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Comprehensive analysis of prostate cancer life expectancy, loss of life expectancy, and healthcare expenditures: Taiwan national cohort study spanning 2008 to 2019

Prostate cancer life expectancy, loss of life expectancy, and healthcare expenditures in Taiwan

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Abstract

Prostate cancer (PCa) is the second most commonly diagnosed cancer worldwide and the 5th leading cause of death from cancer for men in Taiwan. The incidence of synchronous metastatic PCa in Taiwan is higher than U.S. and Europe. We aim to present the latest life expectancy (LE), loss of LE, and lifetime cost associated with PCa in Taiwan. The PCa data are based on Taiwan Cancer Registry and National Health Insurance Database. Total 30,207 new cases of PCa were recorded during 2008-2019 nationwide. LE, estimated loss of LE and lifetime cost were stratified by age, cancer stage, Gleason score, grade group and serum PSA level at diagnosis. We compared LE and healthcare cost outcomes between synchronous metastatic PCa patients in 3 age groups. Among the 30,207 new cases, the low to intermediate risk groups, high-risk groups, and regional and metastatic PCa accounted for 54.1%, 13.2%, and 32.6% of cases, respectively. A considerable proportion of synchronous metastatic PCa was noted in Taiwan when compared with the U.S. For synchronous metastatic PCa, the highest LE is 9.22 years for ages 20-64 years, followed by ages 65-74 (8.29 years) and ages 75-89 years (4.58 years). The loss of LE in the three groups is 13.63, 6.75, and 3.87 years, respectively. The healthcare cost of synchronous metastatic PCa in all age groups is higher than the average cost for PCa patients in Taiwan. This study provides real-world evidence to

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support health care policy-making and clinical decisions regarding PCa. Due to the high proportion of synchronous metastatic PCa in Taiwan, the findings of this analysis emphasize the importance of early detection of PCa, which can save LE and decrease the total cost burden on the healthcare system.

Introductions

Prostate cancer (PCa) was the cancer with the highest incidence for men in 114 countries and the leading cause of cancer-related deaths among men in 56 countries in 2017 [1]. It accounted for 191,930 new cases and 33,330 deaths among U.S. males in 2020. From 2012 to 2017, the incidence of PCa in the United States was 104.1 per 100,000 people, with a mortality rate of 19.1 per 100,000 people [2]. In Taiwan, PCa was responsible for the fifth cancer cause of death among male based on the statistics of cause of death in 2019 announced by the ministry of health and warfare. The estimated crude death rate caused by PCa is 13.1 per 100,000 persons [3]. Statistics indicate a progressive increase in the incidence rate of PCa in Taiwan. Overall, the age-standardized incidence of PCa between 2008 and 2019 increased by 11.22% (from 24.61 to 35.83 per 100,000 people). The accurate reason could be complicated and multifactorial; proposed explanations include an aging population, the

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71 popularization of blood tests, westernized diets, and lifestyle alterations. A previous study
72 revealed a wide variation in the incidence and mortality rates of PCa in Asians. Compared
73 with other Asian countries, the incidence of PCa in Taiwan is second only to Australia, New
74 Zealand, and Turkey. [4].

75 The treatment of PCa imposed a great impact on both individuals and the country's financial
76 burden. Gustavsen, Gary et al. indicated that the cumulative cost of managing localized PCa
77 on a per-patient was estimated to be USD $46,193 over 5 years and USD $110,993 over 10
78 years [5]. Smith-Palmer, J et al. mentioned that total overall cost in the first year after
79 diagnosis of PCa was EUR 385 million in France, followed by EUR 244 million in Germany
80 and then the United Kingdom at EUR 117 million per year in 2006 [6]. PCa also causes a
81 great number of deaths worldwide annually. A study by Withrow, Diana et al. mentioned that
82 3.5 million person-years of life were lost due to PCa in males over 50, with 40% of years of
83 life lost occurring in those aged over 75 [7].

84 However, most of the previous studies are based on materials and documents from Western
85 countries. Hwang et al. developed a novel semiparametric method to improve the accuracy of
86 estimates of life expectancy (LE) and loss of life expectancy (loss of LE) from the date of
87 diagnosis [8-9]. In this study, we estimated the PCa patients LE, loss of LE and lifetime
88 health care expenditures, stratified by age and stage in the Taiwanese population with up to
89 12 years of follow-up.

