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REVIEW

CAG repeat polymorphisms in the androgen receptor and breast cancer risk in women: a meta-analysis of 17 studies

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Abstract: The association between polymorphic CAG repeats in the androgen receptor gene in women and breast cancer susceptibility has been studied extensively. However, the conclusions regarding this relationship remain conflicting. The purpose of this meta-analysis was to identify whether androgen receptor CAG repeat lengths were related to breast cancer susceptibility. The MEDLINE, PubMed, and EMBASE databases were searched through to December 2014 to identify eligible studies. Data and study quality were rigorously assessed by two investigators according to the Newcastle-Ottawa Quality Assessment Scale. The publication bias was assessed by the Begg's test. Seventeen eligible studies were included in this meta-analysis. The overall analysis suggested no association between CAG polymorphisms and breast cancer risk (odds ratio [OR] 1.031, 95% confidence interval [CI] 0.855–1.245). However, in the subgroup analysis, we observed that long CAG repeats significantly increased the risk of breast cancer in the Caucasian population (OR 1.447, 95% CI 1.089–1.992). Additionally, the risk was significantly increased in Caucasian women carrying two alleles with CAG repeats ≥22 units compared with those with two shorter alleles (OR 1.315, 95% CI 1.014–1.707). These findings suggest that long CAG repeats increase the risk of breast cancer in Caucasian women. However, larger scale case-control studies are needed to validate our results.

Keywords: androgen, CAG repeat polymorphism, women, breast cancer, risk, meta-analysis

Introduction

Breast cancer is the most common cause of death due to tumor development and the most common type of cancer in women.[1] In the USA, breast cancer is the leading type of cancer and the second most fatal cancer among female patients.[2] Accumulating evidence has indicated that the risk of breast cancer is strongly related to endogenous hormone levels and genes responsive to such hormones. Recent studies have shown that the human androgen receptor (AR), which is responsive to changes in hormone levels, plays an important role in breast cancer risk.[3]

The human AR is a nuclear receptor. The AR gene is composed of eight exons and maps to Xq11–12. CAG repeats exist in the first exon of the AR gene, which encodes a glutamine tract. The length of this tract varies from 10 to 40 repeat units among individuals.[3] The length of the CAG repeat in exon 1 of the AR might be inversely related to its transactivation efficiency. Alleles with long repeat lengths have been associated with decreased efficacy of androgenic activity, and this decreased activity will inhibit androgen signaling, which inhibits breast carcinogenesis by limiting the proliferation of breast cancer cells.[4] This finding is consistent with in vitro studies, which have shown that androgen inhibits breast epithelial cell proliferation.[5,6] Furthermore, recent investigations have

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indicated that polymorphisms of the AR gene are modulators of the penetrance of BRCA1 mutations in women.[7]

Therefore, CAG polymorphisms might be correlated with the risk of breast cancer.[8] However, the results of previous studies are inconsistent. Some studies have shown that breast cancer in women exhibits an inverse association with CAG repeat length polymorphisms. Shorter CAG repeats have been described as high-risk factors for breast tumors.[9–11] However, some studies have shown opposite results.[12,13] These inconclusive and conflicting results may be partially due to relatively small sample sizes and different statistical models used in each of the published studies. Therefore, we performed a meta-analysis to evaluate the association between CAG repeat length polymorphisms and breast cancer risk.

Methods

Data sources and searching strategy

This meta-analysis was conducted and reported in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines for systematic reviews and meta-analyses (Table S1). A comprehensive search of the PubMed and EMBASE databases was conducted to identify published studies that evaluated the relationship between CAG polymorphism and breast cancer risk in women. We searched the databases using the following medical subheadings and keywords: "androgen receptor" and the abbreviation of the gene "AR", "short tandem repeat", "CAG", "(CAG)n", "polymorphism", and "breast cancer". Other alternative spellings were also considered. The reference lists of included papers, systematic reviews, letters, and commentaries were examined. No language restrictions were implemented.

Study identification and evaluation criteria

The relevant publications were carefully evaluated to obtain any possible related articles. The following inclusion criteria were used to select eligible studies: articles regarding AR CAG polymorphism and breast cancer risk in women; only the most recent or complete study if the same study subjects were included in more than one publication; studies with clear partial or detailed genotyping; and case-control studies using either a hospital-based or a population-based design.

Data extraction

Two authors (QM and MQ) independently extracted the following information from all qualified studies: first author's last name, publication data, population ethnicity, study design, baseline characteristics of the study population, and the genotype distribution of the cases and controls. According to previous investigations, we defined the recessive and dominant genotypes by the length of the CAG repeat. A shorter length CAG repeat (less than 22 repeats) was defined as a recessive genotype. A long length CAG repeat (more than 22 repeats) was defined as a dominant genotype.[6,14,15] Any disagreements encountered were resolved by discussion with another author (FJ) until a consensus was reached.

