



# Association between CYP17A1 polymorphisms and response to abiraterone in patients with metastatic castration-resistant prostate cancer: a systematic review

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**Contributions:** (I) Conception and design: X Zhou, X Li; (II) Administrative support: X Li; (III) Provision of study material or patients: X Zhou, Y Zheng, J Zhang; (IV) Collection and assembly of data: X Zhou, Y Zheng, J Zhang; (V) Data analysis and interpretation: X Zhou, Y Zheng, X Li; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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**Abstract:** We aimed to summarize and clarify the association between cytochrome P450 17 $\alpha$ -hydroxylase (CYP17A1) polymorphisms and outcomes of patients with metastatic castration-resistant prostate cancer (mCRPC) treated with abiraterone. The databases of PubMed, EMBASE, and Web of Science were searched for relevant studies. Overall survival (OS) and/or progression-free survival (PFS) were calculated. Odds ratios (ORs) and/or hazard ratios (HRs) with 95% confidence interval (CI) were utilized to evaluate the strength of the association. A total of 3 studies including 204 patients were analyzed in this systematic review. It was shown that CYP17A1 copy number variations were related to the prognosis of mCRPC patients treated with abiraterone. In addition, rs2486758, a common single-nucleotide polymorphisms (SNPs) in CYP17A1, was significantly associated with a poor biochemical response and a faster biochemical progression. Our systematic review showed that CYP17A1 polymorphisms are associated with response to abiraterone in mCRPC patients. Further research is needed to translate these findings into clinical decisive parameters.

**Keywords:** Cytochrome P450 17 $\alpha$ -hydroxylase (CYP17A1); polymorphisms; metastatic castration-resistant prostate cancer (mCRPC); abiraterone

Received: 01 December 2017; Accepted: 10 January 2018; Published: 03 April 2018.

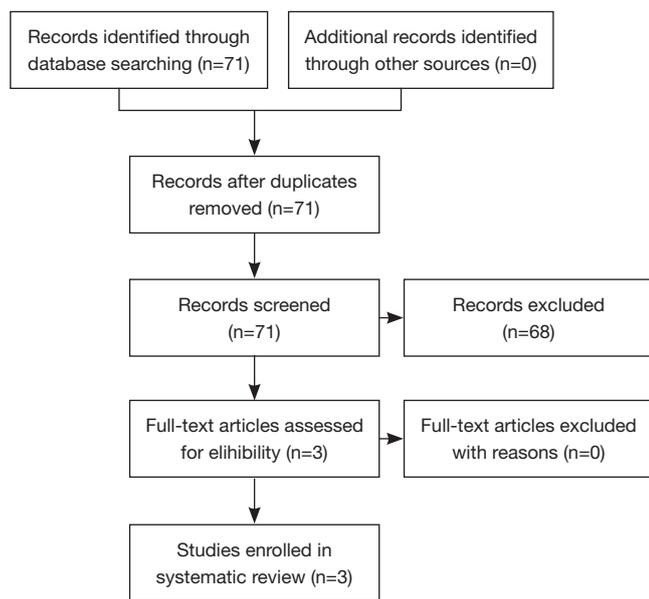
doi: 10.21037/amj.2018.01.11

**View this article at:** <http://dx.doi.org/10.21037/amj.2018.01.11>

## Introduction

Prostate cancer (PC) is expected to affect 161,360 men in the US, accounting for almost 20% of new cancer cases diagnosed in 2017 (1,2). Due to the availability of PSA,

most patients are diagnosed with PC in an early stage. At the same time, metastatic disease is only found in 4% of new cases in America and nearly 10% to 20% in Europe (3,4).



**Figure 1** Flow diagram of the selection process.

Despite apparently effective primary treatment is in general performed, more than 30% of PC patients experience disease progression. Many of these patients and almost all metastatic receive androgen deprivation therapy (ADT) with or without chemotherapy. However, almost all patients eventually experience disease progression to the castration-resistant state. The median time of this is approximately 1 year (5,6). 5-year survival rate of patients with metastatic disease is limited to 25–30% (7).

