Available online at **www.ijmrhs.com**

ISSN No: 2319-5886

International Journal of Medical Research & Health Sciences, 2018, 7(11): 19-25

Risk of Developing Second Primary Prostatic Cancer in Patients with Previously Treated Prostatic Cancer: A Retrospective Cohort Study

Hassan Mohamed Eweidah*, Heba Hamed Salem, Taher Muhammad Abou-Madawi, Mahitab Ahmed Youssef, Hadeer Adel Saad, Hassan Saied Dabbour, Yomna Abbas Abd El Aziz, Ahmed Mohamed Eweidah, Hossam Galal Hamza and Hazem Abdullah El-Sheikh

Faculty of Medicine, Alexandria University, Alexandria, Egypt

**Corresponding e-mail: H_Awaeda2121066@alexmed.edu.eg*

ABSTRACT

Objective: *The present study aims to investigate the risk of developing second primary prostate cancer after treating initial primary prostate cancer and to determine the role played by different variables including age, race, marital status, etc. regarding this risk.* ***Materials and methods:*** *We have conducted a retrospective cohort study to evaluate the risk of developing second primary prostate cancer. Data needed for this investigation was obtained from surveillance, epidemiology, and end results (SEER). Analysis of the risk of developing SPPC compared to the general population was obtained by measuring the standardized incidence ratios (SIRs).* ***Results:*** *Incidence of initial primary prostate cancer was more evident at 60-69 years of age, 38.84% (59,067) than different age groups. Marital status was found to have a significant impact on the incidence of prostate cancer. Married men (83.78% of the study sample) had a higher incidence of developing IPPC in comparison with single ones (p<0.001). Furthermore, the highest SIR values were noted in patients who were diagnosed with the local stage of prostate cancer in comparison with other stages (O/E 0.01, 95% confidence interval (0.01-0.02).* ***Conclusions:*** *The risk of developing second primary prostate cancer after treating the initial one is increased over time and is found to be the highest in old aged patients (60-69 years), who were diagnosed with initial primary distant stage prostate cancer of adenocarcinoma histologic type.*

Keywords: Prostate, Cancer, Risk, Second, Primary, SEER

INTRODUCTION

As the population of cancer survivors continues to grow (over 14 million in 2014) [1], there is a great need to understand the long-term health of this population. According to American Cancer Society (ACS), prostate cancer (PCa) is the third leading cause of cancer-related death in the U.S. There will be an estimated 164,690 new cases to be diagnosed with PCa in 2018, representing 9.5% of new cancer cases and 4.8% of all cancer deaths [1]. Moreover, approximately 11.2% of men will be diagnosed with PCa at some point during their lifetime [1]. Many risk factors have been established for the increasing incidence of PCa including positive family history, advanced age, and African-American race, however, the exact etiology remains enigmatic. Furthermore, due to recent advances in screening, diagnosis, and management of PCa, more than 10% reduction of its incidence was observed in the last decade [2].

The incidence of second primary malignancy (SPM) was 15.2% at 25 years for all cancers, as reported by the Surveillance, Epidemiology, and End Results data (SEER) [3]. Risk of developing SPM has gained recent attention in the scientific research field, as many factors play a crucial role in its incidence. Genetic susceptibility and exposure to carcinogens are among the causes of SPM, yet the impact of radiotherapy or total prostatectomy on the risk of developing SPM still controversial. Although the life expectancy of prostate cancer patients has significantly increased, survivors are nonetheless at risk of developing a second primary cancer after curative surgery and radiation therapy. Accordingly, there is increasing interest in predicting the risk of developing an SPPC following the IPPC. Nevertheless, data regarding the incidence of SPPC after treating patients with IPPC are limited and identifying them is essential to apply for effective surveillance programs as well as to optimize treatment, and to adopt adequate cancer prevention strategies.

The aim of the present study is to investigate the risk of developing second primary prostate cancer (SPPC) after treatment of an initial primary prostate cancer (IPPC) by utilizing cohort data from SEER database, in addition, to evaluate the impact of different variables such as age at diagnosis, race, histologic subtype, SEER stage.

MATERIALS AND METHODS

Data Sources

Patients were recruited from the Surveillance, Epidemiology, and End Results (SEER) database, which is responsible for collecting cancer incidence and survival data from population-based cancer registries covering approximately 34% of the U.S. population. SEER collects data on patient demographics, primary tumor site, tumor morphology and stage at diagnosis, the first course of treatment, and follow-up for vital status (survival). These data are collected on every cancer case reported from 19 U.S. geographic areas.