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Materials and Methods

We identified a study cohort by using the database of Taiwan Cancer Registry (TCR) database from 2011 to 2017, and patients with PCa were identified by ICD-O-3 topography code: C61.9. Patients who were younger than 20 years of age or older than 90 years of age were excluded. TCR provides complete and high quality information on cancer medical records in Taiwan [10]. The data in the database has been de-identified, making it impossible to identify the subjects. Our study used data from TCR including gender, date of diagnosis, age at diagnosis, PCa stage, prostatic specific antigen (PSA), and Gleason's score. PSA value was divided into five levels: <4, 4-9, 10-19, 20-50 and >50 ng/ml. Gleason's score also was divided into five levels, ≤6, 3+4, 4+3, 8 and 9-10. Gleason's score 3+4 indicates the primary pattern was 3 and the secondary pattern was 4. In contrast, 4+3 means the primary pattern was 4 and the secondary pattern was 3.

The survival status of patients was verified by linkage with the National Mortality Registry. All patients were followed until the end date of follow-up, the date of death or December 31, 2019, whichever came first. Survival function was generated via the Kaplan-Meier method until the end of follow-up. LE was estimated by a semiparametric survival extrapolation

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method, which was proposed by Hwang and Wang [8-9]. This method has been applied to various diseases such as rheumatoid Arthritis [11], dialysis [12-13], schizophrenia [14] and cancer [15]. Based on the life table of the National Vital Statistics of Taiwan, a reference group matching the age, sex and calendar year of PCa patients was generated by the Monte Carlo method. Assuming that the survival rate of the reference group was better than patients, the survival ratio between the patients and the reference group was logit-transformed each month. The survival rate of patients for the next month could be predicted by fitting restricted cubic spline models. Further extrapolation of survival rate was predicted by using a rolling extrapolation algorithm. Assuming the survival prediction for the next month was true and ignoring the data of the first month used in the previous prediction, do the prediction again until the survival rate approaches zero. The area under the survival curve of patients was defined as LE. Besides, the difference of LE between the patients and the reference group represents loss of LE. Loss of LE could be used as a measure of life loss because of disease.

The health care expenditures of each patient were confirmed by linkage with the national health insurance reimbursement database. The monthly average cost was calculated by adding the monthly costs of all patients, including the costs of inpatient and outpatient, and dividing by the number of these patients who were still alive in each month. Assuming that the patient's health care expenditures increase in the months before death, the average cost function is estimated by weighting the average cost of the patient's months before death.

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Lifetime cost can be calculated via the monthly average cost function multiplied by the monthly survival function. Annual national health insurance expenditures were adjusted based on the 2019 Consumer Price Index and the exchange rate (1 USD = 30.93 TWDs), and then the estimated costs were adjusted at the annual discount rate (3%). The estimates of LE and lifetime costs were calculated by the free R package iSQoL2, and the study was reviewed and approved by the institutional review board of Tungs' Taichung MetroHarbor Hospital (IRB number:110034). The need for participant informed consent was waived by the ethics committee.

Results

A total of 30,207 patients with PCa were included in the study. Table 1 summarized the estimated LE, loss of LE, lifetime cost and mean cost per year stratified by age and stage. Survival curves of stages 1 to 3 were similar or even better than the matched reference group, which violated the assumption of LE estimation method that the survival rate of the patients should be worse than the reference group. Therefore, the LE and lifetime cost of those groups could not be estimated. In stage 4, the loss of LE for the 20-64 age groups was the highest at 13.63 years, while the loss of LE for the 75-89 age groups was the lowest at 3.87 years. As for

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the lifetime cost, the 20-64 age group is the highest, with 84,089 US dollars, while the 75-89 age group is the lowest, with 35,841 US dollars. The results were similar in the mean cost per year, with $9,893 for the 20-64 age group and $4,573 for the 75-89 age groups.

Table 1. Estimation of life expectancy, loss of life expectancy, lifetimes cost (USD) and means cost per year for prostate cancer, stratified by age and stage.

