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Review Article

Association between steroid 5-alpha-reductase type 2 (SRD5A2) V89L and A49T polymorphisms and prostate cancer risk: a meta-analysis study

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Abstract: Numerous investigations have examined the associations between steroid 5-alpha-reductase type 2 (SRD5A2) V89L and A49T polymorphisms and prostate cancer risk; however, the conclusions were contradictory. The current meta-analysis was performed to comprehensively re-evaluate such associations. Two investigators independently searched the PubMed, EMBASE, and CNKI databases to seek eligible studies. Ultimately, a total of 11,758 cases and 12,397 controls from 33 studies were identified for the V89L, and 5,902 cases and 7,270 controls from 13 studies for the A49T. The pooled analysis did not yield any statistically significant associations between both V89L and A49T polymorphisms and prostate cancer risk (e.g., LL + VV vs. VV for V89L: OR = 1.02; 95% CI 0.97, 1.08, P = 0.425, I^2 = 3.7; TT + AT vs. AA for A49T: OR = 1.20; 95% CI 0.90, 1.59, P = 0.208, I^2 = 68.6). In stratification analyses, we also did not find significant associations between the variants and prostate cancer risk. These results suggested that the SRD5A2 V89L and A49T polymorphisms might not modulate the prostate cancer risk. More well designed studies with large sample sizes are warranted to validate our findings.

Keywords: SRD5A2, prostate cancer, polymorphisms, meta-analysis

Introduction

Prostate cancer is one of the most common cancers and leading cause of cancer deaths in the developed countries, but the etiology of the disease is not well known. Epidemiological studies have suggested that both genetic and environmental factors played important roles in the development of prostate cancer. The incidence of the disease in African-American men is about 60% higher than that in Caucasian men and the mortality death rate is approximately 2.4 fold higher in African-American men [1]. Compared to Asians, the incidence is 30-50 times higher in the African-Americans [2]. A twin study performed in Scandinavia has suggested that 42% of the prostate cancer may be caused by the heritable factors [3]. Although several genome-wide associations have been performed in the past decades, only a small proportion of the heritable factors that may influence the susceptibility of prostate cancer have been identified [4-6] and more studies are warranted to identify those susceptibility genetic factors.

Androgens are required for the prostate gland growth and development, and epidemiological studies have suggested that higher circulating androgens such as testosterone may increase the prostate cancer risk [7]. Besides tests and adrenal glands, androgens could also be synthesized by skin and prostate cells. In prostate, dihydrotestosterone (DHT) is converted from testosterone by the 5-alpha reductase type II (SRD5A2) enzyme. DHT acts as the primary nuclear most potent nuclear androgen and it binds to the androgen receptor, which further promotes the transcription of target genes with androgen receptor-responsive elements and stimulates the proliferation of the prostate cells. Deregulated androgen biosynthesis and

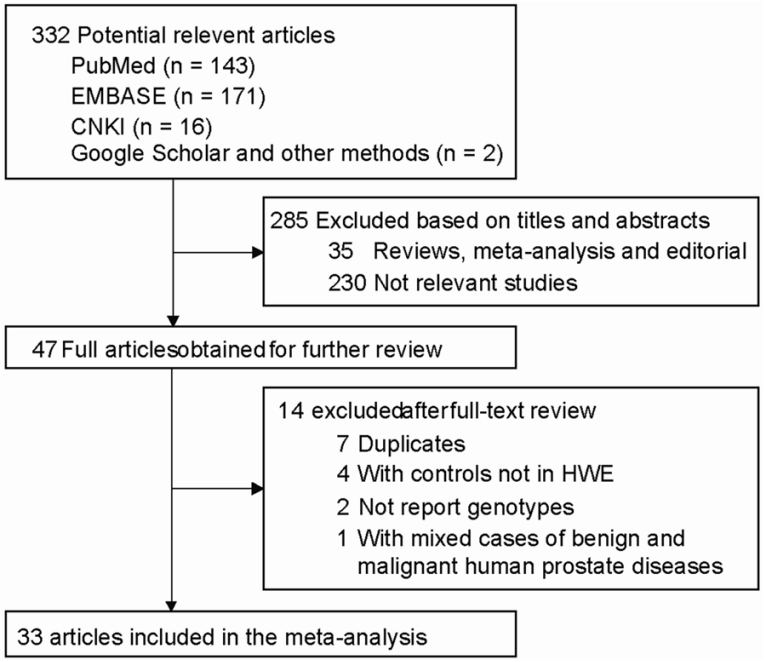

Figure 1. Flow chart of study selection in the meta-analysis.

metabolisms were implicated in the prostate cancer development [8]. SRD5A2 coding gene locates on chromosome 2p23 with 5 exons and 4 introns, and several common single nucleotide polymorphisms (SNPs) on the coding gene have been identified including V89L, A49T, R227Q the (TA)n dinucleotide repeat in the 3'-UTR region. For V89L, which substitutes valine at codon 89 with leucine (rs523349, C > G) was reported to reduce the 5α-reductase activity and resulted in a lower circulating DHT [9], while the A49T (rs9282858, alanine to threonine) substitution leaded an increased 5α-reductase activity of SRD5A2 [10]. It was implicated that these SNPs may influence the susceptibility of the prostate cancer through regulating the DHP level and biological activities in men. Up to date, many meta-analysis studies have assessed the associations of the common SNPs on SRD5A2 and the prostate cancer risk in various ethnic populations; however, the results were not always consistent and no conclusive results have yet reached [11-15]. Because the complexity of the etiology of prostate cancer, the effects of the individual genetic polymorphisms may be small and the statistical power of the studies may be relatively smaller to detect the influences of the variants on the prostate cancer risk. Thus, we aimed to evaluate the associations between the common variants on SRD5A2 and the prostate cancer risk with an updated meta-analysis. These results may provide more insights into the etiology of the prostate cancer development and may be helpful to develop the intervention methods for prostate cancer.