Patient Cohorts and Study Parameters

Inclusion criteria in the present study were set to be; all patients who aged 20 years or older, and in whom an initial primary prostate cancer (IPPC) was diagnosed from 1973 to 2015. Demographic data of the identified patients; age, race, marital status, histologic type, and PCa stage were obtained from SEER-18 registry database.

The prostate cancer diagnosis was defined by SEER International Classification of Diseases for Oncology. A latency period of 6 months was considered to differentiate between SPPC from metastasis of the IPPC. Included patients were classified according to their age into 5 categories (20-49 years, 50-59 years, 60-69 years, 70-79 years, and 80 years or older). Patients' race was evaluated in 3 groups; black, white, and other. Marital status at the time of diagnosis was assessed by categorizing the included patients into 3 groups; single, married, and unknown. Patients were classified according to International Classification of Diseases for Oncology histology recodes broad grouping into 4 groups; transitional cell carcinoma (8120-8139), adenocarcinoma (8140-8389), acinar cell neoplasm (8550-8559), and others (8000-8119, 8500-8549, and 8800-8809). Prostate cancer stage was classified into localized, regional, distant, and unstaged, according to SEER staging system [4].

Statistical Analysis

Data analysis was performed using Statistical Package for Social Sciences (SPSS) version 23 for windows. Demographic data of the recruited patients were analyzed by calculating Pearson's chi-square test. Analysis of the risk of developing SPPC compared to the general population was obtained by measuring the standardized incidence ratios (SIRs) and their 95% confidence interval (CI) using SEER stat program for Windows version 8.3.5. SIR is obtained by dividing the number of observed cases by the number of expected one. Meantime at risk for developing SPPC was obtained and analyzed for each patient. The cumulative risk for developing SPPC was calculated using the Kaplan-Meier method. An alpha level less than or equal to 0.05 was taken to indicate the significant statistical difference

RESULTS

Patients Characteristics

We recruited 152,086 patients who were diagnosed with initial primary prostate cancer (IPPC) between 1973 to 2015. Their demographic data are reported in Table 1. The incidence of IPPC was more evident at 60-69 years of age; 38.84% (59,067) than in different age groups. Marital status was found to have a significant impact on the incidence of prostate cancer. Married men (83.78% of the study sample) had a higher incidence of developing IPPC in comparison with single ones ($p<0.001$). Moreover, patients were categorized according to the SEER stage of IPPC into local (53.85%), regional (7.43%), distant (1.74%), unstaged (36.98%). Second primary prostate cancer was developed in 84 (0.06%) of the identified patients (Table 1).

Table 1 Demographic and disease characteristics of patients age 20 years and older with a diagnosis of malignant first primary prostate cancer in the SEER-18 registry from 1973-2015

Characteristic	All Patients		Development of Second Prostate Primary				p-value
			No		Yes		
	n	%	n	%	n	%	
Total	152086		152002		84		

Age at diagnosis (years)							
20-49 years	1441	0.95%	1439	0.95%	2	2.38%	<0.001
50-59 years	18652	12.26%	18636	12.26%	16	19.05%	
60-69 years	59067	38.84%	59029	38.83%	38	25.24%	
70-79 years	57857	38.04%	57834	38.05%	23	27.38%	
≥80 years	15069	9.91%	15064	9.91%	5	5.95%	
Race							
White	127174	83.62%	127104	83.62%	70	83.33%	<0.001
Black	18350	12.07%	18341	12.07%	9	10.71%	
Other	6364	4.18%	6360	4.18%	4	4.76%	
Unknown	198	0.13%	197	0.13%	1	1.19%	
Marital status at diagnosis							
Single	11186	7.36%	11181	7.36%	5	5.95%	<0.001
Married	127415	83.78%	127344	83.78%	71	84.52%	
Unknown	13485	8.87%	13477	8.87%	8	9.52%	
Histologic type							
Transitional cell carcinomas	88	0.06%	86	0.06%	2	2.38%	<0.001
Adenocarcinomas	146299	96.19%	146226	96.2%	73	86.90%	
Acinar cell neoplasms	2021	1.33%	2017	1.33%	4	4.76%	
Other	3678	2.42%	3673	2.42%	5	5.95%	
SEER stage							
Local	81893	53.85%	81871	53.86%	22	26.19%	<0.001
Regional	11307	7.43%	11298	7.43%	9	10.71%	
Distant	2650	1.74%	2644	1.74%	6	7.14%	
Unstaged	56236	36.98%	56189	36.97%	47	55.95%	
Surveillance, Epidemiology, and End Results (SEER)							

SIR Analysis

SIRs were used to analyze the risk of developing SPPC in previously treated IPPC patients in relation to the general population. Highest SIR values were reported in 60-69 years age group (O/E 0.01, 95% confidence interval: (0.01-0.02), with the white race being associated with the highest incidence of SPPC in comparison with other races (Table 2). Furthermore, the highest SIR values were noted in patients who were diagnosed with the local stage of prostate cancer in comparison with other stages (O/E 0.01, 95% confidence interval: (0.01-0.02). The lowest mean time at risk for developing SPPC was noted to be in an older age group; ≥ 80 years, in whom an IPPC was distant (3.87 years).

