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Original Research

Mortality associated with statins in men with advanced prostate cancer treated with androgen deprivation therapy

Szu-Yuan Wu [a,b,c], Su-Chen Fang [d], Hung-Jen Shih [e,f], Yu-Chin Wen [e,f], Yu-Hsuan Joni Shao [g,h,i,*]

[a] *Department of Radiation Oncology, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan*
[b] *Department of Internal Medicine, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan*
[c] *Institute of Clinical Science, Zhongshan Hospital, Fudan University, Shanghai, China*
[d] *College of Nursing, Taipei Medical University, Taipei, Taiwan*
[e] *Department of Urology, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan*
[f] *School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan*
[g] *Graduate Institute of Biomedical Informatics, Taipei Medical University, Taipei, Taiwan*
[h] *Department of Epidemiology, Rutgers School of Public Health, Piscataway, NJ, USA*
[i] *Clinical Big Data Research Center, Taipei Medical University Hospital, Taipei, Taiwan*

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Abstract ***Objectives:*** Before launching large clinical trials to confirm the effects of statins in improving outcomes among men with prostate cancer (PC), the most appropriate target patient population and the type of statins need to be clearly identified.
Patients and methods: A retrospective cohort study was conducted using the Taiwan Cancer Registry of 2008–2014. This study included 5749 men with locally advanced and metastatic PC who received only androgen deprivation therapy (ADT) in the first year after their cancer diagnosis. Statin users were defined as anyone who was prescribed statins for >28 days. An inverse probability of treatment-weighted Cox model was used to estimate the effects of statin use on all-cause mortality and PC-specific mortality (PCSM) while treating the statin status as a time-dependent variable.

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* *Corresponding author*: Graduate Institute of Biomedical Informatics, Taipei Medical University, 172-1 Keelung Rd., Section 2, Taipei 106, Taiwan. Fax: +886 2 6638 0233.
E-mail address: jonishao@tmu.edu.tw (Y.-H.J. Shao).

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Results: Overall, 2259 patients died, and 1495 of them died of PC during a median follow-up of 3.6 years from 1 year after their diagnosis. Statin use was associated with significant reductions in all-cause mortality (hazard ratio [HR] = 0.78, 95% confidence interval [CI]: 0.70–0.86) and PCSM (HR = 0.76, 95% CI: 0.68–0.86) for metastatic disease and all-cause mortality (HR = 0.66, 95% CI: 0.54–0.81) for locally advanced disease. Patients who received atorvastatin, pravastatin, rosuvastatin or pitavastatin showed a stronger reduction in mortality than those who received other statins. Benefits of statins were consistently observed in men who received post-diagnostic statins, even in those with high comorbidities or an old age.
Conclusions: Our results suggest that only atorvastatin, pravastatin and rosuvastatin were associated with improved survival in advanced PC patients receiving ADT.

1. Introduction

Androgen deprivation therapy (ADT) is the mainstay treatment for men with advanced or metastatic prostate cancer (PC). However, most patients inevitably progress to castration-resistant PC (CRPC) after a period of time. New agents, including docetaxel, abiraterone and enzalutamide, have been approved to manage patients with CRPC, and these demonstrated good disease control [1–3]. However, newer-generation anti-androgens are expensive, and chemotherapy carries significant risks of toxicity [4,5].

Statin use was found to be associated with delayed disease progression and reduced mortality [6–8]. Despite the mechanism by which statins possibly prevent cancer progression is not yet being completely understood, the beneficial effects associated with statins and their relatively safe profile make them good candidates for additional therapy to standard treatment for PC. Before launching large clinical trials to confirm the effects of statins in improving outcomes among men with PC, studies investigating the most appropriate target patient population and the types of statins should generate important additional evidence for trial design.

Studies examining the clinical utility of statins among men with advanced PC are scarce, because current studies are mostly limited by the number of cases, few events of death or a lack of treatment information. To undertake this task, we used a PC cohort identified in the Taiwan Cancer Registry (TCR) which arose from a non-screened detected population. In 2015, more than 55% of PC cases were diagnosed at clinical stage T3 and above. This population provides a relatively homogenous patient group to examine disease progression following ADT. In this study, we examined the all-cause mortality and PC-specific mortality (PCSM) associated with statin use among men with advanced PC who only received ADT in the first year after their cancer diagnosis. We also examined the risk of mortality associated with different types of statins.