Materials and methods

Literature search strategies

A systematic literature search of PubMed, EMBASE, and China National Knowledge Infrastructure (CNKI, http://www.cnki.net) up to July 2016 was performed with the terms "SRD5A2" or "5-alpha reductase type 2" in combination with "prostate cancer". No language restriction was applied; non-English articles were translated if necessary. In addition, we further screened the references of the retrieved studies and the published reviews or comments manually to identify any missing study in the literature search. Related articles generated by PubMed were also retrieved.

Inclusion and exclusion criteria

Studies included in the final meta-analysis should meet the following criteria: (1) be a case-control study, including nested case-control studies; (2) using prostate cancer as an end point; (3) including at least one of the two polymorphisms: V89L and A49T; and (4) providing SNP genotype data and odds ratios (ORs) and corresponding 95% CIs. The studies were excluded if genotype frequency data in the controls for V89L and A49T polymorphisms demonstrated was departure from Hardy-Weinberg equilibrium (HWE). If there exists more than one article published using the same subjects or overlapping data, only the latest or the largest sample size studies were included in our final meta-analysis. In addition, case-only studies, case reports, conference abstract, meta-analyses and other type of studies without detailed data were also excluded. Two reviewers (Ming Liangand Benkang Shi) independent-

Table 1. Characteristics of studies included in the meta-analysis

First author (ref.)	Year	Country	Ethnicity[a]	Cases		Controls		Source of controls	Matching variable (s)	SNP (s)	Quality score	Published language
				N	Age[b]	N	Age[b]					
Febbo PG [42]	1999	USA	Caucasian	584	40-80	799	40-80	PB	Age (± 2 years) and smoking status	V89L	13	English
Lunn RM [44]	1999	USA	Mixed	108	63	156	64	HB	Race	V89L	5	English
Margiotti K [45]	2000	Italy	Caucasian	108	60-80	121	70-110	PB	Residence	V89L	6	English
Hsing AW [43]	2001	China	Asian	191	73	304	-	PB	Age (± 5 years)	V89L	11	English
Latil AG [46]	2001	France	Caucasian	226	70.5	156	71.7	PB	Age and ethnicity	V89L, A49T	9	English
Mononen N [47]	2001	Finland	Caucasian	449	68	811	>65	HB	-	A49T	8	English
Yamada Y [48]	2001	Japan	Asian	92	72	203	71.6	HB	Age (± 2 years)	V89L	7	English
Pearce CL [49]	2002	USA	Mixed	921	-	1259	-	PB	-	V89L	11	English
Soderstrom T [50]	2002	Sweden	Caucasian	175	71	160	71	PB	Age (± 10 years)	V89L, A49T	10	English
Chang BL [51]	2003	USA	Caucasian	245	58.6	222	58	PB	-	V89L, A49T	6	English
Lamharzi N [52]	2003	USA	Caucasian	300	61.2	300	60.8	PB	Race, age (± 5 years), study center and year of randomization	V89L, A49T	13	English
Li Z [53]	2003	Japan	Asian	302	72.04	471	72.79	PB	-	V89L	9	English
Nam RK [54]	2003	Canada	Caucasian	483	66.6	548	66.4	PB	-	V89L	10	English
Cicek MS [55]	2004	USA	Mixed	440	62	480	63	PB	-	V89L, A49T	11	English
Liu JH [56]	2004	China	Asian	112	68.6	190	65.7	HB	-	V89L, A49T	6	Chinese
Forrest MS [57]	2005	UK	Caucasian	288	51.1	700	-	PB	-	V89L, A49T	8	English
Giwercman YL [30]	2005	Sweden	Caucasian	89	69.3	268	64.5	HB	Race	A49T	6	English
Salam MT [58]	2005	USA	Caucasian	100	66.5	506	66.8	PB	-	V89L	9	English
Lindstrom S [59]	2006	Sweden	Caucasian	2826	-	1705	-	PB	Age (± 5 years) and residence	V89L	11	English
Okugi H [60]	2006	Japan	Asian	102	69.9	117	71	HB	Age and residence	V89L	8	English
Sobti RC [61]	2006	India	Asian	100	66.21	100	60.71	HB	Age	V89L	6	English
Berndt SI [62]	2007	USA	Mixed	481	65.8	614	65.4	PB	Age (± 5 years) and race	V89L	13	English
Cunningham JM [63]	2007	USA	Caucasian	495	65	488	61	PB	-	V89L	12	English
Hayes VM [64]	2007	Australia	Caucasian	827	62	736	<70	PB	Age	V89L, A49T	13	English
Neslund-Dudas C [1]	2007	USA	Mixed	633	<75	242	<75	PB	Age (± 5 years) and race	V89L	12	English
Onen IH [65]	2007	Turkey	Caucasian	100	65	105	62	PB	Age	V89L	9	English
Pearce CL [66]	2008	USA	Mixed	2155	68.3	2204	67.9	PB	-	A49T	12	English
Sarma AV [67]	2008	USA	African	131	67.2	342	62.1	PB	-	V89L	11	English
Scariano JK [68]	2008	USA	Mixed	33	53	36	77	HB	-	V89L	5	English
Torkko KC [69]	2008	USA	Mixed	585	66.0	761	62.3	PB	-	V89L, A49T	12	English
Rajender S [70]	2009	India	Asian	87	67.5	136	66.2	PB	-	V89L	4	English
Tong M [71]	2010	China	Asian	112	70	89	68	HB	-	V89L	6	Chinese
Fernandez P [72]	2012	South Africa	Mixed	438	68.1	621	56.0	HB	-	A49T	5	English
Dusenka R [73]	2014	Slovakia	Caucasian	260	63.6	196	62.3	HB	Age	V89L	7	English
Choi SY [74]	2015	Korea	Asian	272	68.2	173	67.3	HB	-	V89L	7	English
Ersekerci E [75]	2015	Turkey	Caucasian	32	68.2	58	63.8	HB	-	V89L	6	English
Poniah P [76]	2015	Malaysia	Asian	81	70.33	91	68.56	HB	-	V89L	6	English

