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Original Article

Association of estrogen receptor alpha gene polymorphisms with the risk, therapeutic outcome and prognosis of ADT-resistant prostate cancer in Chinese Han population

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Abstract: Estrogen receptor alpha (ESRα) gene expresses in prostate stromal cells and may associate with prostate cancer risk, while the relationship between ESRα polymorphisms and therapeutic outcome as well as prognosis of patients with prostate cancer in Chinese Han population has not been clarified. Genotypes of rs2234693 and rs9340799 in ESRα gene were detected in 168 ADT-resistant patients with prostate cancer and 220 healthy controls by PCR-RFLP. The associations of these polymorphisms with the risk, object response rate (ORR), disease control rate (DCR) and progression free survival (PFS) of prostate cancer were analyzed by chi-square test, Kaplan-Meier method and log-rank test. The distributions of rs2234693 and rs9340799 genotypes in patients and controls were significantly difference (all $P<0.05$). ORR was significantly higher in TT genotype of rs2234693 ($X^2=7.288$, $P=0.026$) or GG genotype of rs9340799 ($X^2=9.118$, $P=0.010$) carriers. DCR was no significantly difference among each genotypes (rs2234693: $X^2=4.541$, $P=0.103$; rs9340799: $X^2=5.063$, $P=0.080$). Median PFS (mPFS) in T-allele of rs2234693 carriers were 1.33 folds higher than CC carriers (Log rank $P<0.05$), while mPFS in combined cohort of GA+AA of rs9340799 was 2 folds higher than GG carriers (Log rank $P<0.05$). Stratified by Gleason score, the mPFS in CT and the combined cohort of CT+TT of rs2234693 carriers were 1.5 folders higher than that in CC (Log rank $P<0.05$) carried patients with lower (≤6) Gleason score. The polymorphisms rs2234693 and rs9340799 in ESRα gene were associated with the therapeutic outcome and short-term prognosis of patients with ADT-resistant prostate cancer in Chinese Han population, and could be considered a valuable biomarker for survival.

Keywords: Estrogen receptor alpha, polymorphism, prostate cancer, therapeutic outcome, prognosis, association

Introduction

Prostate cancer has become one of the most common non-skin malignancies among men with an incidence of approximately 0.01% worldwide, whose mortality has also dramatically increased in China [1, 2]. Efficacious therapy is beneficial to improve the outcomes and reduce the mortality of prostate cancer, while androgen deprivation therapy (ADT) has been identified to be useful in approximately 80% of untreated patients with prostate cancer [3]. Nevertheless, the prognosis of the patients with the disorder, especially metastatic and ADT-resistant cancer, remains poor [4]. Hence, the prediction of therapeutic outcome and prognosis through their risk factors are important for patients' survival and treatment options.

To date, biomarkers, such as prostate specific antigen (PSA), have been approved for use in the detection and prognosis evaluation for prostate cancer [5]. Various gene polymorphisms including single nucleotide polymorphisms (SNPs) have also been considered to be that valuable biomarkers [6]. Association studies have found several susceptible genes for prostate cancer risk, such as CYP19A1, RNASEL, MTHR, and XRCC1, while SNPs in these genes were strongly associated with oncogenesis of prostate [7, 8]. Furthermore, the susceptible genes may also have a potential ability for predicting therapeutic outcomes

Table 1. Demographic and clinical characteristics of participants

Characteristics	Patients	Controls	*P*
Sample size	168	220	
Age (years)	57.76±8.50	56.49±9.28	0.17
Smoke history (*N*)	53 (31.55%)	66 (30.00%)	0.81
Drink history (*N*)	24 (14.29%)	29 (13.18%)	0.82
BMI (kg/m^2)	20.53±4.56	20.87±4.22	0.45
PSA at diagnosis (*N*)			
<10	112 (66.67%)		
10-20	40 (23.81%)		
>20	16 (9.52%)		
Clinical stage* (*N*)			
T1/T2	56 (33.33%)		
T3/T4/N1	73 (43.45%)		
M1	39 (23.22%)		
Gleason score (*N*)			
≤6	60 (35.72%)		
7	77 (45.83%)		
≥8	31 (18.45%)		

*Clinical stage diagnostic criteria of AJCC 2010.

and prognosis of survival [9, 10]. Prostate cancer patients with variant allele of rs4775936 in CYP19A1 have significantly shorter cancer-specific survival [11], and patients carried rs12757998 variant allele in RNASEL may be more sensitive to radiation therapy [7].

