Association between CAG repeat polymorphisms and the risk of prostate cancer: A meta-analysis by race, study design and the number of (CAG)n repeat polymorphisms

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Abstract. Although a number of studies have been conducted on the association between prostate cancer and CAG repeat polymorphisms of the androgen receptor gene, this association remains elusive and controversial. In this meta-analysis, we aimed to evaluate the effects of (CAG)n repeat genetic polymorphisms on the incidence of prostate cancer, particularly as regards race, study design and the number of (CAG)n repeats. To collect articles published on the association between CAG repeats and prostate cancer, publications were identified from the National Center for Biotechnology Information (NCBI) database of epidemiological studies published up to October 2011; our identification of publications was not limited by a language barrier. The following search keywords were used: prostate cancer risk, CAG repeat polymorphism, androgen receptor gene and human. Stata version 10 was used for the meta-analysis and the publication bias was measured through the Begg's test and Egger's test. This meta-analysis included 47 studies with 13,346 cases and 15,172 control or non-cases and consisted of 31 reports based on Caucasians, ten on Asians, one on Hispanics and four on combined ethnic groups. The carriers of a shorter CAG repeat sequence had an increased risk of prostate cancer (OR 1.21, 95% CI 1.10-1.34 for all subjects; OR 1.21, 95% CI 1.10-1.34 for prospective studies; OR 1.32, 95% CI 1.15-1.51 for retrospective studies) regardless of the exact length of the CAG repeat, compared with carriers of a longer repeat sequence. In terms of race, the risk of carrying a shorter CAG repeat sequence was 1.10- and 1.83-fold higher than that of a longer repeat sequence in Caucasians and Asians, respectively. For the specific number of CAG repeat polymorphisms, carriers of <22 repeats were observed to have a higher risk of prostate cancer (OR 1.16, 95% CI 1.04-1.29) compared with carriers with ≥22 CAG repeat polymorphisms, particularly for Asians (OR 2.06, 95% CI 1.00-4.24). This meta-analysis suggests that a shorter CAG repeat polymorphism may increase the risk of prostate cancer compared with the longer CAG repeat; in particular, the effect of shorter CAG repeats on the increased risk of prostate cancer was predominantly observed in Caucasians and Asians.

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Introduction

Prostate cancer is ranked as the second major cause of cancer-related mortality in developed countries (1). Although the incidence of latent prostate cancer appears to be constant worldwide, the incidence of its clinical forms varies substantially (2). African-American males have long been known to have the highest rates of prostate cancer worldwide, whereas native Japanese and Chinese males have the lowest known prostate cancer rates (3). This difference is likely due to both environmental and genetic factors. In addition to the role of age and race on the risk of prostate cancer, family history appears to be one of the most important risk factors (4): the incidence of prostate cancer is positively associated with relevant family history with a strong genetic dose-effect (5).

Androgen plays an important role in the growth and functions of both normal and malignant prostate glands and can affect the carcinogenesis of prostate cancer (3). Androgen function is achieved by the androgen receptor, which is a ligand-dependent nuclear transcription factor (6,7). Dihydrotestosterone, transformer of testosterone, combines with the carboxyl-terminal of an androgen receptor, which is activated and changed into a form with greater structural stability. Subsequently, it enters the nucleus to combine with the androgen response elements (AREs) in the DNA to induce transcription (8). The androgen receptor gene is located on chromosome Xq11-12 and is composed of eight exons. These eight exons each perform in the transcription of the amino-terminal transcriptional activation (transactivation) domain, the DNA binding domain (a hinge region) and the carboxyl-terminal ligand binding domain. Among these three

domains, the transactivation domain has several polymorphisms, which regulate the manifestation of the target gene. Three microsatellite trinucleotide repeats exist in this transactivation domain. In particular, CAG presents with a different length for each person and exists upstream and downstream of each domain to encode polyglutamine and polyglycine (9). An experimental study discovered that the replication of the androgen receptor gene within prostate epithelial cells was increased with a shorter CAG repeat (10).

The average CAG repeat length has a wide ethnic variety: Africans possess a slightly shorter CAG repeats than Caucasians, whereas Asians have a longer CAG repeat than other races. In general, the CAG repeat length is measured as 19, 22 and 23 for Africans, Caucasians and Asians, respectively (11). Therefore, in this meta-analysis, we aimed to evaluate the effects of (CAG) n repeat polymorphisms of the androgen receptor gene in relation to the risk of prostate cancer, as regards race and the number of CAG repeat polymorphisms simultaneously, as well as the characteristics of the study design.