PB: population-based; HB: hospital-based; [a]Mixed of Caucasian, Asian, or African; [b]Mean, median or range of age.

Table 2. Steroid 5-alpha reductase type II gene two genotype distributions among prostate cancer cases and controls of the included studies

First author	Year	Cases			Controls			HWE[a]
V89L		VV	VL	LL	VV	VL	LL	
Febbo PG [42]	1999	295	239	50	391	330	78	0.493
Lunn RM [44]	1999	47	53	8	79	63	14	0.778
Margiotti K [45]	2000	54	51	3	67	40	9	0.386
Hsing AW [43]	2001	40	86	60	62	136	105	0.144
Latil AG [46]	2001	105	98	23	84	64	8	0.343
Yamada Y [48]	2001	22	43	27	56	97	50	0.535
Pearce CL [49]	2002	423	387	111	577	578	140	0.791
Soderstrom T [50]	2002	78	74	23	77	66	16	0.738
Chang BL [51]	2003	114	89	18	100	70	17	0.355
Lamharzi N [52]	2003	147	124	29	150	120	30	0.409
Li Z [53]	2003	101	160	41	139	244	88	0.294
Nam RK [54]	2003	250	194	39	257	238	53	0.845
Cicek MS [55]	2004	207	189	44	247	184	49	0.095
Liu JH [56]	2004	53	49	10	38	35	16	0.126
Forrest MS [57]	2005	144	123	42	358	276	52	0.905
Salam MT [58]	2005	34	46	15	225	206	55	0.453
Lindstrom S [59]	2006	1262	1223	286	815	707	164	0.555
Okugi H [60]	2006	33	46	23	42	50	25	0.170
Sobti RC [61]	2006	47	30	23	37	43	20	0.253
Berndt SI [62]	2007	266	175	40	300	256	58	0.752
Cunningham JM [63]	2007	258	191	41	251	190	41	0.555
Hayes VM [64]	2007	393	359	74	360	301	75	0.305
Neslund-Dudas C [1]	2007	303	271	59	120	98	24	0.546
Onen IH [65]	2007	55	37	8	61	38	6	0.980
Sarma AV [67]	2008	71	51	9	177	136	28	0.794
Scariano JK [68]	2008	15	13	5	11	21	4	0.202
Torkko KC [69]	2008	282	255	48	370	314	77	0.390
Rajender S [70]	2009	25	39	23	41	58	37	0.088
Tong M [71]	2009	53	49	10	38	35	16	0.126
Dusenka R [73]	2014	97	110	53	73	87	36	0.266
Choi SY [74]	2015	81	135	56	52	86	35	0.959
Ersekerci E [75]	2015	19	9	4	29	26	3	0.353
Poniah P [76]	2015	39	35	7	52	33	6	0.806
A49T		AA	AT	TT	AA	AT	TT	
Latil AG [46]	2001	219	6	1	150	6	0	0.807
Mononen N [47]	2001	422	26	1	763	47	1	0.755
Soderstrom T [50]	2002	168	7	0	155	5	0	0.841
Chang BL [51]	2003	203	10	0	168	13	0	0.616
Lamharzi N [52]	2003	279	21	0	281	18	1	0.232
Cicek MS [55]	2004	413	26	1	444	35	1	0.724
Liu JH [56]	2004	104	7	1	81	8	0	0.657
Forrest MS [57]	2005	297	15	1	500	37	0	0.408
Giwercman YL [30]	2005	74	12	0	240	18	0	0.562
Hayes VM [64]	2007	752	75	0	691	43	0	0.414

ly identified articles eligible for further review by performing an initial screen of titles and abstracts.