2. Patients and methods

2.1. Study population

We conducted a population-based cohort study using Taiwan National Health Insurance Research Data (NHIRD) linked to the TCR. The TCR was established in 1979 and contains 97% of the cancer cases in Taiwan [9]. The NHIRD includes all medical claims data on disease diagnoses, procedures, drug prescriptions, demographics and enrolment profiles of all beneficiaries [10]. The NHIRD and TCR are linked by encrypted patient identifiers. NHIRD data are additionally linked to the Death Registry to ascertain vital status and the cause of death of each patient.

Our cohort included 28,983 PC patients aged ≥40 years in 2008–2014. Data on patients who were missing their age or the date of diagnosis were excluded. We excluded patients with missing information on the cancer stage (n = 2801), who had had another cancer diagnosis before PC (n = 1934) and those who died within 1 year after the cancer diagnosis as recommended in the literature (n = 1630) [11,12]. We further excluded patients who were diagnosed with T1 or T2 disease (n = 12,089) and those who had received surgery, radiation or local treatment in the first year after their cancer diagnosis (n = 4990). We defined the ADT group as those who received gonadotropin-releasing hormone (Gn-RH) agonists, luteinising hormone-releasing hormone (LHRH) antagonists/agonists or Gn-RH or LHRH combined with anti-androgen. After applying the exclusion criteria, 5749 patients in total who received only ADT in the first year after their cancer diagnosis were included in the analysis.

2.2. Study covariates

We included other covariates to adjust for potential confounding effects. Patients were divided into the following age groups: <65, 65–74 and ≥75 years at diagnosis. Clinical stage was categorised into T3, T4,

N1 and M1 using the American Joint Committee on Cancer classification system [13]. The TCR describes cancer stages as 'well', 'moderately', and 'poorly' differentiated based on respective Gleason scores of 2–6, 7 and 8–10. We also included metabolic-related conditions, including diabetes (ICD-9-CM 250), hypertension (ICD-9-CM 401–405), coronary heart disease (ICD-9-CM 410, 428, 440–449) and stroke (ICD-9-CM 433–436, 453) at the baseline as covariates because these conditions are associated with survival [14]. Charlson comorbidity index (CCI) and individual comorbidities were abstracted from the NHIRD claims during 1 year prior to the PC diagnosis to assess the burden of comorbidities. We also searched for prescriptions of metformin, non-steroidal anti-inflammatory drugs and aspirin during follow-up and claims records of chemotherapy, new-generation anti-androgens, enzalutamide and abiraterone from 365 days after the cancer diagnosis to define secondary treatment in these patients.

2.3. Outcome variables

Our primary outcomes were all-cause mortality and PCSM. The occurrence of all-cause and PC-specific deaths was determined from cause of death data in a death registry from the PC diagnosis to death or the end of the study (December 31, 2015).

2.4. Exposure to statins

We defined statin users as those who received statin prescriptions for more than 28 days between the cancer diagnosis and either death or the end of the study. Prescriptions for statins were coded according to the Anatomical Therapeutic Chemical (ATC) coding system of the NHIRD Pharmaceutical subsidies and were used as an interface for retrieving pharmaceutical claims data. In accordance with the ATC classification system, we selected lipophilic (atorvastatin, fluvastatin, lovastatin, simvastatin and pitavastatin) and hydrophilic (pravastatin and rosuvastatin) statins [15] as the major exposures of interest. Statins initiated 1 year prior to the cancer diagnosis were also abstracted to distinguish current users versus new users. Additionally, we examined the intensity of statin use by continually estimating the average statin dose as the cumulative number of defined daily dose (DDD) divided by the total prescription days. The intensity of statin use was divided into average daily doses below or above one DDD.

2.5. Statistical analysis

We used inverse probability of treatment-weighted (IPTW) [16] Cox regression models to adjust the imbalance in baseline characteristics between statin and non-statin users considering age and baseline comorbidities. A time-dependent Cox hazard model was used to compare overall survival and PC-specific survival of men who did and those who did not receive statins, while adjusting for cancer stage, cancer grade and secondary treatment, such as chemotherapy and next-generation ADT. Data on statin prescriptions were collected every 3 months to define a user's status and were estimated as a time-dependent variable. 'Event-free' person-times of users before their first prescription and during the 3-month period without a statin prescription were classified as unexposed follow-up times to avoid bias. Additionally, we estimated the risk of overall and PC-specific survival by individual statins. The Fine and Gray method was adapted to estimate the hazard of PC-specific survival considering competing risks from other causes of death [17]. Analyses were also performed in subgroups for which we adjusted for baseline characteristics using stratification instead of weighting and post-diagnosis statins which yielded similar results.