Materials and methods

Search strategy. To collect articles published on the association between CAG repeats and prostate cancer, publications were identified from the National Center for Biotechnology Information (NCBI) database of epidemiological studies. The following keywords were used: prostate cancer risk, CAG repeat polymorphism, androgen receptor gene and human. We further examined citations for all retrieved articles of studies that had not been initially identified. If more than one geographical or ethnic population was included, we considered each population or group independently.

We identified studies that fulfilled the following criteria: i) evaluation of the association between prostate cancer and CAG repeat polymorphisms; ii) nested case-control, case-control or cross-sectional study; and iii) sufficient information on CAG repeat distributions between patients and controls for estimating the odds ratio (OR) and the 95% confidence interval (95% CI).

Data extraction. The two authors of this article independently extracted the following information from all available studies. Original studies were blinded for authors, affiliations, journal names, publication year and acknowledgments. Each study was categorized as one of the following items: general information (publication year and geographical area), population characteristics (size of the study, population and ethnicity) and patient and control subject characteristics (number, mean age at diagnosis and their respective status in terms of to what extent the prostate cancer of the subject had progressed). To investigate the potential influence of the timing of diagnosis, all studies were classified as either prospective (cohort) studies or retrospective (case-control and cross-sectional) studies. For stratified analysis by ethnicity, each article was classified into Caucasians, Asians and Africans based on the respective number of participants, apart from one study on Hispanics. If the results of various races were included in one report, the results of each race were separately used during the subgroup analysis. Finally, 47 studies were included in this meta-analysis (13-18,23-24,30-68).

For each study, we extracted an OR to evaluate the risk of CAG repeat polymorphisms in relation to the risk of prostate cancer. If the OR was not presented, but the number of case and controls were reported, we calculated the OR. We analyzed 47 studies by using shorter/longer repeats presented in each article regardless of the exact cut-off length of the CAG repeat. In addition, we focused on two widely evaluated dichotomous comparisons, viz. ≥23 repeats of the CAG sequence vs. others and ≥22 repeats vs. others. This was done as no studies provided the specific distributions of the repeat counts.

Statistical analysis. The strength of the association between the cut-off values of the repeat number and the risk of prostate cancer was assessed by calculating the OR and the 95% CI. In this meta-analysis, we used the random-effects model instead of the fixed-effects model. Estimates were also stratified by study design (prospective vs. retrospective), the CAG repeat polymorphism (shorter vs. longer) and ethnicity (Caucasian vs. Asian vs. African). The effect, standard error and variability were measured for the heterogeneity test in accordance with the log OR and calculated through function Meta. In addition, meta-regression was employed to estimate the covariates which could explain the heterogeneity.

The heterogeneity between the studies was presented through the random effects model. The between-study heterogeneity was assessed by the χ^2 test-based Q statistic. A P-value <0.05 was considered to indicate a statistically significant difference. A meta-regression was conducted to identify sources of between-study heterogeneity.

An estimate of potential publication bias was carried out by the funnel plot and Egger's linear regression test (69). The potential publication bias was examined visually in a funnel plot of log (OR) against its standard error (SE) and the degree of asymmetry was tested by Egger's test ($P<0.05$ was considered a significant publication bias). Begg's test (70) and Egger's test can detect funnel plot asymmetry by determining whether the intercept deviates significantly from zero in a regression of the standardized effect estimates against their precision. If publication bias existed, the non-parametric 'trim and fill' method was used to adjust for it (71). We predicted the contribution of the CAG repeat polymorphism to the risk of prostate cancer using Stata software version 10.0.

Results

After an extensive literature search, we finally identified 47 reports that satisfied our inclusion/exclusion criteria and conducted at least one of the aforementioned comparisons. Our search and selection process is described in Fig. 1. The selected literature included nine nested case-control studies, 31 case-control studies and seven cross-sectional studies. We focused on two widely evaluated dichotomous comparisons: as considering overlap, 16 and 27 studies reported the comparison of ≥23 repeats of CAG sequences vs. others and ≥22 repeats vs. others, respectively. Studies were classified according to race: 31 reports on Caucasians, ten on Asians, six on Africans, one on Hispanics and four on mixed race subjects.

