



Incidence trends and survival outcomes of penile squamous cell carcinoma: evidence from the Surveillance, Epidemiology and End Results population-based data

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Background: To provide the latest incidence trends and explore survival outcomes of penile squamous cell carcinoma (PSCC) patients with or without a previous primary malignancy.

Methods: Patients diagnosed with PSCC between 1975 and 2016 in the Surveillance, Epidemiology, and End Results (SEER) database were retrospectively included. Then, we calculated the age-adjusted incidence rates (IRs) and annual percentage changes (APCs). Multivariate Cox analysis and Kaplan-Meier (KM) survival curves were conducted to investigate prognostic variables for cancer-specific survival (CSS).

Results: A total of 6,122 PSCC patients were enrolled, 1,137 of whom had a prior malignancy. The age-adjusted IR for the general population in men declined before 1987, fluctuated slightly between 1987 and 1997, and showed an upward trend after 1997, which was basically consistent with that in patients without a previous primary malignancy. The incidence trend of PSCC in the general population was similar with that in those without a previous malignancy. However, the IRs of PSCC in men with a previous malignancy have been increasing since 1975 regardless of race. Furthermore, age at diagnosis, pathological grade, extent of disease, marital status, the administration of surgery and presence of previous primary malignancy were identified to be significantly related to CSS.

Conclusions: The IRs of PSCC have been increasing in recent years. Several independent prognostic factors for CSS were identified, allowing surgeons to assess the individualized risk in advance.

Keywords: Penile squamous cell carcinoma (PSCC); Surveillance, Epidemiology, and End Results (SEER) database; incidence; prognosis

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Introduction

Penile cancer, accounting for approximately 0.3% of all male malignant tumors, is a rare urological malignant tumor. The estimated new cases and deaths of penile cancer in 2018

were 34,475 and 15,138 globally (1). The most common type of penile cancer is squamous cell carcinoma. Moreover, the incidence of penile cancer is closely related to the prevalence of human papilloma virus (HPV), which may be

an important cause of the variation in incidence. In Uganda, penile cancer is the most common male malignancy, particularly in the uncircumcised ethnic groups (2,3).

Although the pathogenesis of penile squamous cell carcinoma (PSCC) is still unclear, previous studies have found many potential risk factors, including phimosis, HPV infection, human immunodeficiency virus (HIV) infection, balanitis, excessive sexual partners, and immunodeficiency. Meanwhile, tobacco use, age and race may also be associated with the development of PSCC (4-11). In the past few decades, the prognosis of advanced penile cancer has been poor (12,13). The 5-year overall survival (OS) rates for regional and distant PSCC diseases were only 50% and 12% between 2009 and 2015 (<https://www.cancer.org/cancer/penile-cancer/detection-diagnosis-staging/survival-rates.html>). Therefore, it is critical to investigate the risk predictors and prognostic factors for PSCC patients. Currently, most studies (14,15) on PSCC are case reports or retrospective studies based on small populations due to the rarity of PSCC itself. Moreover, only few studies have been performed to evaluate the temporal incidence trends and survival outcomes of PSCC.

The Surveillance, Epidemiology and End Result (SEER) program is a large population-based database that collects cancer cases in the United States. It contains detailed information on cancer incidence, mortality and prognosis of approximately 30% of the US population. We conducted this study based on the SEER database to investigate the latest incidence trends and survival outcomes of patients with PSCC. We present the following article in accordance with the PRISMA reporting checklist (available at <http://dx.doi.org/10.21037/atm-20-1802>).

Methods

Database

Original data of this study were collected from the SEER database. The SEER registry is a public registry supported by the National Cancer Institute (NCI). SEER 9 included data from nine registries in Connecticut, Hawaii, Iowa, New Mexico, Utah, Detroit (Michigan), San Francisco Oakland (California), Seattle-Puget Sound (Washington) and Atlanta (Georgia) since 1975. SEER 13 collected cancer cases diagnosed since 1992 with four additional registries [Alaska Natives, Los Angeles, San Jose-Monterey (California) and rural Georgia]. At the beginning of the 21st century, SEER 18 was developed with five new registries added (including

Greater California, Greater Georgia, Kentucky, Louisiana and New Jersey). Data agreement was signed before this study with the username of 15440-Nov2018. This study was exempt from Institutional Review Board (IRB) approval because the original data were from a public database.

Patient identification

In this study, patients diagnosed with PSCC were respectively extracted from SEER 18 using the “Case Listing Session”. The inclusion criteria were as follows: (I) diagnosed as PSCC (International Classification of Diseases for Oncology: C60.0-Prepuce, C60.1-Glans penis, C60.2-Body of penis, C60.8-Overlapping lesion of penis and C60.9-Penis, NOS. Histologic Type: 8050-8089) with microscopical confirmation; (II) complete data were available with active follow-up; (III) type of reporting source was not autopsy only or death certificate only; (IV) cancer patients (behavior =3); (V) male sex.

Age at diagnosis was mainly categorized into <35, 35–49, 50–64, 65–79 and ≥80 years old. Primary tumor site was classified into prepuce, glans penis, body of penis, overlapping lesion of penis and not specified. Extent of disease was designated as distant, regional and localized. Race was coded as white, black, or other. The included patients were further divided into two groups based on the existence of a previous primary malignancy.