Quality evaluation

The Newcastle-Ottawa Scale was used to assess the quality of the included case-control studies, which evaluated three aspects of the studies including selection, comparability, and exposure.[16] A study was awarded a maximum of one "star" for each high-quality item within the "selection" and "exposure" categories and a maximum of two "stars" for the "comparability" category. The quality assessment was conducted by two authors (QM and MQ) independently.

Statistical analysis

Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to estimate the relationship between CAG polymorphism and breast cancer risk. The following comparison models were calculated: SS versus all SL-LL (SS, women carrying two shorter alleles; SL, women carrying at least one long allele; and LL, women carrying two long alleles) in all 17 studies; and a homozygote comparison (SS versus LL), recessive model (SS-SL versus LL) and dominant model (SS versus SS-LL) were performed in 12 studies, including a detailed comparison of SL and LL. Additionally, a subgroup analysis was performed based on ethnicity.

A Q-statistic test was performed to evaluate the between-study heterogeneity.[17] If the result of the heterogeneity test was $P<0.10$, the pooled ORs were analyzed using the random-effects model. Otherwise, the fixed-effects model was selected. These two models provided similar results when between-study heterogeneity was absent. The potential publication bias was evaluated with a funnel plot and Begg's linear regression asymmetry test. Begg'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.[18] All statistical analyses were performed using Stata version 12.0 software (Stata Corporation, College Station, TX, USA).

Results

Search process

Ninety-nine studies were primarily identified. The search and selection process is described in Figure 1. After an

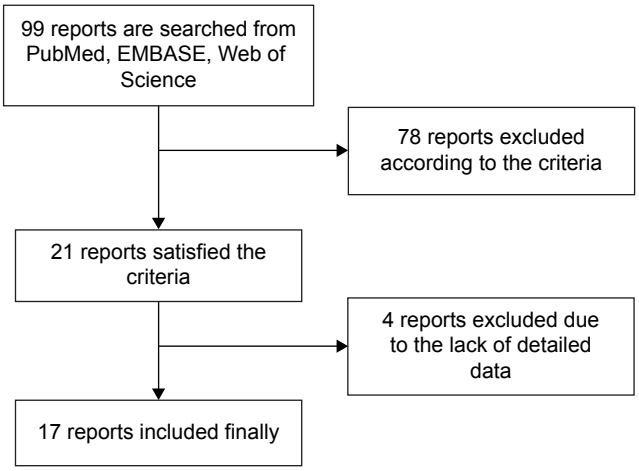

Figure 1 Flow diagram.

extensive literature search, we finally identified 17 reports that met our inclusion criteria and conducted at least one of the aforementioned comparisons.[6,9–15,19–27]

Characteristics of eligible studies

Seventeen reports were examined in this meta-analysis, which included 10,919 cases and 14,002 control subjects. The characteristics of the study population are shown in Table 1. Eleven studies were conducted among the Caucasian population, and four studies were conducted among the Asian population. Other studies were conducted among African populations. The distributions of CAG repeat lengths in alleles of the AR gene were shown in all studies. However, five studies showed only the distribution of women who carried two shorter alleles (SS) and women who carried one or two long alleles (SL-LL; Table 2).

CAG polymorphism and cancer risk

Because the *P*-value of the heterogeneity was less than 0.1, the random effects model was selected. Seventeen studies, including 10,919 cases and 14,002 control subjects, were pooled to estimate the comparison of SS and SL-LL (D + L pooled OR 1.031, 95% CI 0.855–1.245, $P<0.05$; Figure 2). Neither the comparison of SS versus LL nor that of SS-SL versus LL showed significant differences in breast cancer risk (D + L pooled OR 1.062, 95% CI 0.784–1.439, $P<0.05$; D + L pooled OR 0.994, 95% CI 0.819–1.207; $P<0.05$).

Because differences in race could influence the results, we divided the studies into three groups according to ethnicity. In the Caucasian subgroup, a 1.4-fold increased risk was observed in women carrying one or two long alleles (D + L pooled OR 1.447, 95% CI 1.089–1.992) in eight studies that included 8,827 cases and 11,526 control subjects (Figure 3). Additionally, compared with women who carried two shorter alleles, those with two long alleles had a substantially increased risk of breast cancer (D + L pooled OR 1.315, 95% CI 1.014–1.707; Figure 4). These results indicate that the breast cancer risk was elevated in Caucasian women who carried one or two long alleles. However, women who carried one or two long alleles showed a protective effect against breast cancer in the Asian subgroup (D + L pooled OR 0.589, 95% CI 0.307–1.129), which included three studies with 1,595 cases and 1,968 control subjects. An additional analysis was performed in the African subgroup. There were no major differences between the SS and SL-LL groups in the African subgroup (D + L pooled OR 0.962, 95% CI 0.681–1.358), which included two studies with 497 cases and 508 control subjects. These results are presented in Table 3.

