



Hypercholesterolemia Is Associated with a Shorter Time to Castration-Resistant Prostate Cancer in Patients Who Have Undergone Androgen Deprivation Therapy

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Purpose: The goal of this study was to investigate the association between hypercholesterolemia and the time required for progression to castration-resistant prostate cancer (CRPC) in patients who have undergone androgen deprivation therapy (ADT).

Materials and Methods: Data from 154 patients with prostate cancer between 2005 and 2012 were reviewed retrospectively. ADT was employed as a treatment modality for these patients either due to multiple bone metastases at the time of diagnosis or due to old age in combination with other morbidities. Serum cholesterol levels and statin use were reviewed. We analyzed the factors associated with the development of CRPC after ADT treatment. The mean follow-up period was 34.8 months.

Results: The mean age of the patients was 71.3 years old and their mean prostate-specific antigen level was 141.8 ± 212.6 ng/mL. Their mean cholesterol level was 175.9 ± 37.7 mg/dL, and 14 patients (9.1%) were statin users. CRPC developed in 44 patients (28.6%), and the mean duration from ADT treatment to CRPC was 24.1 months. In a multivariate analysis, hypercholesterolemia was associated with the development of CRPC (hazard ratio [HR] = 1.017, $p < 0.001$), depending on clinical T stage ($p = 0.005$) and the presence of bone metastasis ($p < 0.001$). A subanalysis showed that hypercholesterolemia was associated with the development of CRPC in patients with bone metastasis (HR = 1.032, $p < 0.001$), but not in patients without bone metastasis.

Conclusions: Hypercholesterolemia may be associated with the development of CRPC after ADT in patients with bone metastasis. Further studies with longer follow-up periods and larger samples are needed to validate this finding.

Key Words: Cholesterol; Prognosis; Prostatic neoplasms

INTRODUCTION

Prostate cancer is the second leading cause of cancer death in men in the United States [1]. Prostatectomy and radiation therapy are the preferred treatment modalities in

men with localized prostate cancer. Androgen deprivation therapy (ADT) is used as an adjuvant therapy after radical prostatectomy and for the treatment of metastatic prostate cancer. Although prostate cancer is generally sensitive to initial ADT, tumors that have overcome the absence

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of gonadal androgens eventually regrow [2]. When prostate cancer progresses despite castration levels of testosterone, it is termed castration-resistant prostate cancer (CRPC) a term that reflects the knowledge that such cases of re-emergent prostate cancer are not independent of androgens, as was once believed. Unfortunately, recurrent tumors are more aggressive, evasive, and deadly [3], and most prostate cancer deaths are from CRPC.

Cholesterol has been implicated in the pathogenesis of diseases such as cardiovascular disease and in many forms of cancer, including prostate cancer [4]. Prostate cancer is associated with elevated levels of cholesterol, which may support cell proliferation by contributing cholesterol for membrane composition and signal transduction [5,6]. Based on these findings, several studies have explored the relationship between serum cholesterol levels and the incidence of prostate cancer and associated mortality. However, these studies have reported inconsistent results [7-11]. Similarly, the effects of statins on the overall risk reduction of prostate cancer remains controversial [12-14], with some studies suggesting that statins have no effect, while others have found statins to be associated with significant risk reduction, especially in advanced-stage tumors [15,16]. However, previous research has not addressed the relationship between levels of cholesterol and tumor progression to CRPC in patients with prostate cancer.

In this study, we aimed to investigate the potential association between hypercholesterolemia and the risk of progression to CRPC in men who have undergone ADT.

MATERIALS AND METHODS

1. Patient characteristics

After Institutional Review Board approval in Ulsan University Hospital (No. 2015-06-009), data from 314 patients who were diagnosed with prostate cancer from 2005 to 2012 were reviewed retrospectively. After excluding 160 patients who underwent radical prostatectomy or were transferred to other clinics, 154 patients who were initially treated with ADT were included. ADT was employed as a treatment modality for these patients either due to multiple bone metastases at the time of diagnosis ($n = 50$, 32.5%) or due to old age accompanied by other

morbidities ($n = 104$, 67.5%), instead of radical prostatectomy or radiotherapy. ADT involved bilateral orchiectomy in nine patients and maximal androgen blockade including luteinizing hormone-releasing hormone agonist injection and oral antiandrogens in 145 patients. The primary outcome was the time to prostate-specific antigen (PSA) progression. In patients with castration serum levels of testosterone (< 50 ng/dL), the time to PSA progression indicative of CRPC while undergoing ADT was defined as the time from the initiation of ADT to a 50% increase in PSA from its lowest level or the time from the initiation of ADT to a 25% increase in PSA levels from baseline, and was confirmed using PSA consensus criteria [17]. The mean follow-up was 34.8 months (median, 25.4 months).