Data extraction and quality assessment

Two investigators (Ming Liang and Yan Sun) independently extracted data and assess the quality of included studies by using a pilot-tested data extraction form. The following information from all eligible studies according to the inclusion and exclusion criteria were extracted: the first author's name, year of publication, country of origin, ethnicity (Caucasian, Asian, African, etc.), control source (population based or hospital based), the total number of cases and controls, mean age of cases and controls, numbers of cases and controls with the VV, VL and LL genotypes for the V89L polymorphism and AA, AT and TT genotypes for the A49T polymorphism. Any disagreement was resolved by discussion.

The quality of included studies was assessed by quality assessment criteria derived from a previously meta-analysis of molecular association studies [16]. This scale consisted of 7 questions with a maximum of 15 points for each study. For the item of control selection, controls did not necessary to match with cases by gender because all of participants in this study were males. Thus the maximum score was 14. Quality was assigned as high-quality with 8-14 points and low-quality with 0-7 points.

Pearce CL [66]	2008	1690	58	1	2152	52	0	0.575
Torkko KC [69]	2008	546	39	0	713	48	0	0.369
Fernandez P [72]	2012	302	125	0	522	77	0	0.093

HWE: Hardy-Weinberg equilibrium; [a]*P* value of chi-square test for HWE among controls.

Statistical analysis

The departure of frequencies from expectation under HWE was assessed by chi-square goodness-of-fit tests in controls for each study. We used crude ORs with their 95% confidence intervals (CIs) to assess the strength of association between SRD5A2 polymorphisms and prostate cancer risk. We used allele comparisons (L vs. V for V89L and T vs. A for A49T) and different genetic models to assess the overall and following stratified effects: (1) additive (homozygote or heterozygote) genetic model: LL or VL vs. VV for V89L and TT or AT vs. AA for A49T; (2) dominant genetic model: LL + VL vs. VV for V89L and TT + AT vs. AA for A49T; and (3) recessive genetic model: LL vs. VL + VV for V89L and TT vs. AT + AA for A49T. We performed subgroup analysis according to ethnicity, source of control, and quality of included studies, respectively. Influence analysis was also performed to assess the effect of each individual study on the summary risk estimates [17].

Statistical heterogeneity between studies was determined by the I^2 statistic, and 25%, 50%, and 75% of I^2 values corresponded to mild, moderate, and extensive statistical inconsistencies, respectively [18]. The pooled OR with 95% CI was calculated using the random-effect models based on the Der-Simonian and Laird method [19]. Because random-effects model was considered as more conservative than the fixed-effects model, as it accounts for both within- and between-study heterogeneity [20]. Publication bias was explored with Egger regression asymmetry test and funnel plot [21]. If publication bias was detected, the number of missing studies and the effect that these studies was explored by using a trim-and-fill method developed by Duval and Tweedie [22]. All statistical analyses were completed using Stata Version 11.0 (College Station, TX, USA).

Results

Study characteristics

A total of 332 articles were retrieved by a literature search (**Figure 1**). Of the publications that were considered to be possibly relevant for the analysis, the following were excluded: seven duplicate publications [23-29], four studies [30-33] with controls not in HWE, two studies with insufficient data to calculate HWE [34, 35], and one study with mixed cases of benign and malignant human prostate diseases [36]. Finally, 33 case-control studies with 11,758 cases and 12,397 controls were used to evaluate the association for SRD5A2 V89L polymorphism and 13 studies with 5,902 cases and 7,270 controls were used to assess the association for SRD5A2 A49T polymorphism.

Tables 1 and **2** shows the characteristics and genotype distributions of included studies. The included studies were published between 1999 and 2015. Total sample sizes ranged from 69 to 4,531 (median 473). Seventeen studies were conducted among Caucasians, ten among Asians, one among Africans, and the remaining 9 were mixed Caucasians, Asian, or African. Controls of 14 studies came from hospital settings, the 23 were population-based. Controls in 14 studies were matched at least by age. The quality scores for all included studies ranged from 4 to 13 with a median of 9.

Quantitative synthesis

For V89L, the pooled results suggest no associations under allele comparison (L vs. V: OR = 1.01; 95% CI 0.96, 1.06, P = 0.686, I^2 = 16.0) and all genetic models without obvious heterogeneity (LL vs. VV: OR = 1.00; 95% CI 0.90, 1.11, P = 0.997, I^2 = 16.4; VL vs. VV: OR = 1.03; 95% CI 0.97, 1.09, P = 0.328, I^2 = 0.0; VL + LL vs. VV: OR = 1.02; 95% CI 0.97, 1.08, P = 0.425, I^2 = 3.7; LL vs. VL + VV: OR = 0.99; 95% CI 0.90, 1.09, P = 0.873, I^2 = 13.0, respectively) (**Table 3** and **Figure 2**). Stratified analyses reveal that there was no significant association observed between SRD5A2V89L polymorphism and prostate cancer risk when data were stratified by ethnicity, source of controls and quality score (**Table 3** and **Figure 2**).

