ARTICLE

Clinical Research

# Metabolic syndrome and its pharmacologic treatment are associated with the time to castration-resistant prostate cancer

Jiun-Hung Geng[1,2,3]✉, Anna Plym[1,4,5], Kathryn L. Penney[4,6], Mark Pomerantz[7], Lorelei A. Mucci[4] and Adam S. Kibel[1]



**BACKGROUND:** Metabolic syndrome and its pharmacologic treatment can potentially influence the progression of prostate cancer in men receiving androgen deprivation therapy (ADT). We aimed to evaluate the association between metabolic syndrome and its pharmacologic treatment with time to castration-resistant prostate cancer (CRPC).

**METHODS:** We identified 409 men with metastatic castration-sensitive prostate cancer receiving first line ADT from 1996 to 2014 at our institution. Information concerning metabolic syndrome, statin use, aspirin use, and metformin use at initiation of ADT was collected from medical records. Time to CRPC was defined as the duration between initiating ADT and diagnosis of CRPC based on the Prostate Cancer Working Group 3 definition. Flexible parametric survival models were used to calculate hazard ratios (HR, and 95% confidence intervals, CI) of the association between metabolic conditions and time from ADT initiation to CRPC.

**RESULTS:** During a median follow-up of 59 months, 87% ($N = 356$) men progressed to CRPC. Median time to CRPC was 19 months. Fifty-six percent of men met the definition of metabolic syndrome. Controlling for demographic and prostate cancer-specific variables, metabolic syndrome was associated with shorter time to CRPC (HR 1.41, 95% CI 1.09–1.81). Importantly, in men with metabolic syndrome, statin use was associated with a slower progression to CRPC (HR 0.70, 95% CI 0.49–0.98).

**CONCLUSIONS:** Our study suggests that metabolic syndrome is a risk factor for earlier progression from castration-sensitive to castration-resistant prostate cancer and raises the possibility that treatment, such as statin use, may slow the time to progression.

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## INTRODUCTION

Prostate cancer is currently diagnosed in 248,000 men in the United States each year [1]. While current controversies focus on overdiagnosis and treatment [2], metastatic prostate cancer remains a growing problem [3, 4]. Although newer treatments for metastatic prostate cancer increase life expectancy [5–7], almost all castration-sensitive prostate cancer (CSPC) patients treated with androgen deprivation therapy (ADT) progress to castration-resistant prostate cancer (CPRC) and death. Multiple mechanisms help to explain the development of CRPC including intracrine androgen synthesis, androgen receptor (AR) amplification, AR mutations, AR splice variants, and bypass pathways [8]. The risk of progression to CRPC is likely a complex interaction of genetic, environmental, and social factors.

Metabolic syndrome is also a major public health problem. It is related to an increased risk of cardiovascular disease, it is also associated with cancer development and progression, including prostate cancer. In a systemic review, metabolic syndrome was associated with a higher incidence of advanced and lethal prostate cancer [9]. An underpowered study of 82 men demonstrated that metabolic syndrome is potentially a risk factor for shorter time to progression to CRPC following treatment with ADT [10]. Furthermore, some of the individual components of metabolic syndrome (specifically obesity, insulin resistance, and dyslipidemia) have been identified as risk factors for the development of aggressive prostate cancer [11].

Pharmacologic treatments for metabolic syndrome and its sequelae, including statins [12, 13], metformin [14, 15], and aspirin [16], have been inversely associated with lethal prostate cancer. Interestingly, hypertension treatment has not been strongly associated with a protective effect [17, 18]. Although there is still a lack of large-scale, randomized trials, pharmacologic interventions for metabolic syndrome hold promise as a potential safe and effective secondary prevention approach for CRPC and prostate cancer death [19, 20]. Since no previous study has investigated the influence of the combination of metabolic syndrome and its

[1]Division of Urological Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA. [2]Department of Urology, Kaohsiung Municipal Siaogang Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan. [3]Department of Urology, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan. [4]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA. [5]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden. [6]Channing Division of Network Medicine, Harvard Medical School and Brigham & Women's Hospital, Boston, MA, USA. [7]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA. ✉email: u9001090@hotmail.com

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pharmacologic treatment on progression of metastatic CSPC, we sought to determine the impact of metabolic syndrome and its pharmacologic treatment on the development of CRPC.