Abiraterone is an oral, selective and irreversible inhibitor of the cytochrome P450 17-hydroxylase (CYP17A1) enzyme (8). One of the functions of abiraterone is to suppress the biosynthesis of testosterone in adrenal glands, testicles and tumour microenvironment, accounting for CYP17A1 catalyzing key reactions in sex-steroid hormone biosynthesis (9). Two phase III trials demonstrated a clear improvement in overall survival (OS) and progression-free survival (PFS) in patients with CRPC (10,11). Based on these data, abiraterone was approved in the United States and Europe for the treatment of CRPC patients regardless of docetaxel treatment (3). However, response to abiraterone is highly heterogeneous with many patients experiencing early failure of therapy. So, it is of great importance to identify particular patients who may benefit the most from the treatment of abiraterone, so that patients who are unlikely to benefit can be allocated to one of other therapies for management of CRPC. A biomarker that could

help in personalized selection is likely to improve survival while reducing adverse events in this late stage of PC.

CYP17A1 is located on chromosome 19q23.4 and is clarified to be correlated to cardiovascular diseases through affecting blood pressure (12). CYP17A1 is an important target in treatment of PC. A PC experimental model indicated that alterations of CYP14A1 activity may be mechanisms of resistance to hormonal treatment (13,14). In one retrospective study, CYP17A1 polymorphisms appeared to be associated with the median PFS and OS in patients with CRPC (15). Conflicting results on CYP17A1 polymorphisms on abiraterone response have been reported (16,17).

Therefore, we conducted this systematic review to provide a more comprehensive understanding.

## Material and methods

### Search strategy

Potential articles included up to date, June 7, 2017. We conducted a systematic search on search engines such as PubMed, EMBASE and Web of Science, based on the ‘PRISMA’ guideline (18). There was no languages limitation. We used the following search term strategies: (“steroid 17-alpha-hydroxylase”, or “CYP17A1”), (“abiraterone”) and (“metastatic castration-resistant prostate cancer”, or “mCRPC”). To discover all studies, we screened the references of all relevant publications. A flow diagram of the research selection process is shown in *Figure 1*.

### Inclusion criteria and exclusion criteria

The inclusion criteria were shown as follows: (I) studies assessing the relationship between CYP17A1 polymorphisms and outcomes of mCRPC patients treated with abiraterone; and (II) different studies without overlapped available data. The following exclusion criteria were applied: (I) studies missing outcomes of patients with mCRPC; and (II) overlapped data appearing in studies.

### Data extraction

All valuable data of included studies were extracted by two independent investigators (X Z and X L). The following information was extracted: name of first author, year of publication, ethnicity, numbers of patients, age, PSA, abiraterone treatment scheme, sample collection method,

**Table 1** Main characteristics of involved studies in this systematic review

First author	Year	Ethnicity	No. of patients	Age <sup>#</sup>	PSA <sup>*</sup>	Treatment	Detected sample	CYP17A1 polymorphism	Gleason score		ECOG performance status		Sites of metastasis		No. of previous chemotherapeutic lines	NOS		
									6-7	8-9	Unknown	0-1	2	Bone metastases			Soft tissue metastases	1
Samanta Salvi (17)	2016	Caucasian	64	73 [57-90]	33.1 <sup>a</sup> (0.35-1,501)	Abiraterone/prednisone	Blood	rs743572/ rs10883783/ rs17115100/ rs284849	NR	36	5	57	1	55	47	30	34	9
Moritz Binder (16)	2016	NR	87	73 [54-90]	66 <sup>b</sup> (0-100)	Abiraterone/prednisone	Blood	rs743572/ rs4919685/ rs17115100/ rs2486758	NR	NR	NR	NR	NR	73	43	56	NR	7
Samanta Salvi (15)	2015	NR	N:38 A:15	N:73 [57-87] A:76 [57-86]	N:21.9 <sup>a</sup> (1-1,501) A:294.2 <sup>b</sup> (13.8-1,435)	Abiraterone/prednisone	Blood	Normal Amplified	N:16 A:7	N:22 A:7	N:- A:1	N:36 A:10	N:2 A:5	N:31 A:13	N:8 A:4	N:20 A:5	N:8 A:10	9

<sup>#</sup>, median age at start of abiraterone treatment (years, range); <sup>\*</sup>, median baseline PSA level; a, ng/mL (range); b, ng/dL (range); NR, not reported; N, normal; A, amplified; ECOG, Eastern Cooperative Oncology Group.

CYP17A1 polymorphisms, Gleason score, Eastern Cooperative Oncology Group (ECOG) performance status, site of metastasis and number of previous chemotherapeutic lines. Hazard ratios (HRs) and odds ratios (ORs) with 95% confidence intervals (CI) in PFS and OS were else extracted from included studies. All detailed information mentioned above is shown in *Tables 1-4*. In addition, Newcastle-Ottawa Scale (NOS) was adopted to evaluate the quality of all studies based on three domains: selection of cohort, comparability of cohorts, assessment of outcomes. The NOS ranges from 0 to 9. The  $\geq 7$  was identified to distinguish studies with high quality.