In total, there were 47 reports with 13,346 patients and 15,172 controls. A total of 11 studies were selected from seven Asian countries (including Japan, China, Singapore, India,

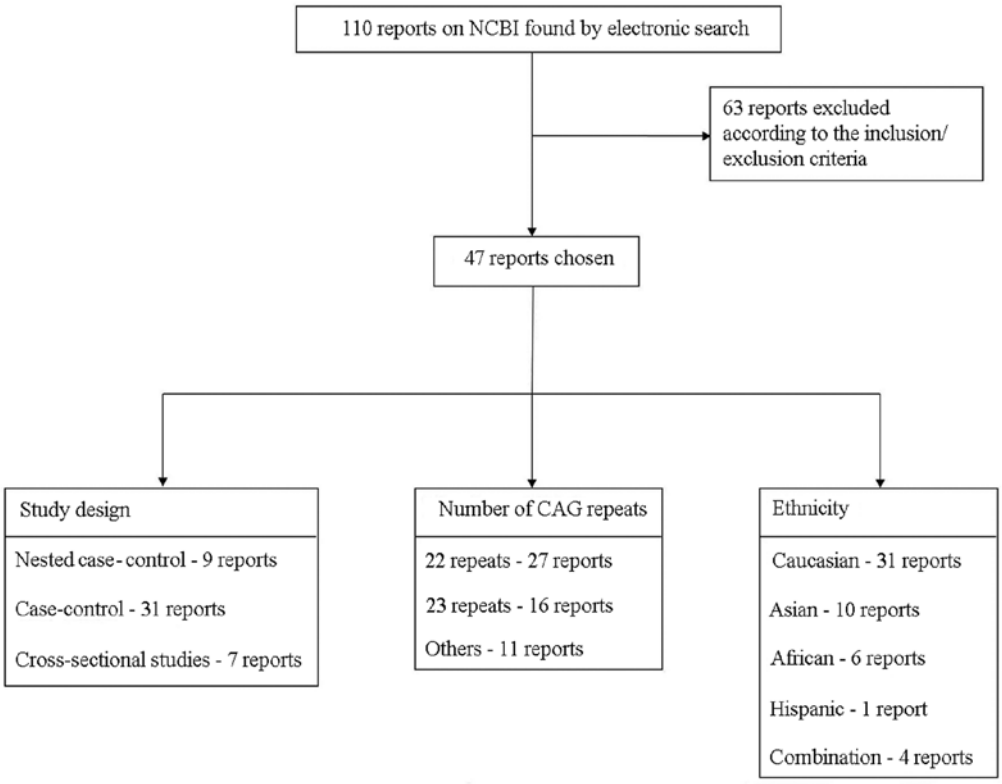

Figure 1. Diagram of the literature search and selection process. Cross-sectional studies were included in case-control studies when conducting analysis according to the study design. Others: <17/≥17, <18/≥18, <19/≥19, <20/≥20, <21/≥21, <25/≥25.

Taiwan, Iran and Israel), 36 studies were selected from nine Western countries (including the USA, Austria, Israel, France, Sweden, Finland, Germany, England and Italy) and seven studies were selected from Brazil, South Africa, Nigeria and Colombia. The age range was from 45 to 76.2 years for the patient group and from 45 to 75 years for the control group. The pathological stage of prostate cancer was presented in 21 reports among the selected literature (Table I).

The carriers of a shorter CAG repeat had an increased risk of prostate cancer (OR 1.21, 95% CI 1.10-1.34) compared with those of a longer CAG repeat based on the presented criteria taken from the original study whatever the exact length of the CAG repeat (Fig. 2). Most prospective studies showed no significant differences between shorter and longer repeats, apart from one report. Therefore, the results of the meta-analysis in relation to the prospective studies did not indicate the association of shorter CAG repeats with the risk of prostate cancer risk (OR 1.04, 95% CI 0.90-1.20). In terms of retrospective studies, 14 studies out of 31 reports presented a higher risk of shorter CAG repeats compared with longer CAG repeats (OR 1.32, 95% CI 1.15-1.51).