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Age group	Stage	N	No. of death	Age*	LE (SE) #	Loss of LE (SE)	Lifetime cost (SE)	Cost per year
20-64								
	Stage 1	1,016	39 (3.84%)	60.5± 4.03	-	-	-	-
	Stage 2	2,733	137 (5.01%)	60.34 ±3.97	-	-	-	-
	Stage 3	718	53 (7.38%)	60.54 ±3.91	-	-	-	-
	Stage 4	1,652	732 (44.31%)	59.95 ±4.2	9.22 (1.36)	13.63 (1.36)	84,089 (5,957)	9,893
65-74								
	Stage 1	1,413	139 (9.84%)	69.92 ±2.83	-	-	-	-
	Stage 2	5,057	631 (12.48%)	70.2± 2.9	-	-	-	-
	Stage 3	1,594	210 (13.17%)	70.42 ±2.79	-	-	-	-
	Stage 4	3,173	1,445 (45.54%)	70.44 ±2.9	8.29 (0.48)	6.75 (0.48)	68,109 (2,825)	8,690
75-89								
	Stage 1	1,053	335 (31.81%)	80.38 ±3.88	-	-	-	-
	Stage 2	5,093	1,742 (34.20%)	80.57 ±3.81	-	-	-	-
	Stage 3	1,681	606 (36.05%)	80.51 ±3.79	-	-	-	-
	Stage 4	5,024	3,268 (6505%)	81.48 ±3.96	4.58 (0.14)	3.87 (0.14)	35,841 (918)	4,573

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163 *Age presented as mean±standard deviation; #SE, standard error of the mean; LE, Life

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164 expectancy, in year; loss of LE, loss of life expectancy

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168 In Table 2, the patients were stratified by age and PSA value. The survival rate of level 4-9

169 and 10-19 ng/ml were similar or even better than the reference group so LE can't be

170 estimated, either. However, the group of <4 ng/ml has worse survival than the reference

171 group. We reviewed the medical history of those patients and the result showed that a higher

172 proportion of transurethral resection of prostate (TURP) was performed one year before

173 cancer diagnosis in this group (S1 Fig). The PSA value usually decreased after TURP [16], so

174 we think the PSA level can't represent the actual value in <4 level group. In other groups of

175 20-50 and >50 ng/ml, regardless of age group, the higher the PSA value, the lower of LE, the

176 greater loss of LE, and higher mean cost per year.

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182 Table 2. Estimation of life expectancy, loss of life expectancy, lifetimes cost (USD) and

183 means cost per year for prostate cancer, stratified by age and prostatic specific antigen (PSA).

Age group	PSA (ng/dL)	N	No. of death	Age*	LE (SE) #	Loss of LE (SE)	Lifetime cost (SE)	Cost per year
20-64								
	< 4	686	115 (16.76%)	60.38 ±3.78	18.55 (2.16)	4.03 (2.16)	66,098 (5,272)	4,139
	4-9	1,899	66 (3.49%)	59.98 ±4.00	-	-	-	-
	10-19	1,309	89 (6.8%)	60.38 ±3.84	-	-	-	-
	20-50	881	113 (12.83%)	60.59 ±3.79	17.85 (3.02)	4.49 (3.03)	82,336 (6,781)	5,250
	>50	1,435	575 (40.07%)	60.18 ±4.03	9.16 (1.34)	13.51 (1.36)	82,887 (6,638)	9,648
65-74								
	< 4	1,280	301 (23.52%)	70.29 ±2.85	12.86 (1.06)	2.31 (1.05)	56,599 (3,215)	4,771
	4-9	2,735	244 (8.92%)	69.92 ±2.87	-	-	-	-
	10-19	2,384	261 (10.95%)	70.10 ±2.94	-	-	-	-
	20-50	1,909	342 (17.92%)	70.50 ±2.83	13.38 (1.29)	1.68 (1.29)	70,688 (4,082)	5,684
	>50	2,907	1,205 (41.45%)	70.49 ±2.87	8.87 (0.57)	6.18 (0.57)	69,031 (2,967)	8,237
75-89								
	< 4	1,500	661 (44.07%)	81.26 ±4.07	7.18 (0.37)	1.47 (0.38)	32,892 (1,207)	4,709
	4-9	1,700	479 (28.18%)	79.93 ±3.71	-	-	-	-
	10-19	2,214	697 (31.48%)	80.28 ±3.73	-	-	-	-
	20-50	2,395	964 (40.25%)	80.75 ±3.81	7.53 (0.34)	1.33 (0.34)	43,763 (1,624)	5,938
	>50	4,808	2,918 (60.69%)	81.45 ±3.95	4.74 (0.16)	3.78 (0.16)	36,005 (833)	7,657

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185 *Age presented as mean±standard deviation; #SE, standard error of the mean; LE, Life

186 expectancy, in year; loss of LE, loss of life expectancy

187

188 Table 3 outlined the estimated LE, loss of LE, lifetime cost and mean cost per year stratified

189 by age and Gleason's Score. The groups of Gleason's Score ≤6 and 3+4 could not estimate

190 their LE and lifetime cost also because of similar or even better survival. Regardless of age

191 group, the group of Gleason's Score 9-10 had the greatest loss of LE. The highest lifetime

192 cost was the group of Gleason's Score 8. However, the highest mean cost was the group of

193 Gleason's Score 9-10.

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199 Table 3. Estimation of life expectancy, loss of life expectancy, lifetimes cost (USD) and

200 means cost per year for prostate cancer, stratified by age and Gleason's score.