## MATERIALS AND METHODS

### Study population and data collection

We identified 431 men with metastatic CSPC evaluated from 1996 to 2014 at either Brigham and Women's Hospital or Dana-Farber Cancer Institute. Clinicopathological data were captured from an institutional clinical database as described previously [21] and from electronic medical records. The inclusion criteria were prostate cancer patients receiving first-line ADT for metastatic disease with longitudinal follow-up. Patients were excluded if they had insufficient follow-up data on prostate-specific antigen (PSA) level after ADT administration ($N = 2$), or if they received primary chemohormone therapy ($N = 15$), or if they received adjuvant ADT due to pathological lymph node positive after radical prostatectomy ($N = 5$), which left 409 patients for analysis. We collected pre-ADT information on metabolic syndrome, statin use, aspirin use, and metformin use within 6 months prior to administration of ADT. The study was approved by the institutional IRB (Protocol No: 2018P002714) with all participants providing written informed consent. There were no external funding sources (institutional resources only) and there are no conflicts of interest.

### Exposure assessment

We used the modified Adult Treatment Panel (ATP) III criteria to define the presence or absence of metabolic syndrome [22]. A subject was categorized as having metabolic syndrome [22] if three or more of the following five criteria were met before start of ADT: blood pressure ≥130/85 mmHg or pharmacologic treatment, fasting triglyceride level ≥150 mg/dl or pharmacologic treatment, fasting HDL cholesterol level < 40 mg/dl or pharmacologic treatment, fasting blood sugar ≥100 mg/dl or pharmacologic treatment, and BMI ≥ 30 kg/m$^2$. We used BMI ≥ 30 kg/m$^2$ as an indicator of obesity as a surrogate for waist circumference >40 inches, because waist circumference was not available. This substitution has been validated previously [10, 23, 24]. Patients were defined as statin/aspirin/metformin users if they were using statin/aspirin/metformin before start of ADT.

### Definition of CRPC

The primary outcome was CRPC using the Prostate Cancer Clinical Trials Working Group 3 (PCWG3) criteria: in a patient with testosterone <50 ng/dl as (1) new metastatic disease, or (2) an increase in two consecutive PSA levels obtained at least one week apart with a minimum PSA greater than 1.0 ng/ml, or (3) initiation of secondary hormone treatment for increasing PSA [25].

### Covariates

The potential covariates included: age at ADT initiation, year of ADT initiation, self-reported race, smoking, biopsy Gleason score at diagnosis, primary treatment, clinical stage at ADT initiation, PSA at ADT initiation, and volume of disease at ADT initiation. The volume of disease was assessed by whole-body scintigraphy and MRI or CT staging scans and based on the CHAARTED trial definition [5]. Synchronous metastasis was defined as metastases within ≤3 months of initial diagnosis of prostate cancer, and metachronous metastasis was defined as metastasis diagnosed >3 months after initial diagnosis [26].

### Statistical analysis

All patients were followed from the date of initiation of ADT until CRPC, death, loss to follow-up, or end of follow-up (July 31, 2019), whichever event came first. Proportional-hazards flexible parametric survival analysis [27] was used to estimate hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) for the association between metabolic syndrome and time to CRPC, both with and without adjustment of potentially relevant epidemiologic (age at ADT initiation, year of ADT initiation, self-reported race, and smoking) and prostate cancer-specific factors (Gleason score, primary treatment, clinical stage at ADT initiation, and PSA at ADT initiation). HRs were also estimated for joint categories of metabolic syndrome and pharmacologic treatment, and for the individual components of metabolic syndrome. In addition to estimating proportional hazards, we fitted flexible parametric survival models [27] including time-dependent effects of metabolic syndrome. We further calculated the cumulative incidence of CRPC by metabolic syndrome status, taking the competing risk of death into account and using regression standardization to control for confounding. All flexible parametric models were fitted with five degrees of freedom for the baseline hazard and three degrees of freedom for time-varying effects [27]. Time since ADT initiation was the underlying time-scale for all analyses. Significance tests for all comparisons were two-sided and $p$ values <0.05 were considered statistically significant. Missing variables were treated as separate categories, or if numbers were too small for a separate category (statin/aspirin/metformin use), coded as zeros. For metabolic syndrome, we performed a worst-case analysis in which all men with missing information were a) assumed to have and b) not to have metabolic syndrome. All analyses were carried out using STATA 15.0 (StataCorp, Texas, USA) and R version 3.6.2 (R Foundation for Statistical Computing, Wien, Austria).

