-200.21)	0	0.02	0 (0-195.43)	0	0.02	0 (0-244.17)
Lung and Bronchus	2	1.3	1.54 (0.19-5.55)	1	0.16	6.36 (0.16-35.43)	1	0.51	1.97 (0.05-10.96)	0	0.35	0 (0-10.44)	0	0.28	0 (0-13.1)
Oral Cavity and Pharynx	2	0.17	11.77# (1.43-42.51)	0	0.02	0 (0-155.98)	2	0.07	27.70# (3.35-100.07)	0	0.04	0 (0-84.53)	0	0.03	0 (0-121.01)
Gum and Other Mouth	1	0.02	59.83# (1.51-333.35)	0	0	0 (0-1626.46)	1	0.01	144.45# (3.66-804.8)	0	0	0 (0-858.52)	0	0	0 (0-1143.35)
Bones and Joints	1	0.02	65.53# (1.66-365.09)	0	0	0 (0-1353.5)	1	0.01	145.16# (3.68-808.8)	0	0	0 (0-1100.41)	0	0	0 (0-1607.56)
Soft Tissue Sarcoma (including Heart)	20	0.05	399.54# (244.05-617.05)	6	0.01	681.56# (250.12-1483.48)	13	0.02	566.31# (301.54-968.41)	1	0.01	89.81# (2.27-500.37)	0	0.01	0 (0-514.92)
Myeloma	1	0.09	11.07 (0.28-61.67)	0	0.01	0 (0-331.93)	1	0.04	28.56 (0.72-159.11)	0	0.02	0 (0-159.34)	0	0.02	0 (0-175.1)
Miscellaneous Malignant Cancer	18	0.38	47.78# (28.32-75.52)	6	0.05	118.24# (43.39-257.37)	12	0.15	78.16# (40.39-136.54)	0	0.1	0 (0-37.89)	0	0.08	0 (0-49.14)
Non-tumor causes															
Diseases of Heart	11	5.21	2.11# (1.05-3.78)	2	0.79	2.52 (0.31-9.11)	8	2.25	3.55# (1.53-6.99)	1	1.24	0.8 (0.02-4.48)	0	0.92	0 (0-4.02)
Septicemia	6	0.29	20.45# (7.51-44.52)	2	0.04	47.21# (5.72-170.55)	3	0.12	24.66# (5.08-72.06)	1	0.07	14.05 (0.36-78.27)	0	0.06	0 (0-63.46)
Accidents and Adverse Effects	5	2.34	2.13 (0.69-4.98)	2	0.49	4.04 (0.49-14.6)	3	1.17	2.57 (0.53-7.5)	0	0.45	0 (0-8.17)	0	0.23	0 (0-16.12)

Cerebrovascular Diseases	2	0.74	2.69 (0.33-9.72)	1	0.11	8.85 (0.22-49.33)	1	0.31	3.18 (0.08-17.74)	0	0.17	0 (0-21.15)	0	0.14	0 (0-26.05)
Suicide and Self-Inflicted Injury	2	0.88	2.28 (0.28-8.24)	0	0.19	0 (0-19.55)	2	0.45	4.43 (0.54-16.01)	0	0.17	0 (0-21.64)	0	0.07	0 (0-55.27)
Other Infectious and Parasitic Diseases including HIV	1	0.9	1.11 (0.03-6.16)	0	0.2	0 (0-18.91)	1	0.44	2.28 (0.06-12.72)	0	0.18	0 (0-20.37)	0	0.09	0 (0-41.16)
Diabetes Mellitus	1	0.8	1.25 (0.03-6.99)	0	0.12	0 (0-31.94)	0	0.33	0 (0-11.08)	1	0.19	5.17 (0.13-28.8)	0	0.16	0 (0-23.69)
Hypertension without Heart Disease	1	0.23	4.43 (0.11-24.67)	0	0.03	0 (0-117)	0	0.09	0 (0-40.22)	0	0.05	0 (0-67.27)	1	0.05	20.95 (0.53-116.74)
Atherosclerosis	1	0.02	53.15# (1.35-296.12)	0	0	0 (0-1469.52)	0	0.01	0 (0-489.81)	1	0	204.89# (5.19-1141.55)	0	0	0 (0-947.44)
Chronic Liver Disease and Cirrhosis	1	0.92	1.09 (0.03-6.05)	0	0.15	0 (0-24.11)	1	0.43	2.3 (0.06-12.83)	0	0.22	0 (0-16.94)	0	0.12	0 (0-32.01)
Other Cause of Death	7	2.48	2.82# (1.13-5.81)	1	0.41	2.43 (0.06-13.54)	4	1.1	3.63 (0.99-9.31)	2	0.57	3.53 (0.43-12.76)	0	0.41	0 (0-9.09)

Abbreviations: SMR, standardized mortality ratio; CI, confidence interval. #P<0.05.