Estrogen receptor alpha (ESRα), expressed in prostate stromal cells, have important biological functions of promoting epithelial cell proliferation and stimulating growth factors release [12]. ESRα gene polymorphism has also been found susceptibility to prostate cancer [13]. Individuals with C-allele of rs2234693 in ESRα may have a significantly increased risk of prostate cancer [14, 15], although some other studies suggested no association of ESRα with prostate cancer risk [8, 16, 17]. Even so, the expression of ESRα have also found in many prostate cancers, and negatively correlated with prognosis survival [18]. However, the association of SNPs in ESRα gene with the therapeutic outcome and prognosis of prostate cancer in Chinese Han population has not been clarified.

In the present study, we hypothesized that polymorphisms in ESRα gene are associated with therapeutic outcome and prognosis of ADT-resistant prostate cancer in Chinese Han population. Then two common SNPs (rs2234693 and rs9340799) in ESRα gene were selected due to their potential risk for prostate cancer. Our results revealed that these two gene polymorphisms were crudely associated with the risk of prostate cancer, and patients with TT genotype in rs2234693 or GG genotype in rs9340799 may have significantly higher object response rate (ORR) after treatment by Docetaxel-based chemotherapy, meanwhile T-allele and A-allele carriers had significantly longer progression free survival (PFS).

Materials and methods

Subjects

One hundred and eighty-two in patients with prostate cancer were recruited from the Xinxiang Central Hospital and affiliated regional hospitals of Xinxiang and Anyang in North of China. But fourteen patients were excluded by the poor quality of DNA amplifications. Finally, one hundred and sixty-eight patients with prostate adenocarcinoma cancer were included and further stratified by Gleason Grading System (2-6 scores as well differentiated, *N*=60; 7 scores as moderately differentiated, *N*=77; 8-10 scores as poorly differentiated, *N*=31) [19]. All pathological diagnosis and Gleason score were evaluated independently by at least two pathologists and clinicians in Xinxiang Central Hospital. All patients in the study had received standardized ADT, but due to the ADT-resistance, they had to transfer to Docetaxel-based chemotherapy under the guidance of NCCN in China (http://www.nccnchina.org/). The follow up of the study was 1 to 24 months, and the median follow-up was 8 months. Meanwhile, two hundred and twenty healthy controls with high quality of DNA sample and without complex disorders including hypertension, diabetes, immunological mediated disease, mental disorders, and cancers were selected from located Henan province. All participants in the study were male Chinese Hans. All subjects consented to participate in the study after reviewing the informed consent. The study was approved by the Institutional Ethics Committee of Xinxiang Central Hospital. All procedures performed in the study were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The demographic and clinical characteristics of the participants were showed in **Table 1**.

Table 2. Association of ESRα polymorphisms with the risk of prostate cancer

SNP	Genotype	Frequency		Adjusted *P*
		Patients (*N*=168)	Controls (*N*=220)	
rs2234693	CC	31 (18.45%)	38 (17.27%)	0.084
	CT	87 (51.79%)	90 (40.91%)	
	TT	50 (29.76%)	92 (41.82%)	
	C allele	149 (44.35%)	166 (37.73%)	0.126
	T allele	187 (55.65%)	274 (62.27%)	
rs9340799	GG	16 (9.52%)	22 (10.00%)	0.018
	GA	66 (39.29%)	55 (25.00%)	
	AA	86 (51.19%)	143 (65.00%)	
	G allele	98 (29.17%)	99 (22.50%)	0.068
	A allele	238 (70.83%)	341 (77.50%)	