All statistical analyses were conducted using SAS, vers. 9.4 (SAS Institute, Cary, NC, USA). This study was reviewed and approved by the Institutional Review Board of Taipei Medical University (TMU-JIRB no. 201502042).

3. Results

From 2008 to 2014, 5749 men in total with PC received only ADT as their primary treatment in the first year. The mean age at cancer diagnosis was 73.3 years, and more than 60% of patients were diagnosed with metastatic disease (Table 1). Overall, 2171 (37.7%) of these patients received statins. Among these statin users, 40.3% of patients received atorvastatin, which was the most prescribed statin, followed by rosuvastatin (22%) and simvastatin (12%).

3.1. All-cause mortality and PCSM

Among these patients, 2259 patients died, and 1495 of them died of PC during the follow-up from 1 year after their diagnosis. Overall, statin users demonstrated lower mortality than non-users. The adjusted hazard ratios (aHRs) were 0.75 (95% confidence interval [CI]: 0.68–0.82) and 0.77 (95% CI: 0.69–0.86) for all-cause mortality and PCSM, respectively (Table 2). In patients with T3/T4 disease, the Cox regression showed that there was a significant reduction in all-cause mortality (aHR: 0.66; 95% CI: 0.54–0.81), but the reduction was not statistically significant in PCSM (aHR: 0.80; 95% CI: 0.58–1.12) (Table 3). In patients with metastatic disease, the multivariate analysis showed significant reductions in both all-cause mortality and PCSM, with respective aHRs of 0.78 (95% CI: 0.70–0.86) and 0.76 (95% CI: 0.68–0.86).

Table 1
Baseline characteristics of the overall cohort and by the statin status.

Characteristic	All		Statin status				*p* value
	N = 5749		Statin users *N* = 2171		Non-statin users *N* = 3578		
	n	%	*n*	%	*n*	%	
Mean age in years (SD)	73.31 (8.82)		73.23 (8.40)		73.36 (9.42)		0.59
Age at diagnosis (years)							0.003
<65	2013	35	818	38	1195	33	
65–74	973	17	341	16	632	18	
≥75	2763	48	1012	47	1751	49	
Clinical stage at diagnosis							<0.0001
N0M0-T3	1684	29	677	31	1007	28	
N0M0-T4	198	3	83	4	115	3	
N1M0	733	13	310	14	423	12	
Any N M1	3134	55	1101	51	2033	57	
Cancer grade							0.2201
Well differentiated	200	3	72	3	128	4	
Moderately differentiated	931	16	378	17	553	15	
Poorly differentiated	4415	77	1650	76	2765	77	
Unknown	203	4	71	3	132	4	
Charlson comorbidity index							<0.0001
0	1980	34	549	25	1431	40	
1	1114	19	510	23	604	17	
2	1392	24	493	23	899	25	
≥3	1263	22	619	29	644	18	
Comorbidity							
Stroke	1520	26	761	35	759	21	<0.0001
Diabetes	2174	38	1209	56	965	44	<0.0001
Hypertension	4279	74	1909	88	2370	66	<0.0001
Coronary heart disease	966	17	515	24	451	13	<0.0001
Secondary treatment							0.0737
Chemotherapy	610	11	202	9	408	11	
Enzalutamide/Abiraterone	32	1	11	1	21	1	
Combination	162	3	58	3	104	3	
None	4945	86	1900	88	3045	85	
NSAIDs	4751	83	1871	86	2880	80	<0.0001
Aspirin	3426	60	1519	70	1907	54	<0.0001
Calendar year							<0.0001
2008	539	9	201	9	338	9	
2009	559	10	226	10	373	10	
2010	815	14	297	14	518	14	
2011	883	15	364	17	519	15	
2012	857	15	337	16	520	15	
2013	933	16	392	18	541	15	
2014	1123	20	354	16	769	21	
Statins							
Lipophilic statins							
Atorvastatin	875	40	875	40			
Lovastatin	136	6	136	6			
Simvastatin	255	12	255	12			
Fluvastatin	196	9	196	9			
Pitavastatin	92	4	92	4			
Hydrophilic statins							
Rosuvastatin	475	22	475	22			
Pravastatin	142	7	142	7			
DDD							
> 1 DDD	1274	59	1274	59			
≤ 1 DDD	897	41	897	41			

NSAIDs, non-steroidal anti-inflammatory drugs; DDD, defined daily dose; SD, standard deviation.