2. Cholesterol levels and statin use

Patients' levels of serum cholesterol at diagnosis and statin use were reviewed. The levels of serum cholesterol were available in all patients. Cholesterol levels were categorized as hypercholesterolemia (> 240 mg/dL, $n = 8$), borderline (200~240 mg/dL, $n = 40$) and desirable (< 200 mg/dL, $n = 106$). High- and low-density lipoprotein (HDL and LDL) cholesterol levels were not present for all patients and, therefore, were not included in the analysis. Patients who took statins before being diagnosed with prostate cancer were categorized as statin users. The statins used in these patients included atorvastatin ($n = 6$), simvastatin ($n = 4$), pravastatin ($n = 2$), and rosuvastatin ($n = 2$). The doses of statin were translated into dose equivalents based on previous published study [18], with 20 mg of simvastatin assigned a value of 1. Dose equivalents of < 1 , 1, and > 1 were present in two patients (14.3%), nine patients (64.3%), and three patients (21.4%), respectively. The duration of statin use was not evaluated.

3. Statistical analyses

Clinicopathological characteristics were compared between patients with and without bone metastasis at the time of diagnosis using the chi-square test and the Student's t-test. Multivariate analysis was performed to evaluate the factors associated with the development of CRPC after ADT treatment. Since statin use and cholesterol could affect each other, multivariate analysis was performed again, including statin use instead of cholesterol. A subanalysis

was performed according to the presence of bone metastasis at the initial diagnosis. PSA levels were measured every three months after ADT treatment. Radiographic evaluation using abdominopelvic computed tomography or pelvic magnetic resonance and radionuclide bone scanning was performed every six months and when clinically indicated. None of the patients experienced severe complications requiring the discontinuation of ADT therapy. SPSS ver. 12.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses, with p -values < 0.05 considered to indicate statistical significance.

RESULTS

The mean age of the patients was 71.3 years old, and their mean PSA level was 141.8 ± 212.6 ng/mL at the time of diagnosis (range, 1.5 ~ 876 ng/mL). The clinical T stage was T1 or T2 in 72 patients (46.8%), T3 in 64 patients (41.6%), and T4 in 18 patients (11.7%). The Gleason score (GS) was ≤ 6 in 34 patients (22.1%), 7 in 62 patients (40.3%), and ≥ 8 in 58 patients (37.7%). The mean level of serum cholesterol was 175.9 ± 37.7 mg/dL and 14 pa-

tients (9.1%) were statin users. Patients without bone metastasis had lower PSA levels (84.8 ng/mL vs. 304.6 ng/mL) and lower cholesterol levels (172.4 mg/dL vs. 185.9 mg/dL) than those with bone metastasis (Table 1). Furthermore, patients without bone metastasis had lower GSs and less advanced T stage findings than patients with bone metastasis.

CRPC developed in 44 patients (28.6%) and the mean duration from ADT treatment to CRPC was 24.1 months. CRPC developed in 16 patients (10.4%) of the patients without bone metastasis, with a mean duration of 24.8 months, and 10 patients exhibited newly developed bone metastasis when CRPC was diagnosed. In contrast, CRPC developed in 28 patients (56.0%) with bone metastasis, with a mean duration of 23.6 months, and all patients in this group exhibited aggravated metastatic bone lesions when CRPC was diagnosed. In multivariate analysis, hypercholesterolemia was associated with the development of CRPC (hazard ratio [HR] = 1.017, $p < 0.001$), depending on the clinical T stage (HR = 4.493, $p = 0.005$ for T3 vs. HR = 15.98, $p < 0.001$ for T4), and the presence of bone metastasis (HR = 7.578, $p < 0.001$) (Table 2). Statin use