## RESULTS

The clinical characteristics of the 409 included patients are summarized in Table 1 (by metabolic syndrome) and Supplementary Table 1 (by statin use). The median age at ADT initiation was 66 years. The majority of patients (85%) self-reported as White. More than half of the patients (54%) had a biopsy Gleason score >7 at cancer diagnosis; and 20%, 74%, 6% of patients had positive lymph node, bone metastasis, and visceral metastasis at ADT initiation, respectively. Forty-nine percent of patients had not received prior local therapy for prostate cancer with curative intent. The median PSA level at ADT initiation was 27.8 (interquartile range [IQR] 9.5–109.0) ng/ml. Metabolic syndrome was present in 56% of patients. In men without metabolic syndrome, 43% had no metabolic factor, 31% had one factor and 26% had two factors.

During a median follow-up time of 59 (IQR 36–105) months, 356 men with prostate cancer developed CRPC. Median time to CRPC in these men was 19 months (IQR 10–45). In multivariable models controlling for both demographic and prostate cancer-specific factors, metabolic syndrome (HR 1.41, 95% CI 1.09–1.81) was significantly associated with a shorter time to CRPC (Table 2). Of the individual components of metabolic syndrome, only an elevated fasting glucose was significantly associated with time to CRPC (Table 2). Results were similar in analysis adjusting for volume of disease instead of M stage (HR = 1.41, 95% CI = 1.09–1.83) (Supplementary Table 2). In a worst-case analysis examining missing information, the HR for metabolic syndrome ranged from 1.18 (95% CI 0.94–1.48) in a scenario in which men with missing information was assumed not to have metabolic syndrome, to 1.50 (95% CI 1.19–1.89) in a scenario in which all men with missing information were assumed to have metabolic syndrome (Supplementary Table 3).

In analyses examining the time-varying effect of metabolic syndrome, the association of time to CRPC was strongest in the second year after start of ADT ($HR_{year\ 2}$ 2.06, 95% CI 1.34–3.16) (Supplementary Table 4). In year five, the rate of progression to CRPC remained elevated among men who had not had an early event ($HR_{year\ 5}$ 1.54, 95% CI 1.00–2.39).

The cumulative incidence of CRPC in men with and without metabolic syndrome, both (a) unadjusted and (b) controlling for confounders is illustrated in Fig. 1. Five years after start of ADT, 82% (95% CI 76–88%) of men with metabolic syndrome had progressed to CRPC, compared with 66% (95% CI 58–74%) of men without.

We additionally examined joint categories of metabolic syndrome and pharmacologic treatments (Table 3). In multivariable models adjusting for demographic factors, men with metabolic syndrome and statin use had a slower progression to CRPC (HR 0.66, 95% CI 0.47–0.93) compared with men with metabolic syndrome but without statin use. The association remained significant in models with additional adjustment for Gleason score, primary treatment, clinical stage at ADT initiation,

**Table 1.** Clinical and epidemiologic characteristics of the study population among men initiating androgen deprivation therapy.