3.2. Risks associated with individual statins

In the multivariate Cox regression model adjusted for cancer stage, cancer grade, secondary treatment, year of the cancer diagnosis and metformin use, we found that men who received atorvastatin, pravastatin, rosuvastatin or pitavastatin demonstrated significant reductions in all-cause mortality and PCSM (Table 4).

Table 2
All-cause and prostate cancer–specific mortality and adjusted hazard ratios (aHRs) associated with statin use among prostate cancer patients who received androgen deprivation therapy as their primary treatment, overall and stratified by cancer stage.

Mortality	No. of deaths	No. of person-years	Mortality rate per 1000 person-years (95% CI)	aHR (95% CI)
Overall				
All-cause mortality				
Statin users	784	9074	86 (80–92)	0.75 (0.68–0.82)
Non-users	1475	13,756	107 (102–113)	Reference
Prostate cancer mortality				
Statin users	499	9074	55 (50–60)	0.77 (0.69–0.86)
Non-users	996	13,756	72 (68–77)	Reference
N0M0 T3+T4				
All-cause mortality				
Statin users	154	3660	42 (36–49)	0.66 (0.54–0.81)
Non-users	271	5149	53 (47–59)	Reference
Prostate cancer mortality				
Statin users	63	3660	17 (13–22)	0.80 (0.58–1.12)
Non-users	95	5149	18 (15–23)	Reference
N1M0 or M1				
All-cause mortality				
Statin users	630	5414	116 (108–126)	0.78 (0.70–0.86)
Non-users	1204	8607	140 (132–148)	Reference
Prostate cancer mortality				
Statin users	436	5414	81(73–88)	0.76 (0.68–0.86)
Non-users	901	8607	105(98–112)	Reference

*The aHR was derived from the inverse probability-weighted Cox model considering statin use as a time-dependent covariate and was adjusted for cancer stage, cancer grade, year of the cancer diagnosis and the use of metformin, non-steroidal anti-inflammatory drugs and aspirin.
CI, confidence interval.

Table 3
All-cause mortality, prostate cancer–specific mortality and adjusted hazard ratios (aHRs) associated by individual statins among advanced prostate cancer patients who received androgen deprivation therapy as their primary treatment.

Mortality	No. of deaths	No. of person-years	Mortality rate per 1000 person-years (95% CI)	aHR (95% CI)
All-cause mortality				
Lipophilic statins				
Atorvastatin	314	3668	86 (77–96)	0.77 (0.67–0.87)
Lovastatin	66	556	119 (93–151)	0.97 (0.76–1.24)
Simvastatin	112	1047	107 (89–129)	0.92 (0.76–1.11)
Fluvastatin	82	818	100 (81–124)	0.84 (0.67–1.06)
Pitavastatin	19	375	51 (32–80)	0.44 (0.28–0.70)
Hydrophilic statins				
Rosuvastatin	149	1983	75 (64–88)	0.64 (0.53–0.75)
Pravastatin	42	627	67 (50–91)	0.56 (0.41–0.77)
Prostate cancer mortality				
Lipophilic statins				
Atorvastatin	190	3668	52 (45–60)	0.74 (0.63–0.88)
Lovastatin	39	556	70 (51–96)	0.88 (0.64–1.21)
Simvastatin	72	1047	69 (55–87)	0.91 (0.72–1.15)
Fluvastatin	57	818	70 (54–90)	0.95 (0.72–1.26)
Pitavastatin	11	375	29 (16–53)	0.44 (0.23–0.82)
Hydrophilic statins				
Rosuvastatin	100	1983	50 (41–61)	0.69 (0.56–0.85)
Pravastatin	30	627	48 (33–68)	0.69 (0.49–0.98)

*The aHR was derived from the inverse probability-weighted Cox model considering statin use as a time-dependent covariate and was adjusted for cancer stage, cancer grade, year of the cancer diagnosis and the use of metformin, non-steroidal anti-inflammatory drugs and aspirin.
CI, confidence interval.