Table 5. Patient characteristics in the external validation cohort (n=200)

Variables	Value
Age at diagnosis (years)	45.2±4.3
Stage, n (%)	
Localized	137 (68.5)
Regional	42 (21.0)
Metastatic	21 (10.5)
Vital Status, n (%)	
Alive	158 (79.0)
Deceased	42 (21.0)
Cause of Death, n (%)	
Prostate Cancer	22 (52.4)
Second Malignant Tumors	10 (23.8)
Non-Tumor Causes	10 (23.8)

general population [n=20, SMR: 399.54 (244.05-617.05)]. The main causes of non-neoplastic death in mPCa patients were heart disease [n=11, SMR: 2.11 (1.05-3.78)] and septicemia [n=6, SMR: 20.45 (7.51-44.52)]. All these results are summarized in **Table 4**.

External validation

The clinical validation cohort included 200 young PCa patients, of whom 68.5% were diagnosed with localized disease, 21.0% with regional disease, and 10.5% with metastatic disease. The median follow-up duration was 8.2 years. During follow-up, 42 patients (21.0%) died, with causes of death attributed to prostate cancer (52.4%), SMTs (23.8%), and non-neoplastic causes (23.8%). Details are shown in **Table 5**.

The SMRs for major causes of death in the clinical cohort were basically consistent with those derived from the SEER database. As shown in **Table 6**, for patients with localized disease, the SMR for prostate cancer-specific deaths was significantly elevated (SMR=18.95, 95% CI: 11.2-29.8), while SMRs for heart disease (SMR=0.65, 95% CI: 0.42-0.93) and accidents (SMR=0.48, 95% CI: 0.25-0.82) were significantly lower than the general population. A similar trend was observed in patients with regional and metastatic disease, supporting the robustness and external validity of the SEER-derived findings.

Discussion

The study provides a comprehensive evaluation of cause-specific mortality in a large and frequently overlooked population: young males (<50 years) diagnosed with PCa. By leveraging a large population-based SEER database and incorporating an independent clinical cohort for external validation, we characterized mortality patterns beyond PCa-specific outcomes. Given their relatively long life expectancy, young PCa patients face unique long-term survivorship challenges that extend well beyond initial cancer treatment. The main conclusion is that for young men with localized or regional PCa, the majority of deaths are from non-prostate cancer causes, and a patient-centric, long-term focus on survivorship should be comprehensive.

Among patients diagnosed with localized disease, only 21.4% of deaths were attributed to PCa, while more than 75% resulted from other causes. Notably, non-neoplastic causes accounted for 55.7%. These findings are consistent with the overall trend that, for malignancies with favorable prognoses, competing risks increasingly outweigh cancer-specific mortality in determining long-term outcomes [12]. Another noteworthy finding is that young PCa patients exhibited a significantly lower risk of death from several major causes compared with the general population. Mortality risks from SMTs such as colorectal and liver cancer, and multiple non-neoplastic conditions, including heart disease, injuries, chronic liver disease, COPD, and diabetes, were significantly reduced, with SMRs substantially below 1.0. Regarding lung cancer, although the SMR was below 1, the corresponding 95% CI contained 1; therefore, the reduction in risk did not reach statistical difference [13, 14].

The observed reductions in risk may be attributable to several factors, commonly described as the “healthy patient” epidemiologic phenomenon or, more appropriately in this context, the “healthier survivor effect”. Following a PCa diagnosis, individuals often become more aware of their health condition and engage in positive behavioral changes, such as smoking cessation, improved dietary habits, increased physical activity, and stricter adherence to

Table 6. Standardized mortality ratios (SMRs) for major causes of death in the validation cohort

Cause of Death	Observed	Expected	SMR (95% CI)
Localized (n=137)			
Prostate Cancer	8	0.42	19.05 (8.2-37.5)
Heart Disease	5	7.69	0.65 (0.21-1.52)
Lung Cancer	3	3.70	0.81 (0.17-2.37)
Regional (n=42)			
Prostate Cancer	10	0.11	90.91 (43.5-167.2)
Cerebrovascular Disease	2	1.65	1.21 (0.15-4.37)
Metastatic (n=21)			
Prostate Cancer	16	0.04	400.00 (228.6-649.0)
Sepsis	2	0.12	16.67 (2.02-60.2)

medical surveillance and physician recommendations [15, 16]. Younger patients, who have fewer comorbidities and better physiological reserve, are more capable of implementing and sustaining such changes compared with older individuals [8, 9]. Additionally, contemporary PCa management involves frequent interactions with medical staff, which may increase the likelihood of receiving preventive care for non-cancer conditions [17, 18]. For instance, medications like statins (widely studied in PCa populations) and metformin (commonly prescribed to patients with diabetes and PC), may confer protective effects against heart disease and metabolic complications, potentially contributing to the reduced mortality caused by these conditions [19-21]. Consistent with our findings, Weiner et al. [13] reported lower risks of cardiovascular disease-related and non-PCa cancer - related mortality in PCa patients, supporting the notion that cancer-directed healthcare systems may indirectly improve overall health outcomes.