Incidence rates (IRs) and annual percent changes

We calculated the age-adjusted IRs between 1975–2016 using the “Rate Session” function (SEER 9 for 1975–1991, SEER 13 for 1992–1999, and SEER 18 for 2000–2016). A 5-year latency was utilized in the development of temporal trend figures. Additionally, annual percent changes (APCs) were calculated to identify the trends of age-adjusted IRs in different groups.

Survival outcomes

Multivariate Cox proportional hazards regression analyses were conducted to explore independent factors which affected cancer-specific survival (CSS) significantly. Co-variables of interest included age at diagnosis, presence of a previous primary cancer, race, decades of diagnosis, primary tumor site, extent of disease, pathological grade, the administration of surgery and so on. Year of diagnosis was divided into 1975–1984, 1985–1994, 1995–2004, 2005–

2016 with 10 years as an interval. Furthermore, based on the results of multivariate Cox analyses, survival curves for different variables were produced by Kaplan-Meier (KM) analyses.

Statistical methods

Age-adjusted IRs were calculated based on the 2000 U.S. standard population using the SEER*Stat software (Version 8.3.6; www.seer.cancer.gov/seerstat). Chi-square tests were utilized to compare categorical variables. Multivariate Cox-proportional hazards analyses were applied to investigate independent factors for CSS. Furthermore, survival curves for different variables were produced by KM analyses. Data were analyzed using SPSS 23.0 software (SPSS Inc, Chicago, IL, USA) and R software (Version 3.4.1). In addition, APCs were calculated using Joinpoint Regression Program (<https://surveillance.cancer.gov/joinpoint/>). Two-sided $P < 0.05$ was considered to be statistically significant during the whole analysis process.

Results

A total of 6,122 patients with PSCC were identified from the SEER 18 database, 1,137 of whom had at least a prior malignancy. As shown in *Table 1*, those with a prior primary cancer were more likely to be older ($P < 0.001$), white race ($P = 0.001$), diagnosed in the last decade ($P < 0.001$) and had worse differentiation ($P = 0.001$). The most common site of PSCC was glans penis (33.02% and 33.42% for patients without/with a prior primary cancer, respectively). More localized diseases were identified in patients with a prior primary cancer ($P = 0.033$). However, blank or ambiguous data existed in many patients in specific variables, such as primary tumor site, pathological grade and extent of disease. After eliminating these meaningless interference data, we found that there were no significant differences in extent of disease between two groups of patients with and without a prior malignancy (details were shown in *Table S1*). The most important treatment type was surgery for all patients (72.50% and 78.63% for patients without/with a prior primary cancer, respectively).

IRs and annual percentage changes (APCs) in PSCC

Tables 2-4 show the case counts and IRs for PSCC by racial group and age group. As shown in *Figure 1*, the age-adjusted IR declined before 1987 and fluctuated slightly between

1987 and 1997 for male population. After 1997, it showed an upward trend. For patients without a previous primary malignancy, the age-adjusted IR was basically consistent with that of the general population. However, for those with previous a previous malignancy, the overall incidence has been increasing slowly.

The incidence trend of PSCC in the general population was similar with that in those without a previous malignancy. In white individuals, the IR was basically in a steady upward trend. However, in blacks and other individuals, the IRs experienced a large decline before 1985, and then gradually stabilized and increased slightly (*Figure 2A,B*). However, the IRs in all races have been increasing for patients with a previous malignancy (*Figure 2C*). Additionally, the IRs in black individuals were the highest while those in other races (AI/AN and A/PI) were the lowest no matter in which population.

The IR trend in the general population was consistent with that in patients without a previous malignancy (*Figure 3*). Among people with a previous primary cancer, the IR trends varied greatly, which may be explained by a small population base and a small number of cases. On the whole, the IRs were basically on the rise among people of all age groups. As for different age groups, the IRs of PSCC in the general population increased along with age. For those younger than 50 years old, the IRs were very low, especially in people younger than 35 years old (tended to be 0).

From 1975 to 2016, the overall IRs of PSCC were on the rise in all populations (*Figure 4*). For the general population, people without/with previous primary cancer, the APCs were 1.33, 0.69 and 4.32, respectively (all $P < 0.05$).

Survival outcomes

A total of 6,079 patients were selected for CSS analysis (43 patients were excluded because of unknown cause of death). Multivariate Cox analysis showed that age at diagnosis, pathological grade, extent of disease, marital status, the administration of surgery and presence of previous primary malignancy were independent prognostic factors for CSS (*Table 5*).