| | All men | | Metabolic syndrome[a] | | | |
|---|---|---|---|---|---|---|
| **Characteristic** | ***N*** | **(%)** | **No** | **(%)** | **Yes** | **(%)** |
| Number of Patients | 409 | (100) | 140 | (100) | 176 | (100) |
| Age at ADT initiation | | | | | | |
| Median, years (IQR) | 66 | (59–72) | 66 | (58–72) | 67 | (62–72) |
| Self-reported race, *n* (%) | | | | | | |
| White | 349 | (85) | 128 | (91) | 152 | (86) |
| Black | 16 | (4) | 2 | (1) | 9 | (5) |
| Other/Unknown | 44 | (11) | 10 | (7) | 15 | (9) |
| Smoking (current or ever), *n* (%) | | | | | | |
| No | 163 | (41) | 60 | (44) | 66 | (38) |
| Yes | 231 | (59) | 76 | (56) | 108 | (62) |
| Unknown | 15 | | 4 | | 2 | |
| Year of ADT initiation | | | | | | |
| 1995–1999 | 44 | (11) | 16 | (11) | 12 | (7) |
| 2000–2004 | 114 | (28) | 38 | (27) | 33 | (19) |
| 2005–2009 | 183 | (45) | 64 | (46) | 97 | (55) |
| 2010–2014 | 68 | (17) | 22 | (16) | 34 | (19) |
| *Metabolic syndrome and its pharmacologic treatment* | | | | | | |
| Metabolic syndrome, *n* (%) | | | | | | |
| No | 140 | (44) | 140 | (100) | 0 | (0) |
| Yes | 176 | (56) | 0 | (0) | 176 | (100) |
| Missing information on subcomponents | 93 | | 0 | | 0 | |
| Statin user | | | | | | |
| No | 266 | (66) | 126 | (90) | 52 | (30) |
| Yes | 137 | (34) | 14 | (10) | 123 | (70) |
| Unknown | 6 | | 0 | | 1 | |
| Aspirin user | | | | | | |
| No | 282 | (70) | 118 | (85) | 89 | (51) |
| Yes | 122 | (30) | 21 | (15) | 86 | (49) |
| Unknown | 5 | | 1 | | 1 | |
| Metformin user | | | | | | |
| No | 380 | (93) | 140 | (100) | 151 | (86) |
| Yes | 28 | (7) | 0 | (0) | 25 | (14) |
| Unknown | 1 | | 0 | | 0 | |
| *Prostate cancer-specific factors* | | | | | | |
| Biopsy Gleason score at diagnosis, *n* (%) | | | | | | |
| ≤7 | 175 | (46) | 65 | (48) | 78 | (49) |
| >7 | 205 | (54) | 71 | (52) | 82 | (51) |
| Unknown | 29 | | 4 | | 16 | |
| Volume of disease at ADT initiation | | | | | | |
| Low | 217 | (53) | 79 | (56) | 94 | (53) |
| High | 185 | (45) | 61 | (44) | 78 | (44) |
| Not classified | 7 | (2) | 0 | (0) | 4 | (2) |
| Sites of metastases, *n* (%) | | | | | | |
| Lymph nodes | 82 | (20) | 33 | (24) | 32 | (18) |
| Bone | 304 | (74) | 98 | (70) | 135 | (77) |
| Visceral | 23 | (6) | 9 | (6) | 9 | (5) |
| Metachronous metastases | 209 | (51) | 72 | (51) | 104 | (59) |
| Synchronous metastases | 200 | (49) | 68 | (49) | 72 | (41) |
| PSA at ADT initiation, ng/ml | | | | | | |
| Median (IQR) | 27.8 | (9.5–109.0) | 25.1 | (7.9–119.1) | 23.3 | (9.0–69.2) |

**Table 1.** continued

| Characteristic | All men | | Metabolic syndrome[a] | | | |
|---|---|---|---|---|---|---|
| | *N* | (%) | No | (%) | Yes | (%) |
| Initial local treatment for prostate cancer, *n* (%) | | | | | | |
| No local therapy | 200 | (49) | 68 | (49) | 72 | (41) |
| Radical prostatectomy | 129 | (31) | 48 | (34) | 59 | (34) |
| Primary radiation | 80 | (20) | 24 | (17) | 45 | (26) |
| Adjuvant radiation, *n* (%) | 16 | (4) | 5 | (4) | 7 | (4) |
| Salvage radiation, *n* (%) | 57 | (14) | 25 | (18) | 27 | (15) |

*ADT* Androgen deprivation therapy, *BMI* Body mass index, *CRPC* Castration-resistant prostate cancer, *IQR* Interquartile range, *PSA* Prostate-specific antigen.
[a]93 men could not be classified as having metabolic syndrome due to lack of information on primarily HDL cholesterol level (93/93 men with missing data) and fasting triglyceride level (91/93 men with missing data).