Similar with V89L, both pooled and stratified analyses found no significant associations under allele comparison and any genetic models for A49T (**Table 3** and **Figure 3**). The heterogeneity for allele and heterozygote comparison, as well as dominant genetic model, showed

Table 3. Total and stratified analysis of steroid 5-alpha reductase type II gene two polymorphisms on prostate cancer

Variables	N[a]	Cases/Controls	Allele comparison			Homozygote comparison			Heterozygote comparison			Dominant genetic model			Recessive genetic model		
			OR (95% CI)	P^b	I^2	OR (95% CI)	P^b	I^2	OR (95% CI)	P^b	I^2	OR (95% CI)	P^b	I^2	OR (95% CI)	P^b	I^2
V89L																	
Total	33	11,758/12,397	1.01 (0.96, 1.06)	0.686	16.0	1.00 (0.90, 1.11)	0.997	16.4	1.03 (0.97, 1.09)	0.328	0.0	1.02 (0.97, 1.08)	0.425	3.7	0.99 (0.90, 1.09)	0.873	13.0
Ethnicity																	
Caucasian	21	9,039/8,957	1.04 (0.98, 1.09)	0.192	13.3	1.05 (0.92, 1.19)	0.476	17.8	1.06 (0.99, 1.13)	0.080	0.0	1.06 (0.99, 1.12)	0.090	2.1	1.02 (0.91, 1.15)	0.729	13.4
Asian	11	1,608/2,056	0.95 (0.86, 1.04)	0.281	0.0	0.91 (0.73, 1.12)	0.349	11.3	0.94 (0.81, 1.10)	0.444	0.0	0.93 (0.80, 1.07)	0.313	0.0	0.95 (0.77, 1.17)	0.615	31.3
African	6	1,073/1,343	0.99 (0.87, 1.13)	0.930	0.0	1.00 (0.74, 1.36)	0.978	0.0	0.98 (0.82, 1.17)	0.823	0.0	0.98 (0.83, 1.16)	0.852	0.0	1.02 (0.76, 1.36)	0.904	0.0
Source of controls																	
Population	22	10,454/11,089	1.01 (0.96, 1.07)	0.663	29.8	1.00 (0.89, 1.13)	0.963	28.8	1.03 (0.97, 1.09)	0.291	0.0	1.03 (0.96, 1.09)	0.434	14.0	0.99 (0.89, 1.10)	0.825	20.2
Hospital	11	1,304/1,308	1.00 (0.89, 1.12)	0.985	0.0	0.99 (0.78, 1.25)	0.918	0.0	0.99 (0.83, 1.19)	0.923	6.7	0.99 (0.84, 1.17)	0.921	0.0	1.01 (0.81, 1.26)	0.917	4.2
Quality score																	
High	20	10,140/10,767	1.01 (0.96, 1.07)	0.661	36.7	1.02 (0.90, 1.15)	31.9	0.806	1.03 (0.97, 1.09)	0.400	0.0	1.02 (0.96, 1.09)	0.540	18.8	1.00 (0.90, 1.11)	0.999	19.9
Low	13	1,618/1,630	1.00 (0.90, 1.11)	0.998	0.0	0.95 (0.76, 1.18)	0.0	0.632	1.04 (0.88, 1.23)	0.639	9.3	1.02 (0.88, 1.18)	0.774	0.0	0.96 (0.78, 1.19)	0.717	7.5
Influence analysis[c]																	
Maximal	32	-/-	1.02 (0.98, 1.07) (53)	0.378	7.7	1.02 (0.92, 1.13) (44)	0.685	9.6	1.04 (0.99, 1.10) (53)	0.146	0.0	1.04 (0.98, 1.10) (53)	0.165	0.0	1.01 (0.92, 1.11) (44)	0.813	6.8
Minimal	32	-/-	1.00 (0.95, 1.05) (50)	0.986	13.1	0.98 (0.90, 1.07) (48)	0.650	0.0	1.01 (0.95, 1.07) (50)	0.790	0.0	1.00 (0.95, 1.06) (50)	0.906	0.0	0.98 (0.89, 1.09) (50)	0.744	14.5
A49T																	
Total	13	5,902/7,270	1.21 (0.94, 1.56)	0.142	63.4	1.76 (0.55, 5.60)	0.339	0.0	1.18 (0.88, 1.57)	0.269	69.9	1.20 (0.90, 1.59)	0.208	68.6	1.77 (0.56, 5.64)	0.333	0.0
Ethnicity																	
Caucasian	12	4,711/5,493	1.15 (0.98, 1.35)	0.086	3.0	2.01 (0.59, 6.84)	0.262	0.0	1.11 (0.93, 1.34)	0.245	14.1	1.14 (0.96, 1.35)	0.151	9.1	2.02 (0.60, 6.87)	0.259	0.0
Asian	2	754/731	1.05 (0.57, 1.93)	0.872	0.0	2.34 (0.09, 58.19)	0.604	-	0.97 (0.52, 1.81)	0.917	0.0	1.01 (0.54, 1.87)	0.981	0.0	2.41 (0.10, 59.83)	0.592	-
African	3	634/874	0.97 (0.18, 5.28)	0.968	42.4	-	-	-	0.96 (0.17, 5.42)	0.964	43.5	0.96 (0.17, 5.42)	0.964	43.5	-	-	-
Source of controls																	
Population	9	4,828/5,513	1.11 (0.91, 1.37)	0.302	19.0	1.66 (0.41, 6.63)	0.477	0.0	1.08 (0.86, 1.36)	0.502	29.6	1.10 (0.88, 1.37)	0.400	24.9	1.67 (0.42, 6.67)	0.471	0.0
Hospital	4	1,704/1,757	1.56 (0.90, 2.73)	0.116	75.0	2.02 (0.25, 16.48)	0.512	0.0	1.53 (0.78, 3.00)	0.217	81.2	1.57 (0.82, 3.01)	0.171	80.1	2.04 (0.25, 16.68)	0.505	0.0
Quality score																	
High	9	5,064/6,143	1.15 (0.97, 1.37)	0.111	2.9	1.69 (0.49, 5.83)	0.410	0.0	1.12 (0.92, 1.36)	0.274	18.7	1.14 (0.94, 1.37)	0.183	11.6	0.69 (0.49, 5.86)	0.406	0.0
Low	4	838/1,127	1.43 (0.73, 2.78)	0.298	74.6	2.34 (0.09, 58.19)	0.604	-	1.38 (0.63, 3.04)	0.419	80.2	1.43 (0.67, 3.06)	0.363	79.2	2.41 (0.10, 59.83)	0.592	-
Influence analysis[c]																	
Maximal	12	-/-	1.26 (0.97, 1.63) (46)	0.081	61.2	2.25 (0.65, 7.80) (43)	0.200	0.0	1.24 (0.93, 1.66) (48)	0.151	68.2	1.26 (0.94, 1.67) (48)	0.120	67.3	2.28 (0.66, 7.89) (43)	0.194	0.0
Minimal	12	-/-	1.14 (0.95, 1.36) (64)	0.155	13.5	1.50 (0.43, 5.19) (48)	0.522	0.0	1.10 (0.90, 1.35) (64)	0.364	27.5	1.12 (0.92, 1.36) (64)	0.252	21.5	1.51 (0.44, 5.22) (48)	0.516	0.0