Genotyping

Global genomic DNA was extracted from the peripheral blood mononuclear cells using standard protocols. The ESRα SNPs, including rs2234693 and rs9340799 polymorphisms, were amplified by the polymerase chain reaction with the following primers: Sense: 5'-CCTTTCTGTGTTCCTCTTCT-3'; antisense: 5'-TACCTCTTGCCGTCTGTT-3'. PCR amplification was performed in a total 25 μL reaction volume containing primer (10 μM, supplied by Genewiz) 1 μL, dNTP mix (2.5 mM, supplied by TaKaRa) 0.5 μL, 10×PCR buffer (supplied by TaKaRa) 2.5 μL, Taq DNA polymerase (5 U/μL, supplied by TaKaRa) 0.4 μL, genomic DNA 1 μL, and sterile deionized water 18.6 μL [20]. After initial denaturation at 94°C for 5 min, the ingredients were mixed at 35 cycles at 94°C for 30 s, 55°C for 30 s, 72°C for 54 s, and a final elongation was done at 72°C for 10 min [20]. Pvu II and Xba I restriction enzymes (supplied by Thermo) used to cleave PCR product at 37°C for 2 h, which were then analyzed by electrophoresis on 1.5% agarose gels [20]. Genotypes of rs2234693 and rs9340799 polymorphisms were identified by two investigators independently.

Clinical measures

Two end points were used to examine the therapeutic outcomes of patients with ADT-resistant prostate cancer after standard Docetaxel-based chemotherapy. The primary end point was progression free survival (PFS), which was defined as the time from Docetaxel-based treatment to progression of PSA, prostate tissue disease (Response Evaluation Criteria in Solid Tumors, RECIST, version 1.118 [21]) or bone metastases, or to bone scans showing two or more new lesions, or tumor-specific death [22]. The secondary end point was object response rate (ORR) and disease control rate (DCR). ORR were defined as a reduction in the PSA level from baseline by 50% or more, as confirmed on an additional PSA evaluation performed at least 3 weeks, or a reduction in the volume of prostate tissue or bone metastases from baseline by 50% or more [21, 23]. Disease controls were defined as the situations failed to get progression.

Statistical analysis

Hardy Weinberg equilibrium was performed using Haploview 4.1 to identify the genotype distributions of these two polymorphisms in ESRα gene. The following statistical analysis was performed in SPSS 18.0 software. The associations of rs2234693 and rs9340799 gene polymorphisms with the risk, clinical baseline and therapeutic outcomes of patients with ADT-resistant prostate cancer were evaluated by Chi-square test (X^2). The Kaplan-Meier method and the log-rank test for analysis of survival were used to examine the prognostic significance of the respective rs2234693 and rs9340799 genotypes for PFS. Cox forward stepwise regression model was used in multivariate analysis to determine the independent risk factors of prognosis. The power analysis was performed using the Genetic Power Calculator software. All statistical tests were two-tailed, and $P<0.05$ was the threshold level for statistical significance. Notably, Gleason score in patients was associated with PFS of our sample. Subgroup analysis was also performed to avoid the confounding factors from Gleason scores.

Results

Association of ESRα polymorphisms with the risk, Gleason score and therapeutic outcome of prostate cancer

The distributions of genotypes and allele frequencies of ESRα gene polymorphisms

Table 3. Association of ESRα polymorphisms with Gleason score and therapeutic outcome of prostate cancer

Factors	rs2234693					rs9340799				
	CC	CT	TT	X^2	*P*	GG	GA	AA	X^2	*P*
Gleason score (*N*)										
≤6	13	28	19	1.540	0.819	6	29	25	5.848	0.211
7	12	43	22			8	29	40		
≥8	6	16	9			2	8	21		
Therapeutic outcome (%)										
ORR	19.4	25.3	44.0	7.288	0.026	62.5	27.3	25.6	9.118	0.010
DCR	38.7	48.3	62.0	4.541	0.103	75.0	43.9	52.3	5.063	0.080

ORR, objective response rate; DCR, disease control rate.