**Table 2.** Hazard ratio for CRPC by metabolic syndrome and individual components of metabolic syndrome.

| Metabolic disease | Unadjusted HR (95% CI) | Adjusted $HR_1$ (95% CI) | Adjusted $HR_2$ (95% CI) |
|---|---|---|---|
| Metabolic syndrome | | | |
| No | 1 (Ref.) | 1 (Ref.) | 1 (Ref.) |
| Yes | **1.37 (1.07–1.75)** | **1.37 (1.06–1.76)** | **1.41 (1.09–1.81)** |
| Blood pressure ≥ 130/85 mmHg (or pharmacologic treatment) | | | |
| No | 1 (Ref.) | 1 (Ref.) | 1 (Ref.) |
| Yes | 1.01 (0.80–1.27) | 1.05 (0.83–1.34) | 1.06 (0.76–1.48) |
| BMI ≥ 30 kg/m$^2$ | | | |
| No | 1 (Ref.) | 1 (Ref.) | 1 (Ref.) |
| Yes | 1.04 (0.84–1.30) | 0.99 (0.79–1.24) | 0.99 (0.73–1.34) |
| HDL cholesterol level < 40 mg/dl (or pharmacologic treatment) | | | |
| No | 1 (Ref.) | 1 (Ref.) | 1 (Ref.) |
| Yes | 1.20 (0.92–1.57) | 1.20 (0.90–1.58) | 0.74 (0.45–1.21) |
| Fasting triglyceride level ≥ 150 mg/dl (or pharmacologic treatment) | | | |
| No | 1 (Ref.) | 1 (Ref.) | 1 (Ref.) |
| Yes | 1.27 (0.97–1.66) | 1.31 (0.99–1.73) | 1.58 (0.95–2.61) |
| Fasting blood glucose ≥ 100 mg/dl (or pharmacologic treatment) | | | |
| No | 1 (Ref.) | 1 (Ref.) | 1 (Ref.) |
| Yes | 1.28 (0.97–1.68) | 1.30 (0.99–1.73) | **1.44 (1.02–2.02)** |

Adjusted HR1: adjusted for demographic factors (age at ADT initiation, year of ADT initiation, race, smoking).
Adjusted HR2: adjusted for demographic factors (age at ADT initiation, year of ADT initiation, race, smoking) and prostate cancer-specific factors (Gleason 7+, primary treatment, M stage at ADT initiation, PSA at ADT initiation).
Hazard ratios for individual components (blood pressure ≥130/85 mmHg, BMI ≥ 30 kg/m$^2$, HDL cholesterol level <40 mg/dl, fasting triglyceride level ≥150 mg/dl, fasting blood glucose ≥100 mg/dl) were also adjusted for the other components of metabolic syndrome.
*ADT* Androgen deprivation therapy, *BMI* Body mass index, *CI* Confidence interval, *CRPC* Castration-resistant prostate cancer, *HDL* High-density lipoproteins, *HR* Hazard ratio, *PSA* Prostate-specific antigen.
Bold values denote statistical significance at the $p < 0.05$ level.

and PSA at ADT initiation (HR 0.70, 95% CI 0.49–0.98). In addition, men who used statins, but did not fulfill the criteria for metabolic syndrome, had the lowest rate of PSA progression (HR 0.32, 95% CI 0.15–0.65). Results were similar in a sensitivity analysis using only increased triglyceride level or decreased HDL cholesterol level as the reference group while adjusting for the other components of metabolic syndrome (Supplementary Table 5). The other medications were not significantly associated with time to PSA progression in the subgroup of patients with metabolic syndrome.