On the other hand, the effect of shorter CAG repeats on the incidence of prostate cancer was predominant among Asians (OR 1.83, 95% CI 1.04-3.22, Table II); the results for Caucasians indicated borderline significance (OR 1.12, 95% CI 0.99-1.26) and there was no significant difference between the CAG repeat polymorphisms and prostate cancer risk among Africans (OR 0.87, 95% CI 0.35-2.17). Based on the specific repeat number of CAG polymorphisms, we carried out an advanced analysis following stratification by race and the number of CAG repeats (Table II). Based on the meta-analysis of 27 studies, which presented the association between the ≥22 CAG repeat polymorphisms and the risk of prostate cancer, we observed a positive association of <22 CAG repeat polymorphisms with the risk of cancer (OR= 1.16, 95% CI 1.04-1.29). In particular, the risk increased by 2.06-fold in Asians (OR 2.06, 95% CI 1.00-4.24), but not in Caucasians (OR 1.07, 95% CI 0.98-1.18) and Africans (OR 0.95, 95% CI 0.53-1.70). On the other hand, there was no association of the <23 CAG repeat polymorphisms with the risk of prostate cancer using 16 studies compared with ≥23 CAG repeats. In the analysis conducted according to race, no difference was presented between longer CAG repeats and shorter CAG repeats in terms of the risk of prostate cancer (Table II).

Publication bias was analyzed according to the study design (Fig. 3). For the prospective studies, the P-value was 0.53 for Begg's test and 0.41 for Egger's test, and no publication bias was identified. For the retrospective studies, we found a publication bias (both Begg's and Egger's test was 0.03). Five retrospective studies contributed to the publication bias based on the deviability from the standard (19,39,43,49,67). Publication bias was observed according to race. For Caucasians, the P-value was 0.07 for Begg's test and 0.03 for Egger's test. For Asians, the P-value was 0.79 for Begg's test and 0.96 for Egger's test. For Africans, the P-value was 0.85 for Begg's test and 0.99 for Egger's test. A statistical significance in terms of the heterogeneity between the 47 studies was observed (Q=196.18; P=0.00).

Table I. Characteristics of published epidemiological studies concerning the association between the length of CAG repeat polymorphisms and the risk of prostate cancer.

Authors (Refs.)	Population		No. of subject case/control	Age		Case Ad. (%)	Cut-off point of repeat no.[a]		
	Ethnicity	Country		Case	Control				