Table 4. Association of ESRα polymorphisms with PFS of prostate cancer

Group	SNP	Genotype	mPFS (months)	Log-Rank *P*	HR*	95% CI
All patients	rs2234693	CC	6		1.000	Ref.
		CT	8	0.024	0.661	0.434-1.007
		TT	8	0.013	0.552	0.345-0.883
		CT+TT	8	0.012	0.620	0.415-0.927
	rs9340799	GG	4		1.000	Ref.
		GA	8	0.056	0.597	0.342-1.041
		AA	8	0.073	0.632	0.368-1.086
		GA+AA	8	0.049	0.617	0.366-1.041
Gleason score ≤6	rs2234693	CC	6		1.000	Ref.
		CT	9	0.006	0.470	0.235-0.939
		TT	9	0.056	0.386	0.177-0.842
		CT+TT	9	0.007	0.437	0.227-0.843
	rs9340799	GG	4		1.000	Ref.
		GA	8	0.132	0.502	0.204-1.236
		AA	9	0.058	0.448	0.179-1.125
		GA+AA	8	0.071	0.477	0.200-1.135
Gleason score =7	rs2234693	CC	5		1.000	Ref.
		CT	6	0.856	0.924	0.483-1.769
		TT	6	0.290	0.747	0.363-1.539
		CT+TT	6	0.606	0.859	0.459-1.609
	rs9340799	GG	3		1.000	Ref.
		GA	5	0.391	0.715	0.323-1.586
		AA	8	0.201	0.630	0.292-1.360
		GA+AA	7	0.238	0.663	0.315-1.393
Gleason score ≥8	rs2234693	CC	3		1.000	Ref.
		CT	8	0.094	0.403	0.144-1.129
		TT	9	0.065	0.458	0.150-1.398
		CT+TT	8	0.057	0.423	0.161-1.111
	rs9340799	GG	3		1.000	Ref.
		GA	7	0.541	0.541	0.105-2.787
		AA	7	0.973	1.041	0.242-4.488
		GA+AA	7	0.851	0.882	0.207-3.750

*Adjusted by age and BMI; HR, hazard ratio; 95% CI, 95% confidence interval.

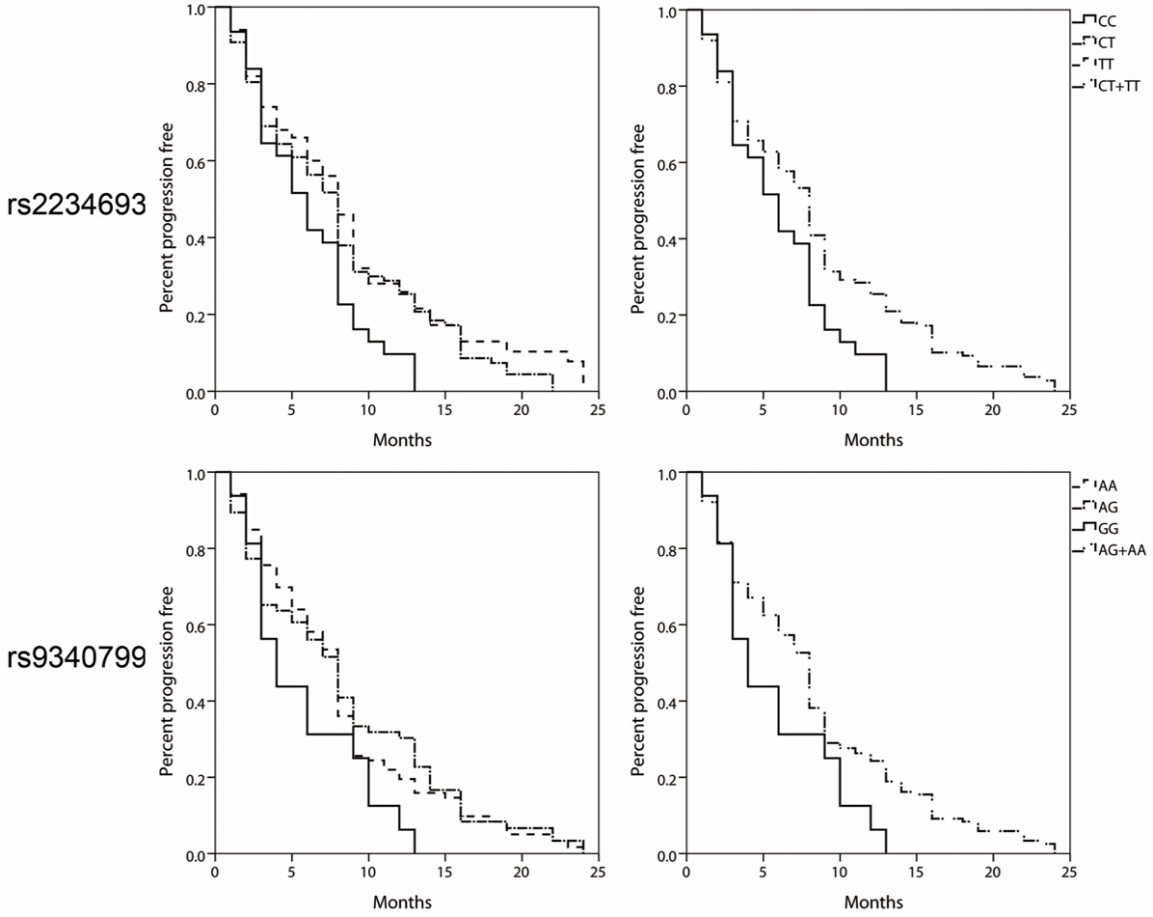

Figure 1. Progression free survival characteristic of all patients.