Table 2 SIR analysis of SPPC in patients with a history of an IPPC by age, race, marital status, histologic type, and SEER stage, 1973-2015, SEER-18 registry

Characteristic	Observed	Expected	O/E	SIR (95% CI)	Time at risk (y) mean
Total	84	6808.80	0.01#	(0.01-0.02)	9.67
Age at diagnosis (years)					
20-49 years	2	29.47	0.04#	(0.00-0.21)	13.01
50-59 years	16	792.04	0.05#	(0.02-0.09)	12.75
60-69 years	38	3170.48	0.01#	(0.01-0.02)	11.16
70-79 years	23	2451.54	0.02#	(0.01-0.03)	8.29
≥80 years	5	365.15	0.04#	(0.01-0.11)	4.87
Race					
White	70	5682.98	0.01#	(0.01-0.02)	9.85
Black	9	928.30	0.01#	(0.00-0.02)	8.60
Other	4	194.07	0.02#	(0.01-0.05)	9.08
Unknown	1	3.46	0.29	(0.01-1.61)	7.74
Marital status at diagnosis					
Single	5	417.31	0.01#	(0.00-0.03)	8.82
Married	71	5957.23	0.01#	(0.01-0.01)	8.55

Unknown	8	434.03	0.02[#]	(0.01-0.04)	8.34
Histologic type					
Transitional cell carcinomas	2	3.98	0.5	(0.06-1.82)	6.92
Adenocarcinomas	73	6538.34	0.01[#]	(0.01-0.01)	9.70
Acinar cell neoplasms	4	139.49	0.03[#]	(0.01-0.07)	11.04
Other	5	115.40	0.02[#]	(0.00-0.08)	6.71
SEER stage					
Local	22	1941.90	0.01[#]	(0.01-0.02)	8.01
Regional	9	288.47	0.03[#]	(0.01-0.06)	8.48
Distant	6	25.42	0.24[#]	(0.09-0.51)	3.87
Unstaged	47	4,553.01	0.01[#]	(0.01-0.01)	8.80

SIR: Standardized incidence ratio; SPPC: Second primary prostate cancer; IPPC: Initial primary prostate cancer; SEER: Surveillance, Epidemiology, and End Results; CI: Confidence interval; y: year, ([#]) p <0.05

Histologic Type and Staging

Our analysis shows that adenocarcinoma was the most common histological type of IPPC representing 96.19% of all IPPC. Moreover, adenocarcinoma was noted to be associated with the highest incidence of SPPC (86.90% of all SPPC cases). In correlation with IPPC histologic types, adenocarcinoma was associated with the incidence of 53.57% of all SPPC histologic types, followed by TCC (11.90%) and others (26.19%) (Table 3).

Table 3 Distribution of SPPC histologic type by IPPC histologic type in patients with a history of an IPPC

IPPC Histologic Type	SPPC Histologic Type								
	TCC		Adenocarcinomas		ACN		Other		Total
	N	%	N	%	N	%	N	%	
TCC	1	0.5000%	0	0.0000%	0	0.000%	1	0.5000%	2
Adenocarcinomas	8	10.9600%	43	0.5890%	5	0.0685%	17	0.2329%	73
ACN	0	0.0000%	1	0.2500%	2	0.5000%	1	0.2500%	4
Other	1	0.2000%	1	0.2000%	0	0.0000%	3	0.6000%	5
Total	10	0.1190%	45	0.5357%	7	0.0833%	22	0.2619%	84

SPPC: Second primary prostate cancer; IPPC: Initial primary prostate cancer; TCC: Transitional cell carcinoma; ACN: Acinar cell neoplasm

Most SPPC patients (26.19%) had initially a localized IPPC, whereas only 10.71% had distant SPPC. The majority of SPPC patients presented with a local stage prostate cancer; 50% (42 cases), and only 10.71% were reported to have a distant stage (Table 4).