Subsequently, KM curves were generated to learn the actual effect of different variables on CSS (*Figure 5*). Older patients had worse prognosis than younger patients ($P < 0.001$). Patients who underwent surgery had better prognosis than those who did not ($P < 0.001$). Additionally, patients with distant diseases or higher-grade pathology

Table 1 Demographic characteristics of patients with penile squamous cell carcinoma based on existence of a prior primary from SEER 18

Variable	Total	No primary, n (%)	Previous primary, n (%)	P value
N	6,122	4,985 (81.43)	1,137 (18.57)	
Age at diagnosis, years				<0.001
<35	116	112 (2.24)	4 (0.35)	
35–49	670	633 (12.70)	37 (3.25)	
50–64	1,789	1,600 (32.10)	189 (16.62)	
65–79	2,377	1,838 (36.87)	539 (47.41)	
≥80	1,170	802 (16.09)	368 (32.37)	
Race				0.001
White	5,103	4,134 (82.93)	969 (85.22)	
Black	671	545 (10.93)	126 (11.08)	
Other (AI/AK, A/PI)	292	250 (5.02)	42 (3.69)	
Unknown	56	56 (1.12)	0 (0.00)	
Year at diagnosis				<0.001
1975–1981	297	276 (5.54)	21 (1.85)	
1982–1988	306	273 (5.48)	33 (2.90)	
1989–1995	439	395 (7.92)	44 (3.87)	
1996–2002	961	804 (16.13)	157 (13.81)	
2003–2009	1,813	1,458 (29.25)	355 (31.22)	
2010–2016	2,306	1,779 (35.69)	527 (46.35)	
Primary site				0.004
Prepuce	792	679 (13.62)	113 (9.94)	
Glans penis	2,026	1,646 (33.02)	380 (33.42)	
Body of penis	278	220 (4.41)	58 (5.10)	
Overlapping lesion of penis	237	202 (4.05)	35 (3.08)	
Penis, NOS	2,789	2,238 (44.89)	551 (48.46)	
Pathological grade				0.001
Grade I	1,577	1,329 (26.66)	248 (21.81)	
Grade II	2,328	1,910 (38.31)	418 (36.76)	
Grade III	1,075	843 (16.91)	232 (20.40)	
Grade IV	36	29 (0.58)	7 (0.62)	
Unknown	1,106	874 (17.53)	232 (20.40)	
Marital status				<0.001
Married	3,450	2,795 (56.07)	655 (57.61)	
Previous married	1,216	954 (19.140)	262 (23.04)	
Never married	961	838 (16.81)	123 (10.82)	

Table 1 (Continued)

Table 1 (Continued)

Variable	Total	No primary, n (%)	Previous primary, n (%)	P value
Unknown	495	398 (7.98)	97 (8.53)	
Extent of disease				0.033
Localized	3,519	2,847 (57.11)	672 (59.10)	
Regional	1,760	1,458 (29.25)	302 (26.56)	
Distant	298	253 (5.08)	45 (3.96)	
Unstaged	545	427 (8.57)	118 (10.38)	
Surgery				<0.001
Unknown/no	1,614	1,371 (27.50)	243 (21.37)	
Yes	4,508	3,614 (72.50)	894 (78.63)	

Grade I, well differentiated; Grade II, moderately differentiated; Grade III, poorly differentiated; Grade IV, undifferentiated; anaplastic.

Table 2 Case counts and incidence rates for penile squamous cell carcinoma by racial group and age group, SEER 9 (1975–1991)

	Total			White			Black			Other		
	Rate	Counts	Population	Rate	Counts	Population	Rate	Counts	Population	Rate	Counts	Population
Total	0.534	729	183,707,355	0.514	604	151,716,668	1.070	106	18,371,455	0.191	17	13,619,232
No primary	0.479	665	183,707,355	0.460	550	151,716,668	0.970	97	18,371,455	0.182	16	13,619,232
Previous primary	0.054	64	183,707,355	0.054	54	151,716,668	0.101	9	18,371,455	0.009	1	13,619,232
Age group												
No primary												
<35	0.009	10	108,234,673	0.006	6	87,299,672	0.009	1	12,353,899	0.025	2	8,581,102
35–49	0.217	71	34,138,599	0.204	56	28,689,163	0.405	12	3,026,549	0.139	3	2,422,887
50–64	0.885	228	24,849,234	0.848	188	21,378,640	1.894	37	1,903,189	0.171	3	1,567,405
65–79	2.101	276	13,652,455	2.027	231	11,834,440	4.237	38	934,294	0.749	6	883,721
≥80	2.862	80	2,832,394	2.789	69	2,514,753	5.757	9	153,524	1.264	2	164,117
Previous primary												
<35	0.001	1	108,234,673	0.001	1	87,299,672	0.000	0	12,353,899	0.000	0	8,581,102
35–49	0.009	3	34,138,599	0.007	2	28,689,163	0.038	1	3,026,549	0.000	0	2,422,887
50–64	0.043	11	24,849,234	0.037	8	21,378,640	0.098	2	1,903,189	0.062	1	1,567,405
65–79	0.201	27	13,652,455	0.185	22	11,834,440	0.619	5	934,294	0.000	0	883,721
≥80	0.807	22	2,832,394	0.873	21	2,514,753	0.582	1	153,524	0.000	0	164,117

Table 3 Case counts and incidence rates for penile squamous cell carcinoma by racial group and age group, SEER 13 (1992–1999)