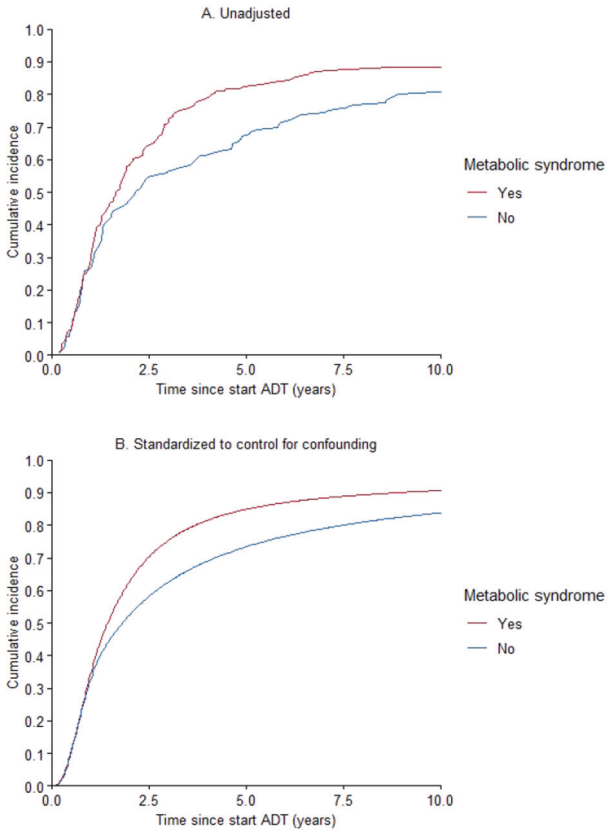


**Fig. 1 Cumulative incidence of CRPC by metabolic syndrome.** **A** The non-parametric (unadjusted) cumulative incidence of CRPC. **B** The standardized cumulative incidence of CRPC controlling for demographic and prostate cancer-specific factors.

The cumulative incidence of CRPC among men with metabolic syndrome but without statin use, both (a) unadjusted and (b) controlling for confounders is present in Fig. 2. Five years after start of ADT, 91% (95% CI 83–98%) of men with metabolic syndrome but without statin use had progressed to CRPC. The corresponding percentage was 79% (95% CI 71–86%) in men with metabolic syndrome and statin use, and 71% (95% CI 63–79%) in men with neither. The median time to CRPC was 15 months in men with metabolic syndrome but without statin use, 23 months

**Table 3.** Hazard ratio for CRPC by joint categories of metabolic syndrome and statin/aspirin/metformin use.

| Combination | No. of patients | Adjusted $HR_1$ (95% CI) | Adjusted $HR_2$ (95% CI) |
|---|---|---|---|
| Metabolic syndrome | | | |
| No | 126 | **0.59 (0.42–0.83)** | **0.59 (0.42–0.83)** |
| Yes, without statins | 52 | 1 (Ref.) | 1 (Ref.) |
| Yes, with statins | 123 | **0.66 (0.47–0.93)** | **0.70 (0.49–0.98)** |
| Statin without metabolic syndrome | 14 | **0.29 (0.14–0.60)** | **0.32 (0.15–0.65)** |
| Metabolic syndrome | | | |
| No | 118 | 0.76 (0.56–1.04) | 0.77 (0.56–1.05) |
| Yes, without aspirin | 89 | 1 (Ref.) | 1 (Ref.) |
| Yes, with aspirin | 86 | 0.94 (0.68–1.30) | 1.05 (0.76–1.45) |
| Aspirin without metabolic syndrome | 21 | **0.50 (0.29–0.87)** | **0.57 (0.33–0.99)** |
| Metabolic syndrome | | | |
| No | 140 | **0.73 (0.56–0.94)** | **0.71 (0.55–0.92)** |
| Yes, without metformin | 151 | 1 (Ref.) | 1 (Ref.) |
| Yes, with metformin | 25 | 0.96 (0.59–1.55) | 0.97 (0.59–1.58) |
| Metformin without metabolic syndrome | 0 | – | – |

Adjusted HR1: adjusted for demographic factors (age at ADT initiation, year of ADT initiation, race, smoking).
Adjusted HR2: adjusted for demographic factors (age at ADT initiation, year of ADT initiation, race, smoking) and prostate cancer-specific factors (Gleason 7+, primary treatment, M stage at ADT initiation, PSA at ADT initiation).
*ADT* Androgen deprivation therapy, *CRPC* Castration-resistant prostate cancer, *HR* Hazard ratio, *PSA* Prostate-specific antigen.
Bold values denote statistical significance at the $p < 0.05$ level.