CI: Confidence interval; [a]Number of comparisons; [b]*P*-value of Z-test for significant test; [c]References refer to studies excluded from the influence analysis.

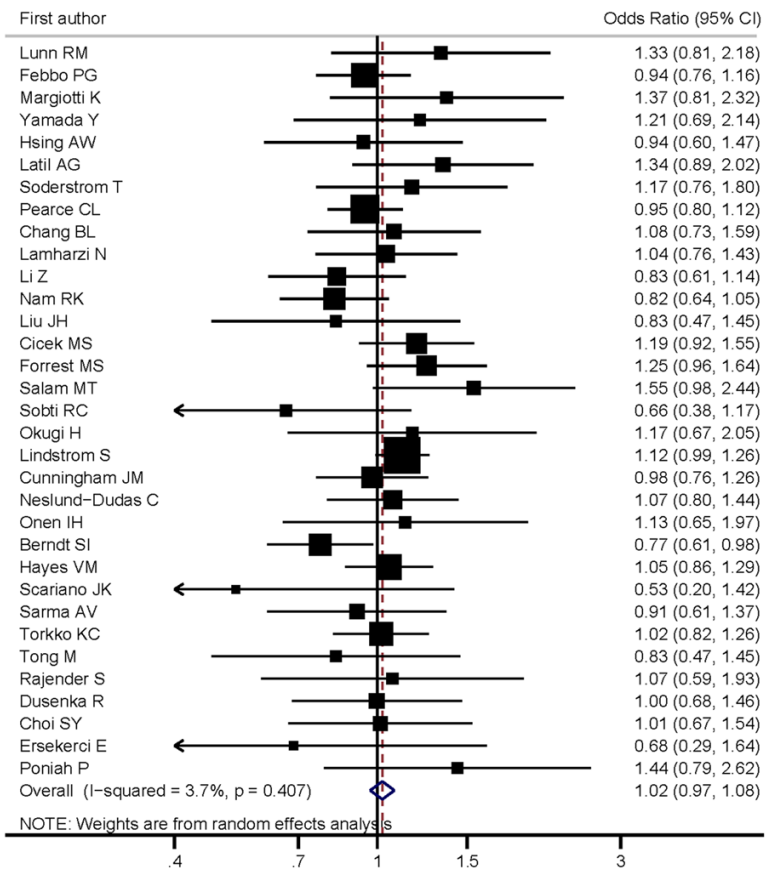

Figure 2. Forest plot of associations between 5-alpha reductase type II (SRD5A2) V89L polymorphism and the risk of prostate cancer.