However, this protection was not uniform across all causes of death. We noticed modestly elevated SMRs for certain SMTs, including pancreatic cancer in localized disease and liver cancer regional disease. These findings should be interpreted with caution given the wide confidence intervals. Nevertheless, they raise the possibility that genetic susceptibility or environmental factors may contribute to site-specific excess risks. For example, individuals with BRCA2-associated hereditary cancer are known to have an increased risk of aggressive PCa as well as other malignancies, including pancreatic cancer [22, 23]. In addition, the psychological and physiological stress associated with cancer diagnosis and treatment may also influence susceptibility to subsequent diseases, although further investigation is required to clarify these mechanisms. Although the SMR for suicide and self-injury was not significantly elevated in our cohort, the absolute risk remains clinically relevant. A diagnosis of PCa, particularly in young men, may provoke substantial psychological distress related to concerns about sexual function, fertility, masculinity, and financial burden. Previous studies have shown that PCa patients are at increased risk of developing depression and committing suicide [24, 25]. Therefore, psychological support and routine mental health screening should be incorporated into standard care for the young PCa population.

In young men with metastatic PCa, mortality patterns differ substantially, compared with those with localized or regional disease. In this subgroup, PCa itself is the dominant cause of death. This observation is consistent with the aggressive behavior and rapid clinical progression of de novo metastatic PCa, and this is associated with notably shortened survival, leaving limited time for other competing mortality risks to manifest [4, 5]. Hence, the SMRs of other non-PCa causes, such as sepsis, appear greatly elevated as the expected number of deaths in the age-matched general population over such a short time span is substantially low [3].

Beyond this statistical explanation, biological mechanisms may also contribute. Advanced cancer is characterized by a chronic inflammatory and immunosuppressive state, which may predispose patients to severe infections, including sepsis [26]. Supporting this hypothesis, Alanee et al. reported that distant metastasis in PCa is an independent predictor of sepsis-related death [27]. Moreover, treatments for mPCa including intensive androgen deprivation therapy and chemotherapy, are associated with substantial systemic toxicity and may increase the risk of cardiovascular disease and other

complications [28]. Although a small number of events in a certain subgroup cannot reach a definite conclusion, these findings highlight that, for young patients with mPCa, optimal outcomes rely primarily on effective cancer control and minimizing treatment-related morbidity to prevent premature non-cancer-related death.

The inclusion of an external validation cohort further strengthens the robustness of our findings. The distribution of causes of death and the trend in SMRs were highly consistent between SEER data and our institutional cohort, supporting the generalizability of our results across different healthcare settings.

Our findings have several important clinical implications. First, in the clinical management of localized PCa in young patients, these results provide additional support for considering active surveillance or watchful waiting strategies, rather than immediate radical intervention, in appropriately selected patients. Survivorship care should be comprehensive, with particular emphasis on preventing cardiovascular events, accidental injuries, and hepatic disease. Patient education on lifestyle modification, including weight control, physical exercises, smoking cessation, and adherence to a well-balanced diet, should be integrated into follow-up care [29, 30]. In addition, mental health screening is also essential. Second, the SMTs associated with increased risk should also be noted. These findings underscore the need for a thorough family history screening in young PCa patients to identify hereditary cancer syndromes [22, 23]. Third, patients with regional disease exhibit a relatively higher risk of PCa-specific mortality; therefore, management should prioritize achieving optimal oncologic control while addressing the long-term sequelae and additional health risks associated with radical therapies.

Several limitations of this study should also be acknowledged. First, the retrospective design precludes some detailed information on lifestyle factors such as smoking history, body mass index, physical activity, all of which may influence cause-specific mortality. Second, although SEER database provides large-scale population-based data, the absolute number of deaths among young PCa patients-particularly for specific causes of death-remains relatively small. Consequently, some cause-specific SMR estimates are inaccurate, as reflected by wide confidence intervals. Third, external validation was limited, especially for patients with mPCa, in whom the number of events was small and SMR estimates were therefore unstable. This cohort was primarily intended for trend validation rather than to provide precise effect estimate. Future prospective studies incorporating more details on lifestyle and treatments will be necessary to further elucidate those associations and underlying mechanisms.

Conclusion

The distribution of causes of death among young prostate cancer patients varies greatly from the stage of diagnosis. Among patients with localized disease, the majority of deaths are attributable to non-prostate cancer causes, including other malignancies and cardiovascular events, highlighting the need for comprehensive survivorship care. Among patients with metastatic PCa, prostate cancer remains the predominant cause of death, underscoring the critical importance of effective oncologic control. These findings emphasize the central role of accurate staging at diagnosis in risk stratification and long-term management. A stage-specific, patient-centered survivorship strategy is essential to optimize overall survival and improve long-term health outcomes in young men with prostate cancer.

Disclosure of conflict of interest

None.

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