Table 4 Distribution of SPPC SEER stage by IPPC SEER stage in patients with a history of an IPPC

IPPC Histologic Type	SPPC SEER Stage								
	Localized		Regional		Distant		Unstaged		Total
	N	%	N	%	N	%	N	%	
Local	13	0.5909%	8	0.3636%	0	0.0000%	1	0.0455%	22
Regional	5	0.5556%	2	0.2222%	1	0.1111%	1	0.1111%	9
Distant	2	0.3333%	1	0.1667%	1	0.1667%	1	0.1667%	6
Unstaged	22	0.4681%	14	0.2979%	7	0.1489%	4	0.0851%	47
Total	42	0.5000%	25	0.2976%	9	0.1071%	8	0.0952%	84

SPPC: Second primary prostate cancer; SEER: Surveillance, Epidemiology, and End Results; IPPC: Initial primary prostate cancer

Cumulative Risk for Developing SPPC

Cumulative risk for developing SPPC was calculated by using the Kaplan-Meier Method. The risk was found to increase over time in patients with IPPC. In addition, adenocarcinoma was found to have the highest risk for developing SPPC in comparison with other histologic types (Figure 1). Furthermore, PCa patients in whom a localized prostate cancer was diagnosed were found to have a higher risk of developing SPPC in comparison with regional or distant stage (Figure 2).

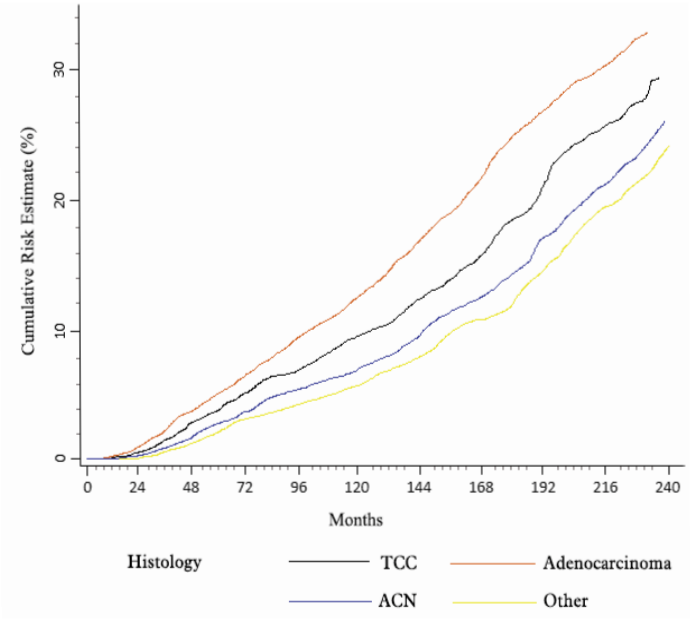

Figure 1 Cumulative risk for developing second primary prostate cancer stratified by histologic type; TCC: Transitional cell carcinoma; ACN: Acinar cell neoplasm

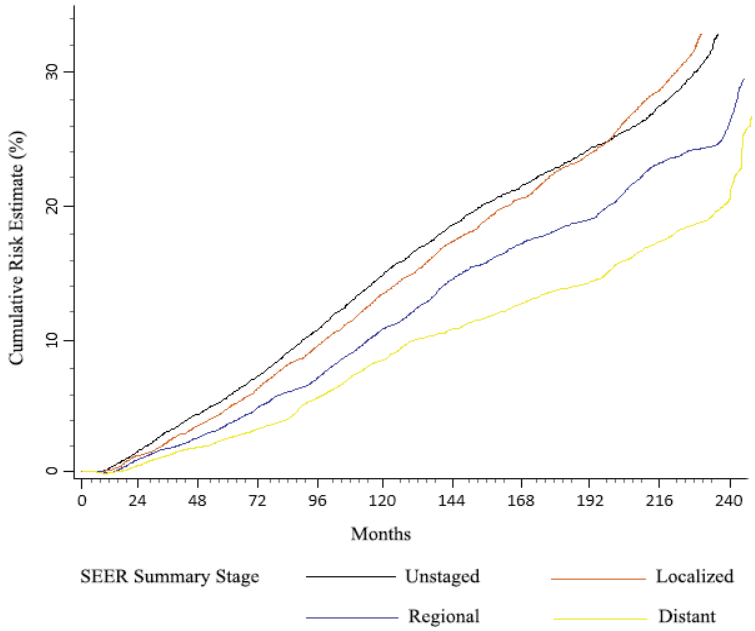

Figure 2 Cumulative risk for developing second primary prostate cancer stratified by SEER stage

DISCUSSION

The present study shows that prostate cancer patients are slightly at a higher risk than the general population in developing second primary prostate cancer (SPPC) after treating the initial one. As we recruited prostate cancer patients from the SEER database we found that the incidence of SPPC is about 0.06% in all identified patients, which is consistent with the previous report from Korean Central Cancer Registry (KCCR) [5]. Furthermore, we assessed many variables that could influence this incidence and play a key role in developing SPPC. Regarding them, we have evaluated age, race, marital status, histologic type, and SEER stage.