### Results

A total of 3 separate studies with 204 individual patients were found (15-17). The median age at start of abiraterone treatment ranged from 54 to 90 years old, and DNA was extracted from blood in all patients. Prior to the start of abiraterone treatment, median baseline PSA level, ECOG performance status, site of metastasis and number of previous chemotherapeutic lines containing docetaxel were assessed in two studies to identify whether patients met eligibility criteria. The third study only reported sites of metastasis, median baseline PSA level and previous ADT use as well as exposure to docetaxel, enzalutamide and cabazitaxel. Ethnicity of patients was mentioned in only one study. The detailed information of these studies is shown in *Table 1*.

Summary of results of the association between CYP17A1 polymorphisms and outcomes of mCRPC patients treated with abiraterone are shown in *Tables 2-4*. All patients received abiraterone acetate and prednisone, 28-day cycles of 1,000 mg abiraterone acetate daily with 5 mg prednisone twice-daily. Median PFS and OS of patients were reported in two studies. Biochemical response to treatment was defined as PSA decrease of  $\geq 50\%$  after starting abiraterone acetate and prednisone. Time to biochemical progression was set as PSA increase of  $>25\%$  on two consecutive tests at least two weeks apart. Salvi *et al.* reported CYP17A1 copy number variations had an association with worse prognosis of abiraterone therapy in mCRPC patients. According to their retrospective analysis, patients with amplified CYP17A1 had significantly a shorter median PFS compared to those with normal CYP17A1 (HR =2.20; 95% CI: 1.02-4.77; P=0.045). This study revealed no statistic association between CYP17A1 copy number variations and

**Table 2** Main results of the association between CYP17A1 polymorphisms and outcomes of mCRPC patients treated with abiraterone of Reference 15

First author	CYP17A1 polymorphism	Progression-free survival			Overall survival		
		HR	95% CI	P value	HR	95% CI	P value
Samanta Salvi	Amplified	2.20	1.02–4.77	0.0450	0.92	0.37–2.29	0.8576
	Normal						

CYP17A1, cytochrome P450 17 $\alpha$ -hydrolase; mCRPC, metastatic castration-resistant prostate cancer; HR, hazard ratio; CI, confidence interval.

**Table 3** Summary results of the association between CYP17A1 polymorphisms and outcomes of mCRPC patients treated with abiraterone of Reference 16

First author	CYP17A1 polymorphism	Biochemical response to treatment			Time to biochemical progression		
		OR	95% CI	P value	HR	95% CI	P value
Moritz Binder	rs17115100	0.82	0.31–2.19	0.689	0.95	0.67–1.35	0.693
	rs743572	1.13	0.58–2.20	0.718	1.03	0.73–1.46	0.889
	rs4919685	1.24	0.64–2.40	0.524	0.82	0.47–1.42	0.429
	rs2486758	0.22	0.07–0.63	0.005	2.23	1.39–3.56	<0.001

CYP17A1, cytochrome P450 17 $\alpha$ -hydrolase; mCRPC, metastatic castration-resistant prostate cancer; OR, odds ratio; HR, hazard ratio; CI, confidence interval.

**Table 4** Summary results of the association between CYP17A1 polymorphisms and outcomes of mCRPC patients treated with abiraterone of Reference 17

First author	CYP17A1 polymorphism	Allele/genotype	PFS			OS		
			Median months	95% CI	P value	Median months	95% CI	P value
Samanta Salvi	rs743572	AA	7.0	4.1–12.7	0.6474	11.8	8.8–19.0	0.4825
		GA + GG	7.2	4.2–11.0		17.7	10.8–26.4	
	rs17115100	GG	6.8	4.6–10.5	0.4054	14.9	10.4–22.3	0.9825
		TG + TT	9.5	2.4–15.0		17.7	6.6–26.4	
	rs10883783	TT	8.5	6.4–12.7	0.5586	17.7	9.6–22.0	0.7668
		TA + AA	5.4	3.4–11.0		17.6	10.5–NR	
	rs284849	GG	9.2	4.0–11.4	0.8282	18.6	11.4–NR	0.5188
		TG + GG	6.7	4.3–9.2		11.8	9.2–22.3	

CYP17A1, cytochrome P450 17 $\alpha$ -hydrolase; mCRPC, metastatic castration-resistant prostate cancer; PFS, progression-free survival; OS, overall survival; CI, confidence interval.