	Total			White			Black			AI/AN			A/PI		
	Rate	Counts	Population	Rate	Counts	Population	Rate	Counts	Population	Rate	Counts	Population	Rate	Counts	Population
Total	0.533	587	146,538,760	0.533	484	113,891,860	0.793	64	15,668,689	0.945	8	2,133,075	0.238	25	14,845,136
No primary	0.453	504	146,538,760	0.451	413	113,891,860	0.671	55	15,668,689	0.945	8	2,133,075	0.204	22	14,845,136
Previous primary	0.081	83	146,538,760	0.083	71	113,891,860	0.123	9	15,668,689	0.000	0	2,133,075	0.034	3	14,845,136
Age group															
No primary															
<35	0.019	16	80,593,684	0.020	13	60,997,131	0.010	1	9,754,820	0.000	0	1,420,150	0.000	0	8,421,583
35–49	0.200	66	34,039,819	0.191	50	26,825,803	0.388	12	3,361,844	0.239	1	430,342	0.092	3	3,421,830
50–64	0.715	132	18,361,415	0.732	109	14,805,481	0.751	12	1,594,839	1.047	2	193,541	0.453	8	1,767,554
65–79	1.865	198	10,850,963	1.826	161	8,978,389	2.974	22	795,007	3.282	3	73,255	1.052	10	1,004,312
≥80	3.474	92	2,692,879	3.505	80	2,285,056	5.547	8	162,179	12.801	2	12,787	0.511	1	229,857
Previous primary															
<35	0.000	0	80,593,684	0.000	0	60,997,131	0.000	0	9,754,820	0.000	0	1,420,150	0.000	0	8,421,583
35–49	0.003	1	34,039,819	0.000	0	26,825,803	0.000	0	3,361,844	0.000	0	430,342	0.032	1	3,421,830
50–64	0.081	15	18,361,415	0.080	12	14,805,481	0.186	3	1,594,839	0.000	0	193,541	0.000	0	1,767,554
65–79	0.430	45	10,850,963	0.444	39	8,978,389	0.762	5	795,007	0.000	0	73,255	0.097	1	1,004,312
≥80	0.830	22	2,692,879	0.876	20	2,285,056	0.714	1	162,179	0.000	0	12,787	0.511	1	229,857

AI/AN, American Indian/Alaska Native; A/PI, Asian or Pacific Islander.

Table 4 Case counts and incidence rates for penile squamous cell carcinoma by racial group and age group, SEER 18 (2000–2016)

	Total						White			Black			AI/AN			API			
	Rate	Counts	Population	Rate	Counts	Population	Rate	Counts	Population	Rate	Counts	Population	Rate	Counts	Population	Rate	Counts	Population	
Total	0.753	4806	709,211,368	0.772	4015	542,920,346	0.899	501	86,576,018	0.699	41	11,168,31	0.366	201	68,546,689				
No primary	0.585	3816	709,211,368	0.599	3171	542,920,346	0.669	393	86,576,018	0.592	37	11,168,316	0.297	167	68,546,689				
Previous primary	0.168	990	709,211,368	0.173	844	542,920,346	0.229	108	86,576,018	0.107	4	11,168,31	0.070	34	68,546,689				
Age group																			
No primary																			
<35	0.024	86	359,005,397	0.026	70	266,408,646	0.007	3	50,048,349	0.014	1	6,795,756	0.020	8	35,752,747				
35–49	0.319	496	153,487,804	0.326	389	117,719,303	0.398	72	17,938,075	0.085	2	2,297,200	0.141	22	15,533,227				
50–64	1.003	1240	121,928,312	1.048	1032	96,899,260	1.111	140	12,657,735	0.968	14	1,472,823	0.382	42	10,898,494				
65–79	2.414	1364	57,542,250	2.446	1133	47,218,836	2.704	130	4,846,351	3.727	18	501,020	1.327	65	4,976,043				
≥80	3.691	630	17,247,506	3.759	547	14,674,302	4.631	48	1,085,509	2.200	2	101,517	2.185	30	1,386,180				
Previous primary																			
<35	0.001	3	359,005,397	0.001	3	266,408,646	0.000	0	50,048,349	0.000	0	6,795,756	0.000	0	35,752,747				
35–49	0.021	33	153,487,804	0.017	21	117,719,303	0.065	12	17,938,075	0.000	0	2,297,200	0.000	0	15,533,227				
50–64	0.131	163	121,928,312	0.138	138	96,899,260	0.146	18	12,657,735	0.000	0	1,472,823	0.064	7	10,898,494				
65–79	0.864	467	57,542,250	0.897	400	47,218,836	1.073	48	4,846,351	0.503	2	501,020	0.379	17	4,976,043				
≥80	1.882	324	17,247,506	1.924	282	14,674,302	2.769	30	1,085,509	1.806	2	101,517	0.742	10	1,386,180				

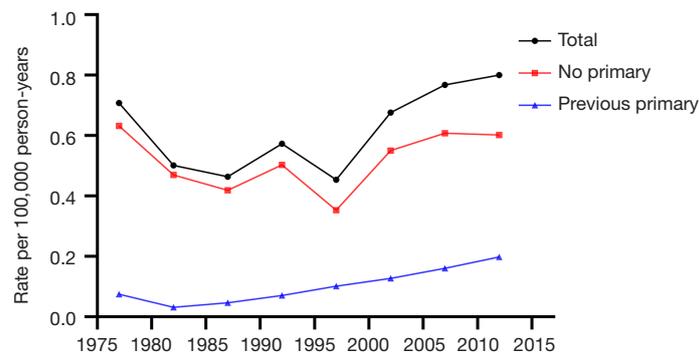


Figure 1 Incidence rates trends of penile squamous cell carcinoma in men from 1975 to 2016.