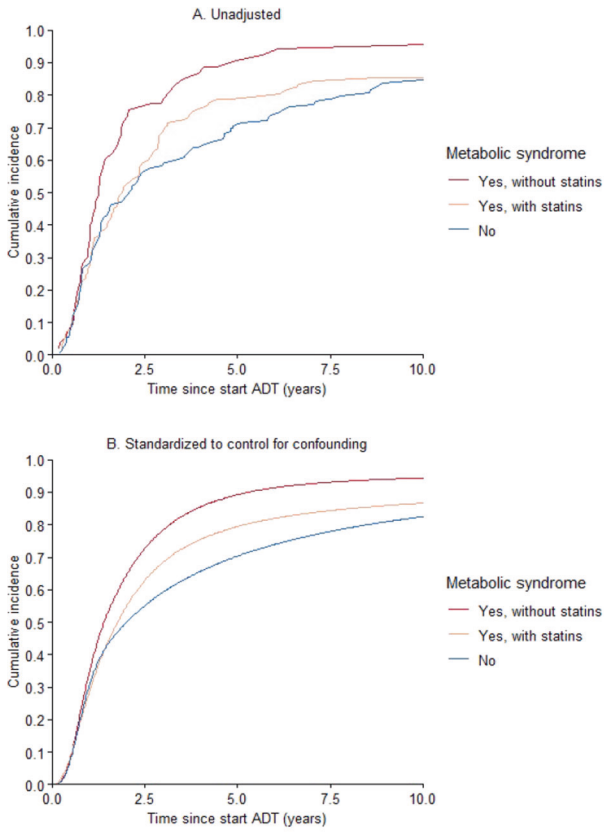


**Fig. 2 Cumulative incidence of CRPC by metabolic syndrome and statin use. A** The non-parametric (unadjusted) cumulative incidence of CRPC. **B** The standardized cumulative incidence of CRPC controlling for demographic and prostate cancer-specific factors.

in men with metabolic syndrome and statin use, and 25 months in men with neither.

## DISCUSSION

In this cohort study of metastatic CSPC men initiating ADT, metabolic syndrome was associated with earlier progression to CRPC. In addition, statin use was significantly associated with a slower progression to CRPC in the subgroup of men with metabolic syndrome, suggesting that this drug might influence prostate cancer outcomes. Overall, the present study suggests that metabolic syndrome and its pharmacologic treatment may affect ADT response in men with metastatic CSPC.

Our research builds upon the results of a smaller study of 82 men [10], in whom metabolic syndrome was associated with a shorter time to CRPC (HR 2.55, 95% CI 1.37–4.77). This study population had a lower prevalence of advanced disease, and one-third of men did not have metastatic prostate cancer and therefore possible should have been followed without treatment or have benefited from potentially curative therapy such as radiotherapy plus ADT.

An additional strength of our study defining metabolic syndrome according to universally accepted ATP III definition, which is the best current predictor of the sequelae of metabolic syndrome including cardiovascular events and progression to type 2 diabetes [28–30]. Moreover, our study sample size and larger number of events over long-term follow-up provided greater power and ability to do subgroup analyses. Lastly, the information of pharmacologic treatment of metabolic syndrome allowed us to investigate whether the excess risk associated with metabolic syndrome could be offset by medications.

In line with previous reports [31–36], we did not observe associations between the individual components of metabolic syndrome (increased blood pressure, obesity, and abnormal cholesterol or triglyceride levels) and ADT response. The only component that demonstrated an association was fasting glucose ≥100 mg/dl. Several prior studies have reported that elevated

fasting glucose level is associated with prostate cancer development and aggressiveness. Wright *et al* examined 1,734 men treated with radical prostatectomy or radiation therapy and demonstrated that a fasting glucose level ≥100 mg/dl was associated with a 50% increased risk of PSA progression compared with those with fasting glucose <100 mg/dl [37]. A second similar study of 5,126 cancer-free men, there was higher risk of fatal prostate cancer in those with hyperglycemia before diagnosis [38]. These studies demonstrate an association, but a large-scale long-term prospective study would be needed to demonstrate if better glucose control could improve ADT response in metastatic CSPC patients.