Prospective studies									
Lange *et al* (26)	Afr	USA	131/340	67.0	62.1	-	22	23	
Platz *et al* (27)	C	USA	448/448	69.8	-	-	22		
Freedman *et al* (28)	A + Afr + C + L	USA	2036/2160	60.0	60.0	-	22		23
Visvanathan *et al* (29)	C	USA	164/324	66.1	66.0	-	22		
Chen *et al* (30)	C	USA	300/300	61.2	60.8	11.5	22		
Latil *et al* (31)	C	France	226/156	70.5	71.7	69.8		23	
Platz *et al* (32)	C	USA	582/794	62.0	-	46.6			20
Giovannucci *et al* (18)	C	USA	587/588	-	-	30.7	22		
Price *et al* (33)	Afr	USA	116/149	63.4	63.6	-			19
	C	USA	1076/1047	63.4	63.6	-			
Retrospective studies									
Nicolaiew *et al* (34)	C	French	1045/814	67.0	63.0	-			17
Silva *et al* (35)	C + U	Brazil	49/51	64.0	59.3	-	22		
Das *et al* (36)	A	Singapore	52/46	66.0	69.0	-			23
Andersson *et al* (24)	C	Sweden	137/125	76.2	60.0	-		23	
Lindström *et al* (37)	C	Sweden	1461/796	-	-	48.0		23	
Okugi *et al* (38)	A	Japan	102/117	69.9	71.0	55.8		23	
Krishnaswamy *et al* (39)	A	india	87/120	67.5	66.5	-			20
Sieh *et al* (40)	Afr + C	USA	193/391	76.7	72.9	34.2	22		
Salinas *et al* (41)	C	USA	591/538	57.3	56.8	-	22		
Forrest *et al* (42)	C	UK	50/76	51.1	-	-			23
Mishra *et al* (43)	A	india	113/133	65.6	63.7	-		23	20
Cicek *et al* (44)	C	USA	397/397	63.0	63.0	-	22		
	Afr	USA	38/38	62.0	63.0	-			
Gilligan *et al* (45)	Afr	Columbia	118/567	66.7	55.5	24.5	22		
Huang *et al* (46)	A	Taiwan	66/104	71.5	71.7	40.9		23	
Gsur *et al* (47)	C	Austria	190/190	65.9	66.5	-		23	
Mononen *et al* (48)	C	Finland	461/574	68.1	-	48.1			19,25
Balic *et al* (49)	H	USA	82/145	64.0	57.0				19
Modugno *et al* (50)	C	USA	88/241	68.9	73.6	-		23	
Xue *et al* (51)	C	USA	57/156	57.8	-	-			20
Lange *et al* (52)	C	USA	133/305	64.0		-	22		
Hsing *et al* (53)	A	China	191/304	72.2	71.9	62.6	22	23	
Correa-Cerro *et al* (54)	C	Fra./Ger.	85/46	68.2	71.2	-	22		
Edwards *et al* (55)	C	UK	178/195	68.1	-	75.3	22		
Ekman *et al* (56)	C	Sweden	59/38	69.0	72.0	-	22	23	
	A	Japan	34/33	71.0	60.0	-			
Ingles *et al* (57)	C	USA	57/169	57.8	58.2	46.0	22		
Stanford *et al* (58)	C	USA	301/277	54.9	54.0	45.9	22		
Hakimi *et al* (19)	C	USA	59/370	62.1	-	42.4			18
Li *et al* (59)	A	Japan	33/43	33.0	-	75.0	22	23	
	C	Sweden	59/98	59.0	-	50.4			
Kuasne *et al* (60)	C	Brazil	160/160	65.4	63.9	-			21
Ashtiani *et al* (61)	A	Iran	110/67	69.5	60.4	-	22		
Akinloye *et al* (62)	Afr	Nigeria	70/73	63.5	62.3	-	22		
Chang *et al* (63)	C	USA	245/222	60.9	58.0	-	22		
Miller *et al* (64)	C	USA	137/69	65.7	66.2	-	22		
Irvine *et al* (65)	C	USA	57/39	57.7	35.0	47.0	22		