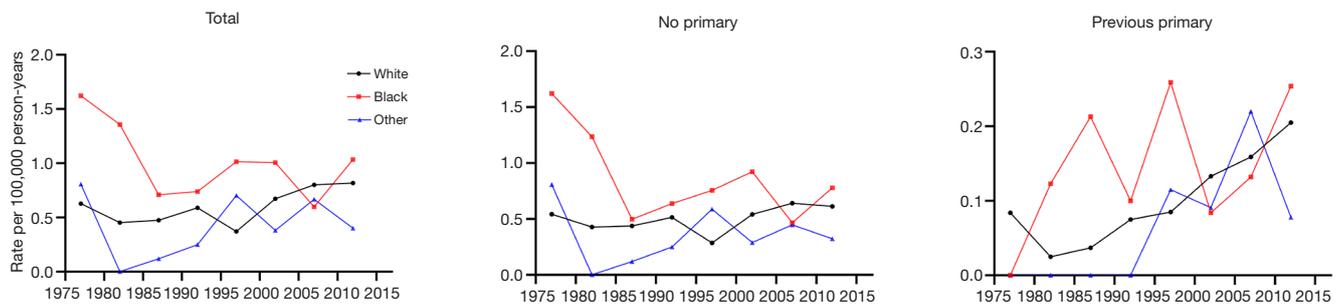


Figure 2 Incidence rates trends of penile squamous cell carcinoma in men by race from 1975 to 2016.

had worse CSS. In our study, the prognosis of married men was relatively better than those who were never married. Interestingly, we found that patients with a previous malignancy had better CSS than those who did not. We believed that many patients would die from the previous cancer, but not PSCC. To verify our conjecture, we analyzed the survival impact of previous malignancies on PSCC patients. Results showed that a previous primary malignancy was tightly associated with worse OS in PSCC patients (Figure 6).

Discussion

This study provided a view of the epidemiological of PSCC in the USA from 1975 to 2016. IRs of PSCC in this study were similar with those in previously published studies. Research conducted by Barnholtz-Sloan *et al.* revealed that there were 5.8 new cases of penis cancer per million men per year on average between 1993 and 2002 in the USA (4). Lagacé *et al.* demonstrated that the IR of penile cancer in Canada was 6.077 per million men per year from 1992 to 2010 (16). This consistency indicated the geographic

continuity of incidence trends, since these studies were all based on populations in North America. In our study, the overall IR of PSCC was basically similar to that in previous studies.

An over-time increase in the overall IR of PSCC was identified from 1997 to 2016. Such a growing trend of IR may be attributed to an increasing rate of HPV infection which was widely recognized as a risk factor of PSCC development, as well as a lower rate of neonatal circumcision (17-20). Neonatal circumcision was negatively associated with the risk of PSCC, since it may reduce the risk of HIV and HPV infection and chronic inflammation by eliminating dirt (10). For those without a previous primary malignancy, the IR experienced a decline before 1987, while for those with a previous primary malignancy, the IR has been increasing since 1975. Therefore, difference in incidence may be attributed to the history of malignant tumors, which may transfer to the penis or make the body in a low immune status, thus promoting this upward trend. Moreover, we found that the IRs in black individuals were the highest, which may because of the early exposure to HPV through sexual contact (4,8,21). Furthermore, our