Table 1. Baseline characteristics of the patients

Variable	Patients without bone metastasis at diagnosis	Patients with bone metastasis at diagnosis	p-value
Total patient	114 (74.0)	40 (26.0)	
Age (yr)	71.8 ± 6.3	70.5 ± 9.0	0.297
Diabetes mellitus	10 (8.8)	4 (10.0)	0.816
Cholesterol (mg/dL)	172.4 ± 35.6	185.9 ± 42.0	0.042
Statin use (%)	12 (10.5)	2 (5.0)	0.296
PSA (ng/mL)	84.8 ± 140.9	304.6 ± 288.4	< 0.001
Biopsy Gleason score			< 0.003
≤ 6	32 (28.1)	2 (5.0)	
7	46 (40.4)	16 (40.0)	
≥ 8	36 (31.6)	22 (55.0)	
Clinical T stage ^a			< 0.001
T1 ~ 2	70 (61.4)	2 (5.0)	
T3	38 (33.3)	26 (65.0)	
T4	6 (5.3)	12 (30.0)	
Clinical N stage ^a			< 0.001
N0	100 (87.7)	24 (60.0)	
N1	14 (12.3)	16 (40.0)	

Values are presented as number (%) or mean \pm standard deviation.

PSA: prostate-specific antigen.

^aClassification according to the standard of 7th edition of the American Joint Committee on Cancer staging system.

Table 2. Multivariate model for time to PSA progression according to age and clinical variables

Variable	HR	95% CI	p-value
Age	0.980	0.939~1.024	0.373
PSA	0.999	0.997~1.000	0.097
Diabetes mellitus	1.692	0.667~4.293	0.269
Cholesterol	1.017	1.009~1.025	<0.001
Biopsy Gleason score			
≤6	Reference	-	-
7	0.619	0.171~2.240	0.465
≥8	1.048	0.292~3.769	0.942
Clinical T stage ^a			
T1~2	Reference	-	-
T3	4.493	1.557~12.957	0.005
T4	15.984	3.885~65.798	<0.001
Clinical N stage ^a			
N0	Reference	-	-
N1	1.713	0.796~3.687	0.169
Bone metastasis at diagnosis	7.578	3.269~17.564	<0.001

PSA: prostate-specific antigen, HR: hazard ratio, CI: confidence interval.

^aClassification according to the standard of 7th edition of the American Joint Committee on Cancer staging system.

Table 3. Multivariate model for time to PSA progression according to age and clinical variables in patients with bone metastasis at diagnosis

Variable	HR	95% CI	p-value
Age	0.881	0.799~0.972	0.011
PSA	0.996	0.993~0.999	0.007
Diabetes mellitus	1.668	0.314~8.862	0.548
Cholesterol	1.032	1.016~1.048	<0.001
Biopsy Gleason score			
≤6	Reference	-	-
7	0.015	0.001~0.240	0.003
≥8	0.136	0.017~1.069	0.058
Clinical T stage ^a			
T1~2	Reference	-	-
T3	15.523	1.677~143.573	0.016
T4	43.051	3.595~515.589	0.003
Clinical N stage ^a			
N0	Reference	-	-
N1	1.073	0.302~3.818	0.913

PSA: prostate-specific antigen, HR: hazard ratio, CI: confidence interval.

^aClassification according to the standard of 7th edition of the American Joint Committee on Cancer staging system.

Table 4. Multivariate model for time to PSA progression according to age and clinical variables in patients without bone metastasis at diagnosis

Variable	HR	95% CI	p-value
Age	1.034	0.932~1.148	0.527
PSA	0.998	0.994~1.002	0.297
Diabetes mellitus	2.689	0.603~11.982	0.194
Cholesterol	0.984	0.965~1.004	0.115
Biopsy Gleason score			
≤6	Reference	-	-
7	1.413	0.250~7.999	0.696
≥8	0.717	0.080~6.459	0.767
Clinical T stage ^a			
T1~2	Reference	-	-
T3	7.967	1.527~41.545	0.014
T4	16.664	1.758~157.892	0.014
Clinical N stage ^a			
N0	Reference	-	-
N1	5.716	1.077~30.329	0.041

PSA: prostate-specific antigen, HR: hazard ratio, CI: confidence interval.