To properly assess the impact of these factors on the development of SPPC, we have calculated SIR for each patient

group, and we found that the highest SIR values were reported in 60-69 age group (O/E 0.01, 95% confidence interval: (0.01-0.02). Like any other cancer, a genetic mutation that accumulates over time increases the incidence of prostate cancer and the drop in the incidence in the oldest age group (≥ 80 years) often indicates reduced diagnostic activity due to general ill health. The age distribution of prostate cancer cases probably partly reflects the age groups in which prostate-specific antigen (PSA) testing and transurethral resection of the prostate (TURP) are carried out. In agreement with previous reports white race was found to have the highest incidence of prostate cancer in comparison with other races ($p<0.001$) and it comprised 83.33% of all cases identified with SPPC [6]. Moreover, the present study showed that married men comprised 84.52% of the cohort, while single men diagnosed with SPPC were found to represent 5.95% of all recruited patients. Tyson, et al., concluded that unmarried men have a higher risk of prostate cancer-specific mortality compared to married men of similar age, race, stage, and tumor grade [6]. However, a multivariant analysis is needed to determine the role played by marital status in regard to the development of prostate cancer.

Our analysis showed that the cumulative risk for developing SPPC increased over time and was higher in patients diagnosed with distant stage PCa and in whom IPPC histologic type was adenocarcinoma. A suggestive explanation of these findings is that distant PCa patients are more likely to have many risk factors such as old age, generalized unwell state, more prone to metastasis, etc. that do not only increase the risk of secondary metastatic cancers but also increases the incidence of second primary cancers.

Adenocarcinomas were found to be the most common histologic type in both IPPC and SPPC patients. We have analyzed the association between different histologic types of the initial and the second primary prostate cancer and found that the occurrence of SPPC of the identical histologic type to the IPPC was about 50% for all different histologic types. This finding outlines the misdiagnosis that could result from failure to distinguish the SPPC from the metastatic one when both SPPC and IPPC have the same histologic type, which could in return affect the treatment strategies and the management of SPPC patients. However, using a latency period during the analysis of prostate cancer patient's data or utilizing molecular genetic methods from the clinical aspect might be of great benefit to resolve this issue. Nevertheless, our analysis showed that SPPC is not necessarily been identical to the initial one.

In general, many co-variants might play a role in the occurrence of SPPC especially smoking, sexually transmitted diseases and chemical exposure which are well-known to have a strong association with the incidence of prostate cancer [7]. Unfortunately, we were unable to evaluate the effects of previously mentioned factors as we could not catch this information from the SEER database, which might be considered as a limitation of the present study.

CONCLUSION

The risk of developing SPPC in IPPC patients is increased over time. This risk was found to be the highest in patients who aged 60-69 years and in those who have been diagnosed with distant stage prostate cancer of adenocarcinoma type. This should attract our attention to implicate future survey programs and to establish newer treatment strategies in patients with higher risk of developing SPPC.

DECLARATIONS

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

REFERENCES

[1] American Cancer Society. Cancer Facts and Figures 2018. Atlanta, Ga: American Cancer Society; 2018.

[2] Siegel, Rebecca L., Kimberly D. Miller, and Ahmedin Jemal. "Cancer statistics, 2017." *CA: A Cancer Journal for Clinicians,* Vol. 67, No. 1, 2017, pp. 7-30.

[3] Ries, Lynn AG, et al. "SEER cancer statistics review, 1975-2003." 2006.

[4] Adamo, M. B., et al. "SEER program coding and staging manual." Bethesda, MD: National Cancer Institute (2010).

[5] Joung, Jae Young, et al. "Risk of second primary cancer among prostate cancer patients in Korea: a population-based cohort study." *PloS One,* Vol. 10, No. 10, 2015.

[6] Tyson, Mark D., et al. "Marital status and prostate cancer outcomes." *The Canadian Journal of Urology,* Vol. 20, No. 2, 2013, pp. 6702-06.

[7] Sadeghi-Gandomani, H., et al. "The incidence, risk factors, and knowledge about the prostate cancer through worldwide and Iran." *World Cancer Research Journal,* Vol. 4, No. 4, 2017, pp. 1-8.