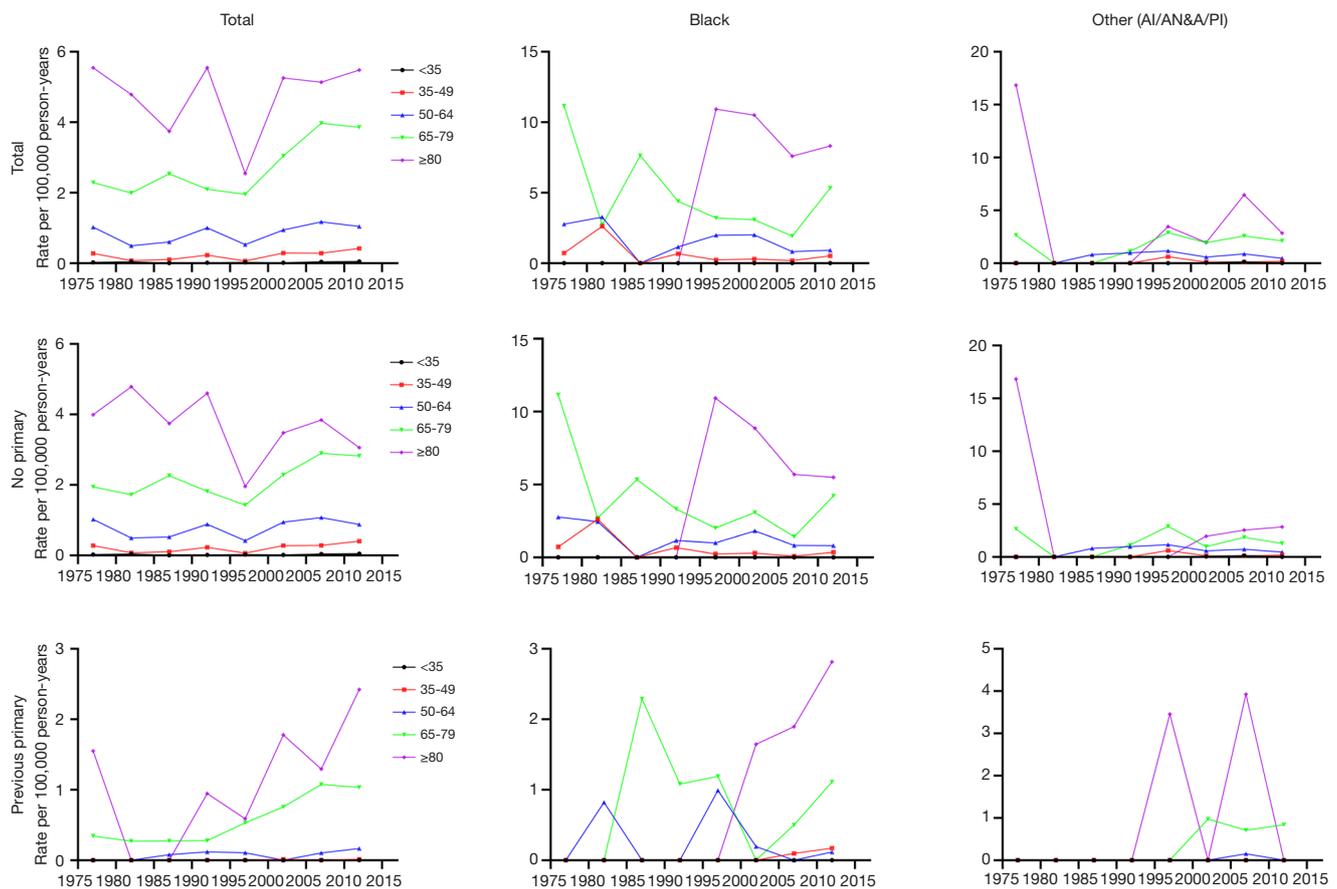


Figure 3 Incidence rates trends of penile squamous cell carcinoma in men by age from 1975 to 2016.

results revealed that the IRs increased along with age, and in people younger than 50 years old, the IRs tended to be zero. Ertoy Baydar *et al.* reported that the average age of PSCC diagnosis was 66.5 years (51–83 years) in their study (22). This age stratification suggested that older patients, especially those older than 50, were at a higher risk of developing PSCC.

In our study, age at diagnosis, pathological grade, extent of disease, marital status, the administration of surgery and presence of previous primary malignancy were identified to be independent prognostic factors for CSS in PSCC patients. Previous studies have reported that age, tumor stage, extent of disease and the administration of surgery were significantly associated with tumor prognosis in many cancer types (23,24). To our knowledge, those patients who were older, poorly differentiated, metastatic, and not surgically resected were bound to have a poor prognosis. Additionally, Ulf-Møller *et al.* found that unmarried men were at increased risk of developing invasive penile

cancer compared to married men (25). In many Western countries, it has been increasingly common for couples to have unregistered partnerships like marriage. It may be biased to use marital status to evaluate prognosis, since marital status may not directly reflect the number of sexual partners. Furthermore, we found that patients with a history of previous malignancies tended to have a poor prognosis. Firstly, those with a prior primary cancer were more likely to be older, diagnosed in the last decade and had worse differentiation. Additionally, patients with previous malignancies were in worse physical condition and psychological health, which were tightly associated with worse prognosis.

The main advantage of our study was the use of large population-based datasets. However, our research still had some limitations. First of all, numerous large-scale population-based studies have been shown to own inherent limitations, including the risk of data loss and patient classification errors. Sanders *et al.* (26) discussed these