In contrast, no significant improvement in either all-cause or PC-specific death was observed in men who received fluvastatin, lovastatin or simvastatin. In analyses stratified by clinical stage (T3/T4 and N1/M1), we observed a similar pattern in the decreased risk associated with individual statins. However, because of small event numbers in the T3/T4 group, no individual statin reached statistical significance in reducing the risk of PCSM.

3.3. Sensitivity analyses

The sensitivity analysis included patients who initiated statin treatment after the cancer diagnosis and those

Table 4
All-cause mortality, prostate cancer–specific mortality and adjusted hazard ratios (aHRs) associated with individual statins among advanced prostate cancer patients who received androgen deprivation therapy as their primary treatment, stratified by cancer stage.

Cancer stage	T3/T4 $N = 1882$			N1/M1 $N = 3867$		
	No. of deaths	No. of person-years	aHR (95% CI)	No. of deaths	No. of person-years	aHR (95% CI)
All-cause mortality						
Lipophilic statins						
Atorvastatin	63	1538	0.63 (0.48–0.83)	251	2130	0.81 (0.70–0.94)
Lovastatin	18	216	1.39 (0.86–2.25)	48	340	0.88 (0.66–1.17)
Simvastatin	22	425	0.82 (0.53–1.27)	90	622	0.94 (0.76–1.17)
Fluvastatin	16	336	0.69 (0.41–1.19)	66	482	0.88 (0.69–1.14)
Pitavastatin	2	167	0.18 (0.05–0.69)	17	208	0.53 (0.32–0.87)
Hydrophilic statins						
Rosuvastatin	25	743	0.51 (0.34–0.78)	124	1240	0.67 (0.55–0.81)
Pravastatin	8	234	0.49 (0.24–1.01)	34	393	0.59 (0.42–0.83)
Prostate cancer mortality						
Lipophilic statins						
Atorvastatin	72	1538	0.80 (0.51–1.25)	164	2130	0.74 (0.63–0.88)
Lovastatin	2	216	0.46 (0.12–1.80)	37	340	0.94 (0.68–1.31)
Simvastatin	10	425	1.21 (0.65–2.28)	62	622	0.87 (0.68–1.11)
Fluvastatin	7	336	1.06 (0.47–2.41)	50	482	0.94 (0.70–1.26)
Pitavastatin	1	167	0.31 (0.04–2.65)	10	208	0.46 (0.24–0.89)
Hydrophilic statins						
Rosuvastatin	13	743	0.74 (0.40–1.39)	87	1240	0.67 (0.54–0.84)
Pravastatin	4	234	0.92 (0.33–2.56)	26	393	0.68 (0.47–0.98)

*The aHR was derived from the inverse probability-weighted Cox model considering statin use as a time-dependent covariate and was adjusted for cancer stage, cancer grade, year of the cancer diagnosis and the use of metformin, non-steroidal anti-inflammatory drugs and aspirin.
CI, confidence interval.

received statins before cancer diagnosis (Table 5). Results showed that statin use was associated with reduced risks of mortality for all-cause mortality and PCSM in both groups. We also examined the intensity of statin use and found that reduced risks were shown in patients who received on average both ≤ 1 and >1 DDD. We also examined the effect of statins in patients with different comorbid conditions (CCI ≤ 1), disease progression (receiving secondary treatment) and older patients (aged ≥ 75 years). Reductions in all-cause mortality and PCSM yielded in the sensitivity analyses were comparable to those in the main analysis.

4. Discussion

This is one of the largest patient populations with advanced PC following ADT, and results indicated the potential of statins as a therapy for men with non-metastatic high-risk and hormone-sensitive metastatic PC. Our study also observed marked differences among individual statins, which provides important evidence for selecting the most appropriate statin for secondary prevention trials.

In our large population study with 3.6 years of follow-up on average, we showed a substantial decrease

Table 5
Sensitivity analyses of the association between statin use and mortality among men with advanced prostate cancer following androgen deprivation therapy.