Consistent with the hypothesis that better control would translate to improve survival, we demonstrated a potential protective effect of statin. Our findings are consistent with statins as a protective factor for prostate cancer progression. Previous research has suggested that statins can reduce disease progression in prostate cancer patients receiving ADT [21, 39] and lower the incidence of prostate cancer mortality in men with PTEN-loss prostate cancer [12]. Pharmacologic intervention being associated with protection was not observed to the same extent in patients with metabolic syndrome taking aspirin or metformin. This is consistent with prior work demonstrating that drugs for metabolic diseases (such as anti-diabetes, anti-dyslipidemia, and anti-hypertension) do not reduce the risk of cancer-specific mortality in patients with ADT [29]. The possible reasons for these conflicting findings include different primary outcome (prostate cancer-specific mortality versus PSA progression), different subjects (all stage prostate cancer patients with primary ADT versus metastatic CSPC patients with ADT), and different categorizations (all subjects versus subjects with metabolic syndrome only). Potentially, it can provide clinicians with guidance for the treatment of men initiating ADT.

Prior work examining metformin has in some but not all studies demonstrate a benefit. Margel et al. retrospectively analyzed 3,837 diabetes mellitus men with prostate cancer and found the increasing duration of metformin use was associated with improvement in both all-cause and prostate cancer–specific mortality [40]. Studies have also demonstrated that metformin is not protective. A 6,537 men Finnish cohort demonstrated a higher risk of prostate cancer death among metformin users compared with nonusers [41]. While our study did not demonstrate a benefit, it was not designed to explore the role of metformin on ADT response in metastatic CSPC patients, given the limited to men with metabolic syndrome and only 25 men received metformin in our study. Randomized trials are underway to investigate metformin and prostate cancer including STAMPEDE which will determine if metformin decreases progression in men with metastatic prostate cancer [42].

To our knowledge, this is the first study to demonstrate a possible influence of statins on ADT response in patients with metabolic syndrome. This is the largest study performed in this patient population to date, with detailed information on established prognostic factors including demographic factors and prostate cancer-specific factors. Despite these strengths, several limitations should be noted. First, this is a retrospective, observational study with the inherent incomplete adjustment for confounders as in all studies of this nature. This might be particularly relevant for the findings related to statin use and time to CRPC. As observed in a previous report [21], statin users tend to have less advanced prostate cancer than non-statin users. Others have found that statin use is a marker of good health and access to high-quality health care [43]. Although we adjusted for several potential confounders in the present analysis, we lacked information on other factors such as the use of antihypertentive drugs, performance status, income, education, health care use, other comorbid conditions, and their medications. Second, we analyzed prevalent use of statins and other drugs, which is possibly susceptible for bias. This is exemplified in a previous meta-analysis, in which the authors found that observational studies using prevalent statin users over-estimated the protective effect of statin use on all-cause mortality in comparison to randomized-controlled trials [43]. Future, preferably randomized controlled trials or observational studies with information on start and end-dates of statin use [44], should address these possible biases. Third, though metastatic CRPC is a uniformly lethal condition, because we lacked detailed information on cause of death, we could not examine prostate cancer-specific death.

In conclusion, our data suggest that metabolic syndrome is a risk factor for earlier development of CRPC. Men with metabolic syndrome may benefit from statins to delay CRPC development. Further research is needed to better understand the possible interplay between metabolic factors and statin use on clinical outcomes of prostate cancer.

## DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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## AUTHOR CONTRIBUTIONS

Conception and design JHG, KLP, ASK, LAM; acquisition of data MP, JHG; analysis and interpretation of data All authors; drafting of the manuscript All authors; critical revision of the manuscript for important intellectual content All authors; statistical analysis JHG, AP; obtaining funding ASK; administrative, technical, or material support ASK; supervision LAM, ASK. All authors have read and agreed to the published version of the manuscript.

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## COMPETING INTERESTS

The authors declare no competing interests.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was performed in accordance with the Declaration of Helsinki. The study was approved by the institutional IRB (Protocol No: 2018P002714). All participants provided written informed consent.

## ADDITIONAL INFORMATION

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**Correspondence** and requests for materials should be addressed to Jiun-Hung Geng.

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