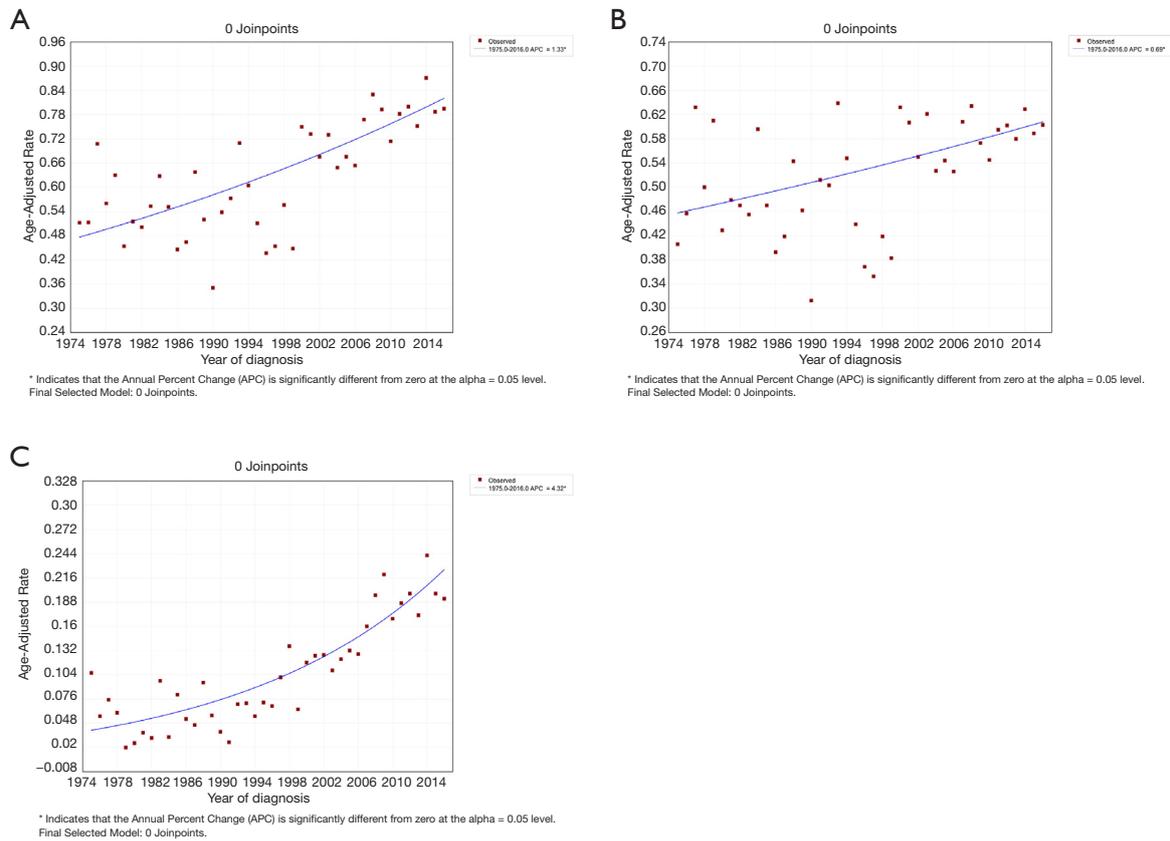


Figure 4 Annual percentage change curves for different populations: the general population (A), people without a primary malignancy (B), people with a primary malignancy (C).

Table 5 Multivariate analysis adjusting for factors affecting the cancer-specific survival

Variable	Multivariate analysis		
	HR	95% CI	P value
Primary cancer			0.000
No primary		Ref	
Previous primary	0.518	0.428–0.628	0.000
Age at diagnosis			0.000
<35		Ref	
35–49	1.059	0.661–1.698	0.810
50–64	1.105	0.701–1.742	0.668
65–79	1.260	0.800–1.987	0.319
≥80	3.253	1.282–3.253	0.003
Race			0.125
White		Ref	

Table 5 (Continued)

Table 5 (Continued)

Variable	Multivariate analysis		
	HR	95% CI	P value
Black	1.034	0.871–1.228	0.701
Other (AI/AN, A/PI)	0.827	0.625–1.095	0.185
Unknown	0.142	0.020–1.017	0.052
Decade of diagnosis			0.050
1975–1984		Ref	
1985–1994	0.929	0.725–1.190	0.560
1995–2004	1.132	0.878–1.458	0.338
2005–2016	1.275	0.985–1.650	0.065
Tumor site			0.072
Prepuce		Ref	
Glans penis	1.006	0.821–1.234	0.951
Body of penis	1.137	0.836–1.544	0.413
Overlapping lesion of penis	1.463	1.078–1.986	0.015
Penis, NOS	1.070	0.878–1.305	0.501
Pathological grade			0.000
Grade I		Ref	
Grade II	2.015	1.704–2.383	0.000
Grade III	2.316	1.923–2.788	0.000
Grade IV	4.130	2.425–7.034	0.000
Unknown	1.063	0.855–1.321	0.583
Extent of disease			0.000
Localized		Ref	
Regional	2.524	2.213–2.879	0.000
Distant	10.964	9.191–13.080	0.000
Unstaged	2.254	1.711–2.970	0.000
Marital status			0.001
Married		Ref	
Previously married	1.216	1.055–1.403	0.007
Never married	1.296	1.110–1.513	0.001
Unknown	0.942	0.736–1.207	0.637
Surgery			0.000
No/Unknown		Ref	
Yes	0.551	0.464–0.655	0.000