Table I. Continued.

Author (Refs.)	Population		No. of subject case/control	Age		Case Ad. (%)	Cut-off point of repeat no.
	Ethnicity	Country		Case	Control		
Panz *et al* (66)	C	USA	20/20	68.0	-	30.0	22 23
	Afr	Israel/ South Africa	20/20	76.0	-	30.0	
Mittal *et al* (67)	A	India	135/142	66.2	64.1	-	22
Santos *et al* (68)	A + Afr + C	Brazil	133/279	65.0	58.0	-	22
Risio *et al* (12)	C	Italy	69/234	65	62.5	24.2	21

Ad. (%), percentage of advanced prostate cancer. That is T3-T4, M0; T0-T4, M1. [a]Each number indicates the cut-off point for CAG repeat polymorphisms. A, Asian; Afr, African; C, Caucasian; L, Latino; H, Hispanic; U, unknown; UK, United Kingdom; Fra., France; Ger., Germany.

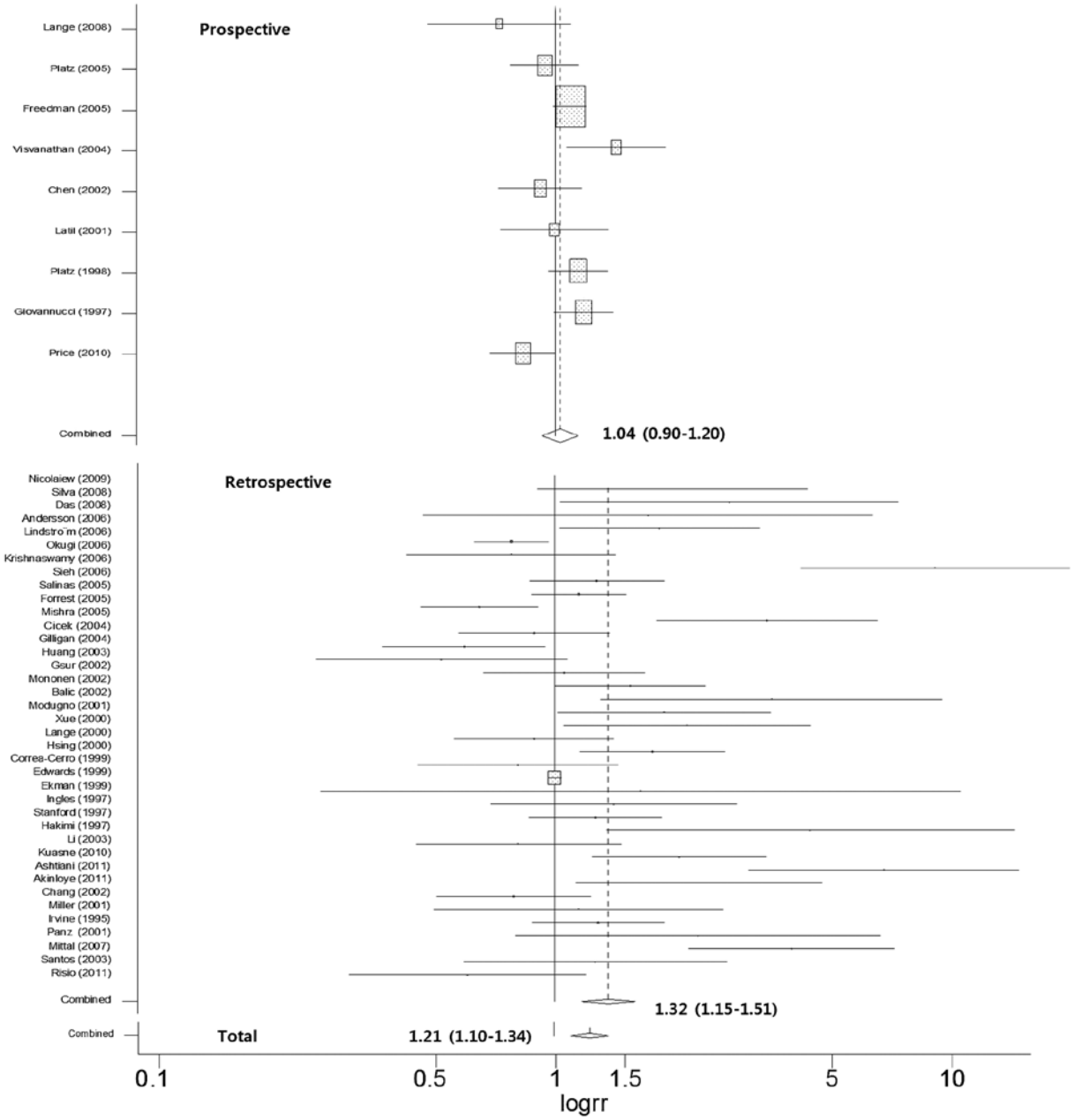

Figure 2. Study-specific estimates (boxes) and corresponding 95% CI (horizontal lines) for the effect of CAG repeat polymorphisms on the risk of prostate cancer. (Q=196.18 , P=0.00).