rs2234693 and rs9340799 were in Hardy-Weinberg equilibrium. The study demonstrated that these two gene polymorphisms were crudely associated with the risk of prostate cancer in Chinese Han population (rs2234693: X^2=6.328, P=0.042; rs9340799: X^2=9.334, P=0.009), but the association was only existence in rs9340799 when P values were adjusted by Bonferroni (**Table 2**). This study had the power of 0.727 overall. However, no significant difference was found in the distribution of genotypes in patients with different Gleason score (rs2234693: X^2=1.540, P=0.819; rs9340799: X^2=5.848, P=0.211; **Table 3**). However, when comparing the therapeutic outcome of Docetaxel-based chemotherapy in patients with different genotypes, TT of rs2234693 carriers had ORR of 44.0%, while CT and CC carriers had 25.3% and 19.4% respectively, the difference was significantly (X^2=7.288, P=0.026, **Table 3**). Furthermore, GG, GA, and AA of rs9340799 carriers had ORR of 62.5%, 27.3%, and 25.6%, the difference was still significantly (X^2=9.118, P=0.010, **Table 3**). However, the DCR in patients with different genotypes was no significantly difference (rs2234693: X^2=4.541, P=0.103; rs9340799: X^2=5.063, P=0.080; **Table 3**).

Association of ESRα polymorphisms with PFS of prostate cancer

In the present study, Kaplan-Meier method and log-rank test were used to investigate the influences of ESRα gene polymorphisms rs2234693 and rs9340799 on short-term prognosis of patients with prostate cancer. In all patients, the median PFS (mPFS) was 8 months in CT, TT, and combined cohort of CT+TT of rs2234693 carriers, which were 1.33 folds higher than CC carriers (CT: Log rank P=0.024, HR=0.661, 95% CI: 0.434-1.007; TT: Log rank P=0.013, HR=0.552, 95% CI: 0.345-0.883; CT+TT: Log rank P=0.012, HR=0.620, 95% CI: 0.415-0.927; **Table 4** and **Figure 1**). For rs9340799, the PFS was 8 months in combined cohort of

Table 5. Multivariate analysis

Characteristics	SE	RR	95% CI	*P*
Age	0.342	1.007	0.987-1.027	0.496
Smoke history				
No	0.528	1.000	Ref.	
Yes	0.022	0.974	0.684-1.386	0.884
Drink history				
No	0.427	1.000	Ref.	
Yes	0.006	1.451	0.926-2.273	0.104
PSA at diagnosis				
<10	0.125	1.000	Ref.	
10-20	0.167	1.222	0.364-4.102	0.746
>20	0.343	1.310	0.437-3.927	0.630
Clinical stage*				
T1/T2	0.410	1.000	Ref.	
T3/T4/N1	0.210	0.819	0.567-1.183	0.287
M1	0.456	1.281	0.828-1.980	0.266
Gleason score				
≤6	0.257	1.000	Ref.	
7	0.351	1.562	1.098-2.223	0.013
≥8	0.249	1.713	1.076-2.728	0.023

*Clinical stage diagnostic criteria of AJCC 2010; SE, standard error; RR, relative risk; 95% CI, 95% confidence interval.

GA+AA, which was 2 folds higher than GG (Log rank *P*=0.049, HR=0.617, 95% CI: 0.366-1.041; **Table 4** and **Figure 1**).

In the multivariate analysis, Gleason score was found to be a potential factor which may influence the prognosis of patients with prostate cancer (**Table 5**). Subsequently, the subgroup analyses were conducted in the included patients who were stratified by Gleason score. In patients with lower (≤6) Gleason score, the mPFS in CT and the combined cohort of CT+TT of rs2234693 carriers were 9 months, and 1.5 folders higher than that in CC (CT: Log rank *P*=0.006, HR=0.470, 95% CI: 0.235-0.939; CT+TT: Log rank *P*=0.007, HR=0.437, 95% CI: 0.227-0.843; **Table 4**). But the mPFS was no significantly difference in the patients with different genotypes of rs9340799 (**Table 4**). Furthermore, for patients with middle (=7) or higher (≥8) Gleason score, the mPFS was also no significantly difference in patients with different genotypes of both rs223493 and rs9340799 (**Table 4**).