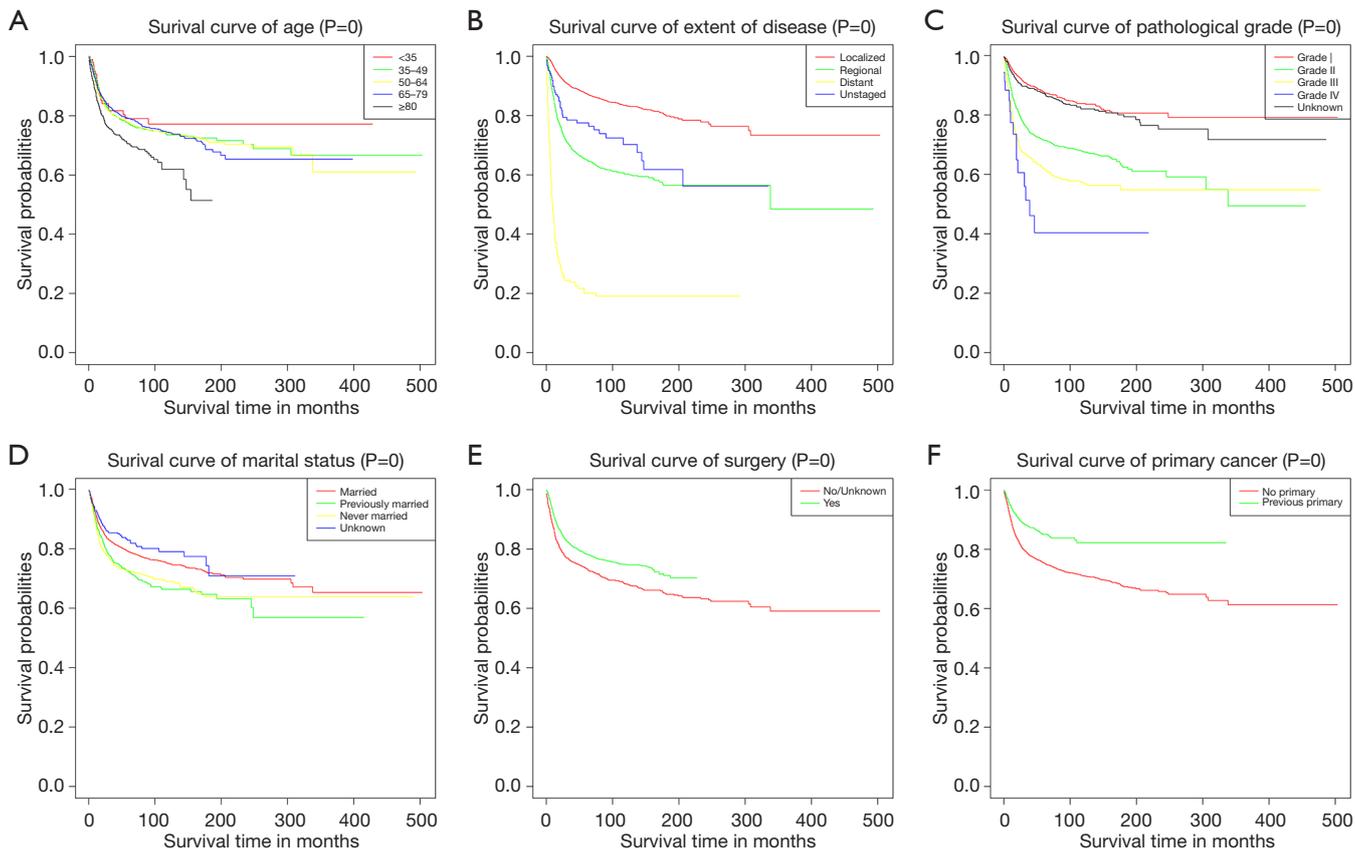


Figure 5 Kaplan-Meier curves of cancer-specific survival stratified by age (A), extent of disease (B), pathological grade (C), marital status (D), use of surgery (E) and presence of a previous primary malignancy (F).

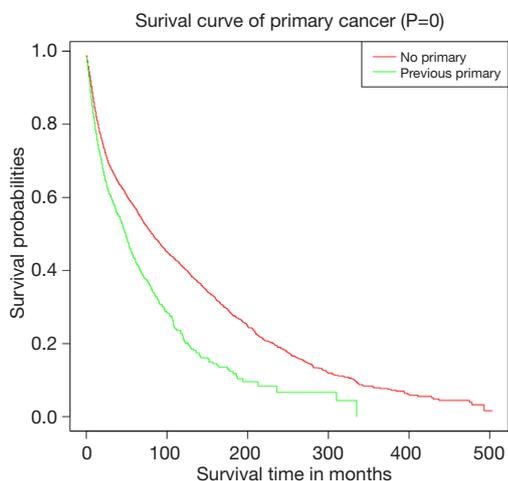


Figure 6 Kaplan-Meier curves of overall survival for stratification by presence of a previous primary malignancy.

limitations in more detail in their article. In addition, selection bias may exist because of the retrospective nature. Moreover, there was a deficiency of available data on certain risk factors related to incidence and prognosis in SEER database, such as smoking history, HPV infection status and chemotherapy status, which may affect the comprehensiveness of the conclusions. Hence, further prospective and well-designed studies are needed to validate our results.

In conclusion, our study provided a view of the epidemiological of PSCC in US from 1975 to 2016. The incidence of PSCC has been increasing in recent years. Moreover, several independent prognostic factors for CSS of PSCC patients were identified, allowing surgeons to assess the individualized risk in advance.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was exempt from Institutional Review Board (IRB) approval because the original data were from a public database.

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