OS (HR =0.92; 95% CI: 0.37–2.29; P=0.86) (Table 2) (15). Furthermore, Binder *et al.* reported that the rs2486758 polymorphism (allele C *vs.* T) was significantly associated with a poor biochemical response (OR =0.22; 95% CI: 0.07–0.63; P=0.005) and a short time to biochemical progression (HR =2.23; 95% CI: 1.39–3.56; P<0.001) (Table 3) (16). However, no significant associations between single-nucleotide polymorphisms (SNPs) in CYP17A1 and clinical outcome, such as PFS and OS, were reported by Salvi *et al.* (Table 4) (17).

## Discussion

Abiraterone acetate irreversibly inhibits CYP17. CYP17 is a critical enzyme in the testosterone biosynthesis, playing an essential role in two sequential reactions: (I) transforming pregnenolone and progesterone to their 17-hydroxy derivatives; and (II) taking part in the formation of dehydroepiandrosterone (DHEA) and androstenedione. Besides the aforementioned information, one study indicated anti-tumor role of abiraterone by activating D4A metabolite, presumably through the blockade of multiple

steroidogenic enzymes and antagonism of the androgen receptor (19). Treatment with abiraterone and prednisone has been demonstrated to greatly improve OS in patients with mCRPC regardless of docetaxel pretreatment (20-25). Recently, a network meta-analysis suggested that abiraterone is the second-most efficacious drug for improving OS in mCRPC patients, after Enzalutamide (26). Though grade 1 or 2 treatment-related adverse events are observed, abiraterone plus prednisone is generally well tolerated in well selected patients (11,27). In addition, a meta-analysis revealed Grade 3-4 complications (fatigue, back pain, anaemia, and bone pain) appeared in less than 10% of patients compared to placebo (28), and only heart failure and grade 3 hyper-transaminase required interruption of abiraterone (29).

Identification of variations in the particular predictive targets of outcome in mCRPC patients treated with abiraterone could assist in distinguishing who will actually benefit from this therapy. However, neither Gleason Score nor type and duration of prior endocrine therapies were evaluated as predictive elements (30,31). CYP17A1 is a potential biomarker that can be future assessed. It is the target of abiraterone and its polymorphisms might predict response to abiraterone in mCRPC patients.

In our review of literature, we could demonstrate that CYP17A1 polymorphisms was statistically associated with the outcomes of mCRPC patients treated with abiraterone. Patients with amplified CYP17A1 seem to experience a worse PFS (15), and amplification of CYP17A1 was associated with a higher expression of CYP17A1. When abiraterone was taken by men, CYP17A1 molecules were partly restricted and cancer was capable of going on with biosynthesis of testosterone (30,32). Modification of splicing process and mechanisms, as well as other pathways, may be utilized by SNPs in gene to change its expression level (33,34). The rs2486758 polymorphism was a predictor of patients with mCRPC (16). The rs2486758 is located in the promoter region of CYP17A1 and consequent up-transcription of CYP17A1 may be responsible for the increased risk (35). However 4 common SNPs, rs743572, rs17115100, rs10883783 and rs284849, were genotyped, but none should be significantly associated with clinical outcomes in mCRPC patients. The drug's wide therapeutic window may be responsible for this result. To reduce the false positive rate, large case series studies and investigations of other SNPs based on better comprehension of therapeutic window of abiraterone are still needed (17).

Our review suffers from several limitations. First, only

3 eligible studies focusing on CYP17A1 polymorphism and outcome of mCRPC patients treated with abiraterone were included in this systematic review. More high-quality, larger sample size studies are required to acquire further confirmation. Second, CYP17A1 polymorphisms were correlated with outcome in only two studies, which limits our conclusion.

In conclusion, we found that CYP17A1 polymorphisms were predictive of response to abiraterone therapy in patients with mCRPC. Our review endorses further research in these biomarkers to serve clinical decision making for patients with mCRPC.

### Acknowledgements

*Funding:* None.

### Footnote

*Conflicts of Interest:* The authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/amj.2018.01.11>). Dr. Xiao Li serves as an unpaid section editor of *AME Medical Journal*. The other authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/amj.2018.01.11

**Cite this article as:** Zhou X, Zheng Y, Zhang J, Zhang C, Jiang G, Sun S, Li X, Carrie C, Shariat SF, Lopez DS, Nielsen TK; on behalf of AME Urology Disease Collaborative Group. Association between CYP17A1 polymorphisms and response to abiraterone in patients with metastatic castration-resistant prostate cancer: a systematic review. *AME Med J* 2018;3:50.