^aClassification according to the standard of 7th edition of the American Joint Committee on Cancer staging system.

was not associated with the development of CRPC. In the subanalysis, hypercholesterolemia was associated with the development of CRPC in patients with bone metastasis at diagnosis (HR = 1.032, p < 0.001) (Table 3). However, in patients without bone metastasis, hypercholesterolemia was not associated with the development of CRPC (Table 4).

DISCUSSION

In this cohort, patients without bone metastasis were found to have lower cholesterol levels than patients with bone metastasis. Our findings are comparable with those from other studies, which have shown an inverse association between statin use and the risk of advanced-stage and high-grade disease, with or without M1 lesions [15,16,19,20]. After excluding statin users, the inverse associations for high-grade tumors persisted. This finding suggests that cholesterol itself may play a role in pathogenesis. The mechanisms through which statins inhibit cancer processes can be classified into cholesterol-mediated and non-cholesterol-mediated mechanisms [12]. Statins decrease cholesterol levels by inhibiting HMG-CoA reductase.

Cholesterol is a major component of lipid rafts, which are involved in signaling pathways regulating prostate cancer cell survival and proliferation [12,21]. Additionally, statins may influence the rate of prostate cancer progression by inhibiting the synthesis of isoprenoids. In observational studies, statin use has been found to be associated with a reduced risk of aggressive prostate cancer [15,16]. However, previous studies analyzing the relationship between cholesterol levels and the incidence of aggressive prostate cancer have reported inconsistent conclusions [7-11]. A possible explanation for these discrepancies is the possibility that cholesterol levels in the environment of the tumor may not be reflective of serum levels.

The present study found hypercholesterolemia to be associated with the development of CRPC after ADT in patients with bone metastasis at the time of the initial diagnosis of prostate cancer. Similarly, a previous study evaluating the association of cholesterol levels with grades of prostate cancer found that men with higher cholesterol levels (> 240 mg/dL) were more likely to develop high-grade or rapidly growing metastatic prostate cancer than men with desirable (< 200 mg/dL) or borderline levels (200 ~ 240 mg/dL) [9]. However, in the present study, it was found that the development of CRPC was not associated with the presence of high, borderline, or desirable cholesterol levels. While cholesterol levels have been reported to increase concomitantly with the transition from non-cancerous to cancerous prostate epithelial cells [22], little is known about how this correlates with the progression to CRPC. A previous study reported that cholesterol homeostasis can be maintained during the progression of prostate cancer [23]. If CRPC cells maintain cholesterol homeostasis, cholesterol accumulation will occur during the progression to the advanced stage of prostate cancer. Thus, hypercholesterolemia at the time of prostate cancer diagnosis might imply that the disease has progressed. However, the relationship between hypercholesterolemia and tumor progression has not yet been fully elucidated. It has not been conclusively determined whether initiating cholesterol-lowering drugs (statins) after the diagnosis of prostate cancer is capable of delaying disease progression.

In this study, statin use was not associated with the development of CRPC (data not shown). Furthermore, the

type and dose of statin were not associated with the development of CRPC. However, considering the cholesterol-lowering effect of statins and the fact that previous studies have demonstrated an association between statins and less progressive prostate cancer, it is possible that further studies with larger populations may lead to meaningful results.

This study has some limitations. First, the present study included a relatively small sample size and was a retrospective study. Second, LDL and HDL cholesterol levels were not analyzed. LDL cholesterol levels are more strongly associated with prostate cancer recurrence after radiotherapy than total cholesterol levels [24]. Nonetheless, our study suggested that hypercholesterolemia may be associated with the development of CRPC in patients with bone metastasis at the time of diagnosis. Clinicians may wish to consider cholesterol levels as a prognostic factor in metastatic prostate cancer before starting ADT treatment.

CONCLUSIONS

Hypercholesterolemia may be associated with the development of CRPC after ADT in patients with bone metastasis. Further studies with longer periods of follow-up and larger samples will be needed to validate this finding.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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