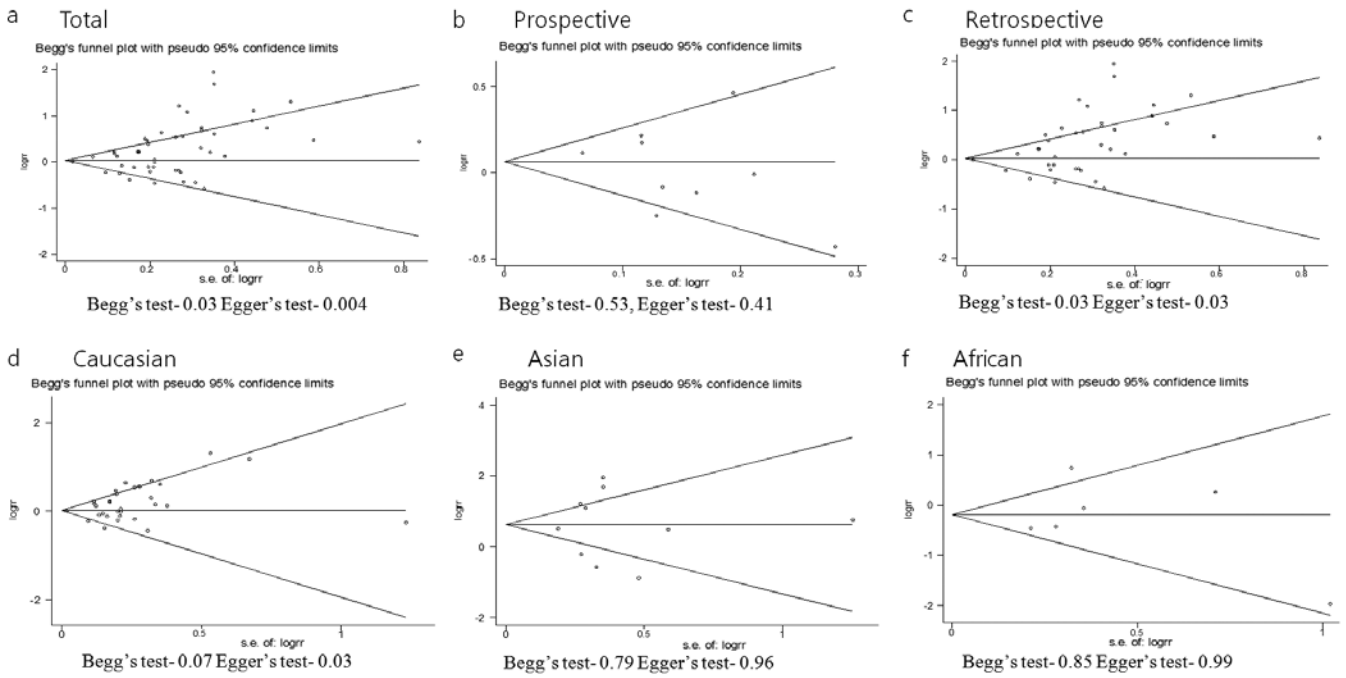

Figure 3. Publication bias plot for CAG repeat polymorphisms.

Discussion

The results of this meta-analysis of 13,346 patients and 15,172 controls from 47 reports suggest that shorter CAG repeat polymorphisms of the androgen receptors are associated with the increased risk of prostate cancer compared with longer CAG repeats regardless of the exact number of CAG repeat polymorphisms. The association was not shown in the meta-analysis using prospective studies, but was observed using retrospective studies. In particular, while the risk of prostate cancer increased predominately among Asians, this was not the case among Africans and Caucasians. Considering the number of CAG repeat polymorphisms, the association was only presented after stratification by dichotomous comparison viz. <22 CAG repeats of CAG polymorphisms vs. others.

Although the majority of studies report a positive association between shorter CAG repeat polymorphisms and the risk of prostate cancer, the cut-off point for the length of CAG repeats differed from each race and study population. The length of a CAG repeat was usually longer in Asians than in Caucasians (12). In general, the majority of studies may have taken the average CAG repeat as the cut-off point for the CAG repeats. Therefore, it is difficult to take a unique and standard cut-off point of the CAG repeat polymorphisms for a meta-analysis. In our meta-analysis, the effect of the shorter CAG repeat polymorphisms on the increased risk of prostate cancer was evaluated using shorter and longer CAG repeats whatever the exact cut-off point of the CAG repeat length in each of the 47 studies. A meta-analysis with 23 studies published in 2004 (13) suggested that prostate cancer patients have a short CAG repeat length (the average difference between cases and controls was 0.26) and reported that the incidence rate of prostate cancer decreased to 1.02 with the increase of one CAG repeat. Another meta-analysis conducted in 2012 (14) was based on 27 studies and reported that the risk decreased by 0.79-fold among subjects aged 45 years and above when the cut-off point of the CAG repeats was taken as <21 vs. ≥21 CAG repeat polymorphisms. On the other hand, a recent and major prospective study in the USA (15) reported no association between the CAG repeat and the risk of prostate cancer based on a continuous model (OR 0.96, 95% CI 0.88-1.08, P(trend) = 0.46, per 10 CAG repeat increment). However, this study did not examine the effect of the CAG repeat polymorphisms in terms of shorter vs. longer.

Testosterone combines with androgen receptors to stabilize the structure and promote the replication of androgen receptors associated with prostate cancer. The testosterone level of African-Americans was 15% higher than that of European-Americans, which may explain the difference in the incidence of prostate cancer between the two ethnic groups (16). An experimental study discovered that the increased transcription of the androgen receptor gene within prostate epithelial cells was associated with shorter CAG repeats (17). Certain studies have suggested that short CAG repeats constantly stimulate androgen, which gives rise to the proliferation of prostate cells and finally induces somatic mutation (6,18). Furthermore, short CAG repeats have been associated with the aggressive forms of prostate cancer, as well as the incidence of other androgen-related diseases (18,19). The decreased formation and fertilization of sperm cased by longer CAG repeats (20), balding (21) and prostatic hypertrophy (22,23) have been associated with shorter CAG repeats. Andersson *et al* suggested two possible mechanisms to explain the association between the length of CAG repeat polymorphisms and androgen receptor transcription. First, the trinucleotide CAG repeat may act as a suppressor of transactivation, where the longer length of the triple region acts as a more effective suppressor. Second, a receptor with a shorter CAG repeat has a more stable structure (24).