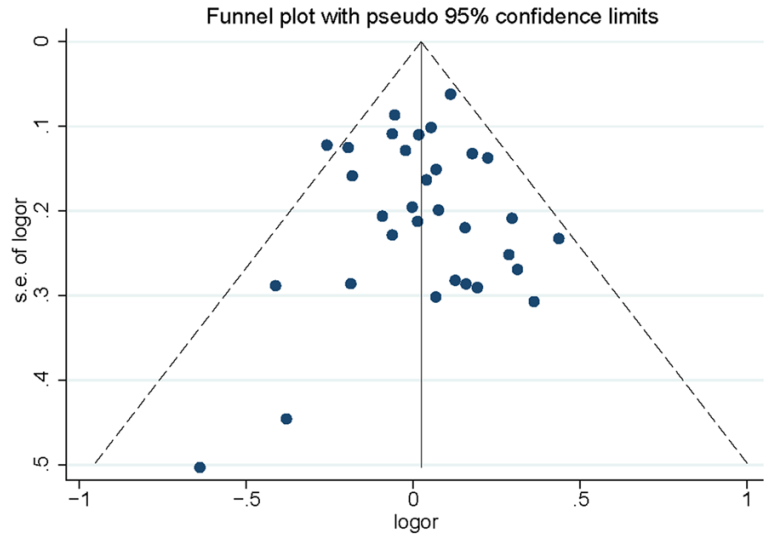

Figure 3. Forest plot of associations between 5-alpha reductase type II (SRD5A2) A49T polymorphism and the risk of prostate cancer.

extensive statistical inconsistencies (I^2 > 60%). After stratified by ethnicity, the heterogeneity significantly reduced, but the results remain insignificant.

Sensitivity analysis and diagnosis of bias

The sensitivity analyses suggested that no single study significantly affected the pooled ORs for both V89L and A49T (**Table 3**). Both Egger's test and funnel plot revealed no significant publication bias for V89L (**Table 4** and **Figures 4** and **5**). But significant publication bias was found for A49T (allele comparison: P = 0.044; heterozygote comparison: P = 0.036 and dominant genetic model: P = 0.045); however, no study was further added by using the trim-and-fill procedure (**Table 4**).

Discussion

In the current meta-analysis including 33 studies with 11,758 cases and 12,397 controls for SRD5A2 V89L polymorphism and 13 studies with 5,902 cases and 7,270 controls for SRD5A2 A49T polymorphism, the associations between SRD5A2 V89L and A49T polymorphisms and prostate cancer risk was comprehensively evaluated, and the overall and stratified analysis found no significant associations under any genetic models.

The etiology and pathogenesis of prostate cancer remain unclear. There is compelling evidence indicated that androgens play important roles in prostate carcinogenesis [37]. Androgens are required for prostate growth, and animal studies found that administration of estradiol-17β or diethylstilbestrol (DES) plus testosterone could induce prostate tumors [38]. Prospective stud-

Table 4. Publication bias tests (Egger's) for steroid 5-alpha reductase type II gene two polymorphisms

Genetic type	Coefficient	Standard error	t	*P* value	95% CI of intercept
V89L					
Allele comparison	-0.013	0.439	-0.03	0.976	-0.909, 0.882
Homozygote comparison	-0.073	0.446	-0.16	0.870	-0.983, 0.836
Heterozygote comparison	-0.089	0.378	-0.24	0.814	-0.860, 0.681
Dominant genetic model	-0.060	0.395	-0.15	0.879	-0.867, 0.746
Recessive genetic model	-0.036	0.444	-0.08	0.936	-0.940, 0.869
A49T					
Allele comparison	-2.40	1.053	-2.28	0.044	-4.717, -0.084
Homozygote comparison	1.602	3.329	0.48	0.651	-6.954, 10.158
Heterozygote comparison	-2.717	1.140	-2.38	0.036	-5.226, -0.208
Dominant genetic model	-2.599	1.151	-2.26	0.045	-5.131, -0.066
Recessive genetic model	1.610	3.353	0.48	0.651	-7.010, 10.230

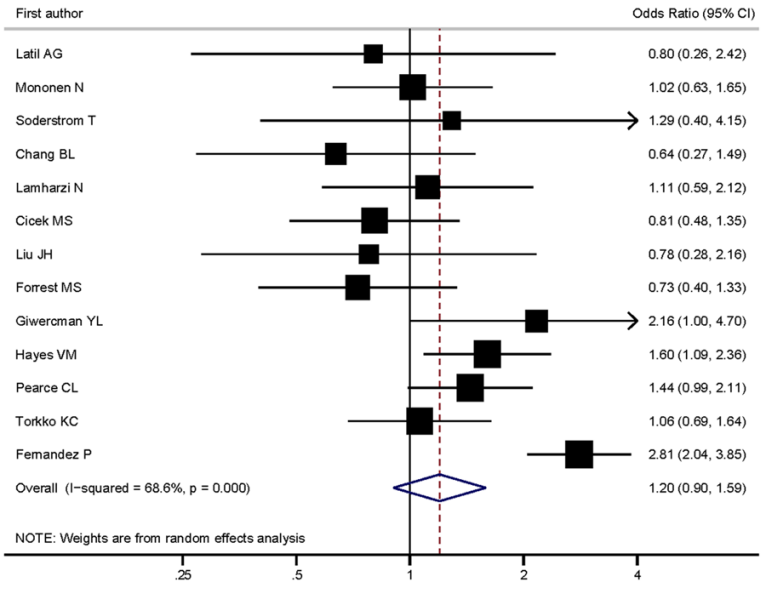

Figure 4. Funnel plot of associations between 5-alpha reductase type II (SRD5A2) V89L polymorphism and the risk of prostate cancer.

ies also suggested that higher serum concentrations of testosterone and 3α-androstanediol glucuronide (3α-diol G) were associated with the increased risks of prostate cancer [7, 39]. The type II steroid 5α-reductase enzyme is a critical enzyme in estrogen metabolism and it is exclusively expressed in the prostate; it is responsible for the conversion of progesterone (P) to the more potent androgen dihydrotestosterone (DHT) in the prostate, which in turn binds to the androgen receptor, thus activating transcription of androgen receptor-responsive elements and inducing cellular proliferation [40].