Subpopulation or exposure	No. of patients	All-cause mortality				Prostate cancer mortality			
		No. of deaths	aHR	95% CI	*p* value	No. of deaths	aHR	95% CI	*p* value
New statin users ($n = 1562$)	5140	1968	0.62	0.56–0.69	<0.0001	1300	0.64	0.56–0.73	<0.0001
Prevalent users ($n = 609$)	4178	1766	0.75	0.68–0.82	<0.0001	1191	0.77	0.69–0.86	<0.0001
Receiving secondary treatment	804	603	0.75	0.62–0.91	0.0030	531	0.78	0.64–0.96	0.0180
Patients with CCI ≤ 1	3094	1138	0.71	0.62–0.80	<0.0001	760	0.69	0.59–0.81	<0.0001
Patients with stroke, hypertension, DM or CVD	4767	1936	0.79	0.72–0.87	<0.0001	1239	0.80	0.71–0.90	0.0002
Metformin users	1393	580	0.72	0.61–0.85	<0.0001	358	0.74	0.60–0.92	0.0070
Age ≥ 75 years	2763	1310	0.82	0.73–0.93	0.0011	775	0.84	0.73–0.98	0.0288
>1 DDD	4852	1991	0.80	0.72–0.89	<0.0001	1321	0.83	0.72–0.95	0.0058
≤ 1 DDD	4475	1743	0.68	0.60–0.78	<0.0001	1170	0.69	0.58–0.81	<0.0001

*The adjusted hazard ratio (aHR) was derived from the inverse probability-weighted Cox model considering statin use as a time-dependent covariate and was adjusted for cancer stage, cancer grade, year of the cancer diagnosis and the use of metformin, non-steroidal anti-inflammatory drugs and aspirin.
aHR, adjusted hazard ratio; CCI, Charlson comorbidity index; DM, diabetes mellitus; CHD, coronary heart disease; CI, confidence interval.

in mortality associated with statin use in men with metastatic disease following ADT. Previous studies mostly focused on patients with localised PC [6,7,18]. Few studies reported results from patients with advanced disease treated with ADT. One retrospective study was conducted on 926 men who had developed biochemical recurrence or metastatic disease when they initiated ADT [19]. That study found that men receiving statins had a longer time to disease progression than did non-users, but the estimates did not reach statistical significance. Another study demonstrated that statin use was associated with delayed development of CRPC in 171 metastatic patients treated with ADT [20]. One retrospective study showed that statin use was not associated with disease progression in men primarily receiving ADT [21]. In 2017, a study of a Danish population reported a reduction in mortality associated with statin use in non-localised patients, but the type of treatment was not specified [7]. Combining ADT with either abiraterone or docetaxel was shown to significantly prolong overall survival compared with ADT monotherapy in patients with advanced PC [22,23]. Clinical trial data directly comparing the effect of abiraterone with docetaxel when used along with ADT are still being established. Our data and results from previous studies support the potential of a secondary prevention trial to evaluate whether the use of statins can improve therapeutic outcomes in men with metastatic PC.

On the other hand, patients with locally advanced PC demonstrated a significant decrease in the risk of all-cause mortality and a marginal decrease in PCSM. In this study, we included patients who received ADT only in the first year after their cancer diagnosis. However, locally advanced patients usually receive a combination of either external beam radiation therapy or brachytherapy plus ADT. Our patients received only ADT possibly because they were not suitable candidates for radiation therapy because of comorbidities, old age or their personal choice. Although receiving only ADT is not the best treatment option for patients with T3/T4 disease, we still observed strong effects of statins in reducing all-cause mortality. Statins' effects in reducing PCSM in these patients need to be confirmed in a few years when event numbers are large enough to reach statistical power. In addition, research studying how statins interact with current treatment modalities to possibly identify factors that predict responses will increase the benefit.