Table II. Association of CAG repeat polymorphisms with the risk of prostate cancer following stratification by study design, cut-off point for repeat number and ethnicity.

	Refs.	Meta-analysis (OR)
Overall		
Shorter/ longer	(47)	1.21 (1.10-1.34)
Subgroup		
Study design		
Prospective		
All	(9)	1.04 (0.90-1.20)
Caucasian	(7)	1.09 (0.95-1.25)
African	(2)	0.75 (0.49-1.15)
Retrospective		
All	(38)	1.32 (1.15-1.51)
Caucasian	(24)	1.12 (0.99-1.26)
Asian	(10)	1.83 (1.04-3.22)
African	(4)	0.87 (0.35-2.17)
Length of CAG repeat no.		
<22/≥22	(27)	1.16 (1.04-1.29)
<23/≥23	(16)	1.09 (0.90-1.33)
Ethnicity		
Caucasian		
All	(31)	1.10 (1.00-1.21)
<22/≥22	(17)	1.07 (0.98-1.18)
<23/≥23	(9)	1.07 (0.83-1.39)
Asian		
All	(10)	1.83 (1.04-3.22)
<22/≥22	(5)	2.06 (1.00-4.24)
<23/≥23	(7)	1.16 (0.65-2.00)
African		
All	(6)	0.86 (0.52-1.43)
<22/≥22	(5)	0.95 (0.53-1.70)
<23/≥23	(2)	0.71 (0.43-1.19)

The average CAG repeat length has a wide ethnic variety (11). Africans possess a slightly shorter CAG repeat than Caucasians, whereas Asians have a longer CAG repeat than subjects from other races. In general, the length of the CAG repeat was measured respectively as 19, 22 and 23 for Africans, Caucasian and Asians (11). The risk of prostate cancer generally increases in Western countries but decreases in Asian countries (3). This suggests that there is a clear association of the CAG repeat polymorphisms with the risk of prostate cancer (25). Our meta-analysis also presents the protective effect of longer CAG repeat polymorphisms on prostate cancer in Caucasians and Asians; the cut-off point of criteria for the meta-analysis was 22 and 23 for Caucasians and Asians, respectively. Although shorter CAG repeats were associated with a higher risk of prostate cancer than longer CAG repeats in case-control studies, no significant results were observed in nested case-control studies. The results of Caucasians and Asians in case-control studies were identical. Otherwise, the significance was still not observed in the analysis of nested case-control studies following stratification by race. Therefore, we should carefully explain the difference by race, as the association may not be independent of study design or the number of CAG repeats.

The strength of this meta-analysis is its large number of subjects, including 13,346 cases and 15,172 controls based on 47 studies (nine nested case-control studies, 31 case-control studies and seven cross-sectional studies). A meta-analysis conducted in 2004 composed of 4,274 cases and 5,275 controls and quoted a total of 23 studies: five nested case-control studies and 19 case-control studies (13). Another meta-analysis (14), which reported the association between androgen receptor CAG repeat polymorphisms with ≥22 repeats and the risk of prostate cancer among subjects aged 45 years or older, was composed of 3,835 cases and 4,774 controls and only quoted a total of 27 studies. Furthermore, in the present meta-analysis, an advanced analysis was conducted according to study design, race and the number of CAG repeat polymorphisms, in contrast to previous meta-analysis reports.

However, this meta-analysis also had certain limitations. Confounding factors could not be used as we were unable to retrieve common information from all these original publications for a variety of confounding factors, such as smoking history or other lifestyle factors. Therefore, the findings from our meta-analysis require further confirmation or validation. On the other hand, the association between the risk of prostate cancer and androgen receptor CAG repeat polymorphisms was not observed in all races or studies. It is insufficient to explain the incidence of prostate cancer based on genetic factors only, as it does not correspond with the results of the genetic variation of previously presented studies. Individual differences in the sensitivity of prostate cancer cells must be explained in relation to other reasons, such as lifestyle (including smoking history and other environmental factors).

In conclusion, in this meta-analysis, it was verified that shorter CAG repeats increase the risk of prostate cancer compared with longer CAG repeats, whatever the exact length of the CAG repeat. In particular, race and the length of the CAG repeat polymorphisms may influence the association between the CAG repeat polymorphisms and the risk of prostate cancer.

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