The type II steroid 5α-reductase enzyme is encoded by SRD5A2 gene and this gene is located on chromosome 2p23 [41]. To date, a number of polymorphisms have been identified in the SRD5A2 gene in human, most of which are nonsense mutation. In 1999, Febbo et al. [42] published the first study exploring the relationship between the SRD5A2 V89L polymorphism and prostate cancer risk. Men with the LL genotype of the V89L had significantly higher serum levels of testosterone and significantly lower serum levels of 5-androstane-3,17 β-diol glucuronide than men with other genotypes [43]. Researchers had consecutively reported the associations between SRD5A2 polymorphisms and prostate cancer risk, but conflicting results were identified. Even though the SRD5A2 plays an important role in estrogen metabolism, and even though these two polymorphisms modulate its activity, no conclusive evidence has indicated that the levels of hormone have an effect on the risk of prostate cancer. Thus, the association between SRD5A2 polymorphisms and prostate cancer risk should be validated carefully by abundant studies.

Previously, five meta-analyses were published focusing on SRD5A2 polymorphisms (V89L and

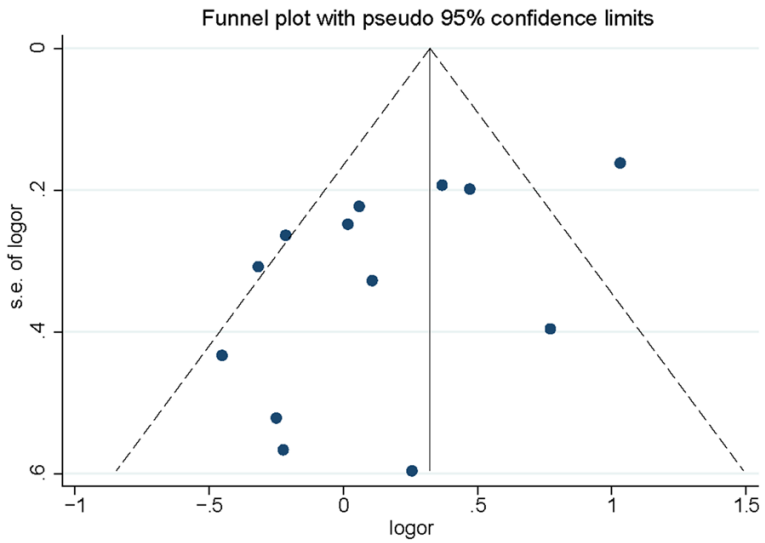

Figure 5. Funnel plot of associations between 5-alpha reductase type II (SRD5A2) A49T polymorphism and the risk of prostate cancer.

A49T) and the preeclampsia risk [11-15]. The latest one was performed by Li et al. [11]. included 28 original studies of 9,178 cases and 9,701 controls for V89L, and 12 studies of 6,385 cases and 5,684 controls for A49T in 2013. In the meta-analysis by Li et al. [11], an increased risk of prostate cancer was observed for A49T under allele comparison model (OR = 1.24; 95% CI = 1.02-1.50, P = 0.024) with significant between-study heterogeneity, but no association was observed for V89L. Another meta-analysis published in 2011 by Li et al. [15] included 25 studies for V89L and 11 studies for A49T showed similar results with study by Li et al. [11] conducted in 2013. Other three studies with less participants showed little evidence of SRD5A2 polymorphisms (V89L and A49T) on prostate cancer risk [12-14]. Our study, with the largest sample size, found no significant associations between SRD5A2 polymorphisms (V89L and A49T) and prostate cancer risk, which were partially consistent with the previous meta-analyses.

Limitations of the present study also need to be taken into consideration. First, significant heterogeneity was found for A49T. After stratified by ethnicity or influence analyses, the heterogeneity significantly reduced, but the results did not change. Second, the literature review was mainly based on PubMed, EMBASE, and CNKI databases, some publications may be missing. Third, some analysis for A49T, e.g., the pooled sample sizes for the subgroup analyses among Asians and Africans were relatively small (< 500 for cases), and these analyses may not have enough statistical power. Fourth, due to missing information about disease status (e.g., early or late onset; mild or severe disease status), we cannot explore the associations between SRD5A2 V89L and A49T polymorphisms and prostate cancer risk by disease status, and this may influence the interpretation. Finally, the lack of original data, such as environment exposure variables and lifestyles, limited our ability to further evaluate adjusted OR and gene-environment interactions.

In summary, our meta-analysis showed that the SRD5A2 V89L and A49T polymorphisms might not confer susceptibility to prostate cancer. More well-designed studies with large sample sizes are invited to validate the findings in the present meta-analysis.

Disclosure of conflict of interest

None.

Abbreviations

SRD5A2, steroid 5-alpha-reductase type 2; OR, odds ratio; 95% CI, 95% confidence interval.

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