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Age group	Gleason's score	N	No. of death	Age*	LE (SE) #	Loss of LE (SE)	Lifetime cost (SE)	Cost per year
20-64								
	≤ 6	2,118	102 (4.82%)	60.25 ±3.87				
	3+4	999	63 (6.31%)	60.26 ±3.94				
	4+3	816	96 (11.76%)	60.25 ±3.92	16.91 (3.4)	5.75 (3.42)	77,071 (7,569)	5,068
	8	827	143 (17.29%)	60.3± 3.82	16.75 (2.15)	5.84 (2.15)	91,875 (6,472)	6,234
	9-10	1,151	454 (39.44%)	60.24 ±4.03	10.1 (1.48)	12.52 (1.47)	79,800 (6,667)	8,565
65-74								
	≤ 6	3,346	348 (10.4%)	70.04 ±2.89				
	3+4	1,849	250 (13.52%)	70.19 ±2.88	-	-	-	-
	4+3	1,700	294 (17.29%)	70.39 ±2.87	13.3 (1.56)	1.8 (1.56)	66,139 (4,099)	5,335
	8	1,602	374 (23.35%)	70.3± 2.83	11.63 (1.35)	3.51 (1.35)	73,643 (4,930)	6,748
	9-10	2,316	902 (38.95%)	70.48 ±2.9	10.01 (0.82)	5.03 (0.83)	70,173 (3,750)	7,548
75-89								
	≤ 6	2,693	818 (30.38%)	80.32 ±3.81				
	3+4	1,734	615 (35.47%)	80.39 ±3.74	-	-	-	-
	4+3	1,997	805 (40.31%)	80.67 ±3.8	7.23 (0.47)	1.69 (0.47)	42,540 (1,857)	5,984
	8	2,045	912 (44.6%)	80.98 ±3.96	7.2 (0.35)	1.56 (0.36)	43,089 (1,802)	6,152
	9-10	3,468	2,085 (60.12%)	81.43 ±3.92	5.2 (0.22)	3.32 (0.22)	38,175 (1,159)	7,483

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202 *Age presented as mean±standard deviation; #SE, standard error of the mean; LE, Life

203 expectancy, in year; loss of LE, loss of life expectancy

204

205

206 Discussion

207

208 This study estimated the LE, loss of LE, and lifetime health care costs of PCa. LE was

209 estimated by a semiparametric survival extrapolation method, which was proposed by Hwang

210 and Wang [9-10]. This method has been applied to various diseases such as rheumatoid

211 arthritis [11], dialysis [12-13], schizophrenia [14] and cancer. It is the first time it has been

212 used to analyze the LE of PCa. The LE (shown in Table 1) of stages 1 to 3 PCa were similar

213 or even better than the matched reference group. The same result can be observed when LE,

214 loss of LE and lifetime healthcare costs has been stratified by age and PSA or age and

215 Gleason's score (shown in Table 2, 3). There are some possible explanations. First, the early

216 stage PCa has a good prognosis under the care of Taiwan's national health system. The

217 majority of the treatment can be subsidized by the national health system. Early-stage PCa

218 does not affect a patient's average LE. There is no significant difference in the statistics of LE

219 between stages 1-3 of PCa, whether in the 20-64 year old group or the 75-89 year old group.

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Second, being diagnosed with cancer raises awareness of a patient's own health. Patients become more conscious of their health after being diagnosed with PCa. They also come to the hospital more often for follow-up of PCa, and if they have other health problems, they will be found earlier.

Our study also revealed another characteristic of PCa in Taiwan: a high proportion of synchronous metastatic PCa across all three age stratification. Synchronous metastatic PCa accounts for 27% in age group 20-64, 28.2% in age group 65-74, and 39% in age group over 75, respectively. Among all newly diagnosed PCa patients, Taiwan exhibits a considerably high rate of synchronous metastatic PCa when compared to the United States. (32% vs. 5%). [18] Based on the data presented, it's evident that a significant number of Taiwanese PCa patients receive late-stage diagnoses. Early detection of PCa has the potential to substantially decrease the incidence of synchronous metastatic PCa in Taiwan.