To our knowledge, this is the first study to successfully demonstrate the effects of different statin types on mortality. Our study revealed that men who took atorvastatin, pravastatin, rosuvastatin or pitavastatin demonstrated a significant reduction in all-cause mortality and PCSM compared with non-users. Possible mechanisms included inhibition of the proteasome pathway [24], inhibition of downstream products of the mevalonate pathway [25], triggering of tumour-specific apoptosis [26] and inhibition of cholesterol synthesis [27,28]. Preclinical research demonstrated that statins can inhibit PC growth through cholesterol-mediated and non–cholesterol-mediated mechanisms that affect PC growth. While cholesterol is the precursor of androgens [29], statins contribute to reducing androgen bioavailability through controlling cholesterol. Pitavastatin, pravastatin, atorvastatin and rosuvastatin are actually more effective at lowering triglycerides and low-density lipoprotein cholesterol and raising high-density lipoprotein cholesterol than other statins in patients with hypercholesterolemia [27,28]. Statins which are more effective at lowering lipid profiles demonstrated a stronger effect in reducing mortality in PC. Our findings suggest that the reduction in mortality might be partially explained by the various abilities to lower lipid profiles. Also, statins interfere with levels of mevalonate and its associated products through 3-hydroxy-3-methyl-glutaryl-CoA reductase-dependent and 3-hydroxy-3-methyl-glutaryl-CoA reductase-independent pathways. The mevalonate pathway plays roles in mediating cell growth, differentiation and survival [30]. In addition to inhibiting cholesterol formation, statins suppress tumours by inhibiting small guanosine triphosphatases involved in proliferation, inflammation, angiogenesis and metastasis in PC [31,32].

Lipophilic statins were suggested to have greater effects on cancer than hydrophilic statins because lipophilic statins have greater intracellular access and are able to cross biological membranes without requiring specific transport mechanisms compared with hydrophilic statins [33–37]. However, observational studies did not reach this conclusion [34–37]. In this study, hydrophilic statins and two lipophilic statins (atorvastatin and pitavastatin) demonstrated promising reductions in mortality. Hydrophilic statins appeared superior to lipophilic statins in reducing mortality. Our findings are relatively new, while previous studies mainly reported results from patients who received lipophilic statins. Further studies are warranted to fill in gaps in our understanding of how statins might modify the risk of PC death.

The effects of statins on the risk of mortality were reported in both new users and prevalent users [6,38]. We observed that decreased mortality was associated with all statin users in the main analysis, and a similar trend was observed in both new and prevalent users in the sensitivity analysis. Similar results were reported by a Danish study [7], in which comparable reductions in PC mortality were found for continuing and new statin users. The effect estimates for statin use associated with mortality are strong, and they are unlikely to be explained by a selection bias between prevalent users and new users.

The major strength of this study was its large number of incident PC patients with data of clinical cancer stage, cancer grade, treatment modalities and cause of death. In addition, as a result of a low prevalence of prostate-specific antigen screening, more than 25% of patients in this population died from their disease, which enabled us to evaluate the clinical utility of statin use in subgroups of patients. Moreover, a considerable portion of patients received hydrophilic statins, such that we could evaluate the effects of different types of statins as rarely seen in previous studies. However, some limitations of this study should be noted. First, this study was conducted using a claims database. Lab values or levels of lipid profiles were not available. Therefore, we could not evaluate if changes in lipid profiles following initiation of statin use were associated with mortality. Second, we could not completely avoid the possibility that statin users might be a different population compared with non-users, which might have been an unmeasured confounding factor in our study. We used IPTW to balance the difference in covariates. Also, several subgroup analyses were conducted to examine potential bias coming from unmeasured confounders. Regarding the cancer burden, we found consistent results in men at different clinical stages and those receiving secondary treatment during follow-up. We also examined statins' effects in patients with different comorbidities. The reduction in mortality with statin use was similar for healthy men and those with a higher number of comorbidities. Third, we did not have information on the body mass index and other lifestyle factors at the time of cancer diagnosis. Therefore, we were unable to evaluate the impacts of those factors in contributing to mortality. Fourth, event numbers were small in some of the subgroups of single statins which limited our statistical power. Last, our study population was 95% Han Chinese [39], which does limit the generalisability of our results to other ethnic groups. The prevalence of statin use is approximately 76.5% in North Americans, 69.9% in Western Europeans and 60.5% in Asians [40]. Therefore, we expect that other ethnicities which have higher rates of statin use might have slightly different results. However, previous studies conducted in different ethnic populations also demonstrated a reduction in mortality risk associated with statin use.

5. Conclusions

Our results suggested the potential of atorvastatin, pravastatin and rosuvastatin as secondary prevention for men with non-metastatic high-risk and hormone-sensitive metastatic PC.

Conflict of interest statement

All authors declare that they have no conflict of interest.

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