Discussion

In this study, we focused on two potential prostate cancer risk polymorphisms in ESRα gene and systematically investigated that significance in therapeutic outcomes and short-term prognosis in ADT-resistant prostate cancer. Our results suggested that the two gene polymorphisms were crudely associated with the risk of prostate cancer in Chinese Han population, and ADT-resistant patients carried TT genotype in rs2234693 or GG genotype in rs9340799 may have significantly higher object response rate after treatment by Docetaxel-based chemotherapy for two periods of treatment, in addition, T-allele and A-allele carriers had significantly longer progression free survival, and implied a potential candidate biomarker for predicting prognosis of prostate cancer. The findings in our study are novel, especially in Chinese Han population.

ESRα is a member of superfamily of nuclear receptors, which belong to ligand-dependent transactivators [20]. Various studies have demonstrated that the expression of ESRα in prostate cancer tissues may correlate with recurrence and progression of patients with prostate cancer, while patients' absence of its expression may have a better prognosis [18, 24, 25]. Notably, the polymorphisms in ESRα gene are the influencing factors for expression of ESRα levels in cells [13], hence, they may further interfere with the prognosis of patients with certain cancers. Our study suggested that the polymorphisms in ESRα gene were associated with the risk, therapeutic outcomes and short-term prognosis of patients with prostate cancer. It is mostly consistent with an earlier study in Iranian and Caucasian cohort, which revealed that T allele of rs2234693 and A allele of rs9340799 carriers had a decreased risk of prostate cancer, and patients with prostate cancer and carried two copies polymorphisms in ESRα gene had shorter progression free survival, but T-allele of rs2234693 carried had better improved [13, 26]. However, Sun [27] demonstrated that variations in ESRα were not associated with aggressiveness of prostate cancer or efficacy of androgen deprivation therapy. This difference may be due to these reasons: on one hand, the therapeutic methods in the former two studies were Docetaxel-based chemotherapy, while the last was androgen deprivation therapy; on the other hand, the subjects in our and Sissung's [26] study was ADT-resistant prostate cancer, but Sun's [27] was not. Actually, patients with ESRα gene variants was found associated with development of ADT

resistant [28], which also implied poorer prognosis.

Prostate is mainly considered to be targeted by androgen, however, it is also an estrogen target organ [29]. Accumulating evidence indicates that the development and function of prostate is regulated by estrogen, which could cause squamous metaplasia with the retrieval of androgen effect [30, 31]. The estrogen in the plasma enters prostate tissues and could further bind to both ESRα and ESRβ (another type of estrogen receptor) [32] on the nucleus of epithelium and stroma, while the binding of estrogen and ESRα seems to be involved in the carcinogenesis of prostate [29]. Furthermore, the ESRα-signaling considered to be involved in the 3,4-QE2 metabolites, which may cause estrogen-purine DNA lesions and oppose the therapeutic efficacy of Docetaxel in prostate cancer through covalently binding the drug and destabilizing tubulin polymerization reactions [26, 33, 34]. Hence, we infer that the polymorphisms such as rs2234693 and rs9340799 in ESRα gene cause effects on the risk and prognosis of prostate cancer through the participation of these variants in the ESRα-signaling pathway. The mechanism of the effects needs further study.

In summary, we presented an association analysis of ESRα polymorphisms with the risk, therapeutic outcome and prognosis of ADT-resistant prostate cancer in Chinese Han population. The conclusion is helpful for the comprehension of the role and function of ESRα in prostate cancer, as well as for estimating whether the polymorphisms in ESRα gene could be considered to be a valuable biomarker for survival of prostate cancer. But limitations also existed in the study. As only two polymorphisms (rs2234693 and rs9340799) in ESRα gene were selected, but they do not represent the effects of the whole fragment gene, more variants should be considered in the further study. Furthermore, we only included the patients with ADT-resistant and treated by Docetaxel that may cause inadequate sample size. It is encourage us to next focus on the significant mechanisms of ESRα in the carcinogenesis, progression, and overall survival of prostate cancer.

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Disclosure of conflict of interest

None.

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