Health care expenditures are crucial for shaping national health policy and allocating public health resources within a finite budget. Early detection of PCa through PSA screening and digital rectal examination may allow for early disease stratification, thereby improving disease prognosis and enabling treatment before disease progression. Our data (Table 1) support this point of view: there is no significant difference in the statistics of LE, loss of LE, and lifetime health care costs between stages 1-3 of PCa. In end-stage PCa, it causes a loss of LE by 13.63, 6.75, and 3.87 years in the 20-64, 65-74, and 75-89 age groups, respectively.

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The lifetime cost of end-stage PCa is $84,089, $68,109 and $35,841 in the 20-64, 65-74, and 75-89 age groups, respectively. In Table 2, the annual cost for PCa stratification by PSA level can be observed across all three age stratifications ($9,648, $8,237 and $7,657, respectively). Early detection of PCa can save patients from experiencing a loss of LE and reduce the total lifetime cost and national health care expenditures.

PCa is the fifth leading cause of cancer-related deaths in Taiwan. However, routine PSA screening is not standard in Taiwan. There remains controversy of PSA screening for PCa within countries. Currently, only the five major cancers in Taiwan, namely colorectal cancer, oral cancer, cervical cancer, lung cancer, and breast cancer, have screening plans subsidized by the government. Taiwan's national health system disapproves of population-wide PSA screening programs for PCa. The lower incidence and mortality rate of PCa in Taiwan compared to those in Europe and the United States is a major reason for this decision. The health-care authority considers population-wide PSA screening to have low cost-effectiveness. Apart from this, the government has ignored the characteristics of PCa in Taiwan: a high proportion of synchronous metastatic PCa compared with other developed countries. On the other hand, unnecessary PSA screening might cause overdiagnosis and overtreatment, doing more harm than benefits to the patients [16]. The Taiwan Urological Association recommends early PSA testing only in male aged more than 50 year-old or male more than 45 year-old with family history of PCa. However, early PCa has few symptoms and

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is often diagnosed as advanced PCa while symptomatic. As a result, many men diagnosed with PCa never know they have the disease unless they undergo an examination. To make matters worse, Taiwan's national health care system does not cover approaches like Magnetic Resonance Imaging and biomarkers, such as the Prostate Health Index, for the diagnosis of PCa.

Taiwan has had a national health insurance system since 1995, covering most of the medical expenses for PCa patients. This coverage extends from treatment modalities of radical prostatectomy, internal or external radiation therapy in the localized cancer, to androgen deprivation therapy, second-generation antiandrogens, and chemotherapy in the advanced stage of the disease. However, the nature of social welfare, universal cost coverage of national health insurance also places a heavy economic burden on itself. The increasing incidence and mortality rate of PCa make it a critical public health issue, posing a great economic burden on the national health system. Despite the growing number of therapies and treatments for PCa, it is associated with substantial societal costs and healthcare expenses. These costs are expected to rise with the incorporation of novel and more expensive technologies for managing PCa in the future. Early detection and treatment of PCa can contribute to reducing overall PCa medical costs. This is particularly relevant for the considerable medical costs associated with synchronous metastatic PCa. If the national healthcare system were to initiate strategies such as the introduction of a PSA screening program, it could further decrease

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overall PCa costs and healthcare expenditures. This approach becomes especially crucial in Taiwan, where a high rate of synchronous metastatic PCa has been recorded.

The strength of our study lies in its nationwide cohort and long-term follow-up period. The data were obtained from the TCR database, which provides exhaustive, complete and high quality information on cancer medical records in Taiwan. Although, the limitation is that the study is inherently retrospective. Second of all, the total cost cannot exclude the cost caused by other diseases.

In conclusion, this study provides real-world evidence to support early detection of PCa can save LE and decrease the total cost burden on the healthcare system. The results of this study contribute to better national healthcare resource allocation and policy decisions in PCa treatment. Furthermore, it also raises awareness and public concern about PCa and highlights its impact on the people of Taiwan, both in terms of loss of LE and lifetime cost.

Conclusions

This study provides real-world evidence to support health care policy-making and clinical decisions regarding PCa. Due to the high proportion of synchronous metastatic PCa in Taiwan, the findings of this analysis emphasize the importance of early detection of PCa, which can save LE and decrease the total cost burden on the healthcare system.

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353 Supporting information

354 S1 Figure The proportion of PCa patients who underwent TURP one year before PCa

355 diagnosis.