Table 1 Baseline characteristics of included studies

References	Year	Country	Ethnicity	Cases	Controls	Treatment	Mutation gene	OR (95% CI)
Tsezou et al[10]	2008	Greece	Caucasian	78	154	No chemotherapy or radiotherapy	AR_(CAG)n	0.089 (0.016–0.486)
Wu et al[27]	2008	People's Republic of China	Asian	88	334	No chemotherapy or radiotherapy	AR_(CAG)n	2.70 (1.00–7.31)
Iobagiu et al[11]	2006	France	Caucasian	139	145	No chemotherapy or radiotherapy	AR_(CAG)n	1.93 (1.05–3.55)
Zheng et al[15]	2012	USA	African	258	259	No chemotherapy or radiotherapy	AR_(CAG)n	1.08 (1.01–1.15)
Dunning et al[6]	1999	UK	Caucasian	508	426	No chemotherapy or radiotherapy	AR_(CAG)n	0.82 (0.62–1.09)
De abreu et al[20]	2007	Brazil	Caucasian	54	72	No chemotherapy or radiotherapy	AR_(CAG)n	–
Mehdipour et al[23]	2011	Iran	Asian	500	432	No chemotherapy or radiotherapy	AR_(CAG)n	2.03 (1.56–2.6)
Sakoda et al[14]	2011	People's Republic of China	Asian	614	879	No chemotherapy or radiotherapy	AR_(CAG)n	2.6 (1.3–5.4)
Suter et al[26]	2003	USA	Caucasian	524	461	No chemotherapy or radiotherapy	AR_(CAG)n	0.97 (0.63–1.48)
Haiman et al[21]	2002	America	Caucasian	727	960	No chemotherapy or radiotherapy	AR_(CAG)n	1.70 (1.20–2.40)
Wedren et al[9]	2007	Finland	Caucasian	1,496	1,340	No chemotherapy or radiotherapy	AR_(CAG)n	1.26 (1.04–1.51)
Abbas et al[19]	2010	Germany	Caucasian	2,942	5,252	No chemotherapy or radiotherapy	AR_(CAG)n	1.10 (1.03–1.18)
Spurdle et al[25]	1999	Australia	Caucasian	368	284	No chemotherapy or radiotherapy	AR_(CAG)n	1.40 (0.94–2.09)
Liede et al[22]	2003	Philippines	Asian	393	323	No chemotherapy or radiotherapy	AR_(CAG)n	0.47 (0.28–0.8)
Wang et al[13]	2005	USA	African	239	249	No chemotherapy or radiotherapy	AR_(CAG)n	3.18 (1.08–9.36)
Slattery et al[24]	2007	USA	Caucasian	1,734	2,039	No chemotherapy or radiotherapy	AR_(CAG)n	0.87 (0.62–1.23)
Gonzalez et al[12]	2007	Spain	Caucasian	257	393	No chemotherapy or radiotherapy	AR_(CAG)n	1.49 (1.06–2.09)

Abbreviations: OR, odds ratio; CI, confidence interval.

Table 2 Distribution of androgen receptor alleles

References	Ethnicity	SS (case)	SL (case)	LL (case)	SS (control)	SL (control)	LL (control)
De abreu et al[20]	Caucasian	36	11	7	20	39	13
Tsezou et al[10]	Caucasian	51	24	3	31	77	46
Wu et al[27]	Asian	16	51	21	92	159	83
Iobagiu et al[11]	Caucasian	35	72	32	30	66	49
Zheng et al[15]	African	124	102	32	127	110	22
Dunning et al[6]	Caucasian	84	215	209	54	212	160
Mehdipour et al[23]	Asian	130	228	142	210	164	58
Sakoda et al[14]	Asian	50	248	316	74	366	439
Suter et al[26]	Caucasian	121	255	148	122	206	133
Haiman et al[21]	Caucasian	179	374	174	247	481	232
Wedren et al[9]	Caucasian	376	698	422	301	651	388
Abbas et al[19]	Caucasian	736	1,489	717	1,291	2,526	1,435
Spurdle et al[25]	Caucasian	78	290		71	213	
Liede et al[22]	Asian	178	215		152	171	
Wang et al[13]	African	145	94		156	93	
Slattery et al[24]	Caucasian	400	1,334		464	1,575	
Gonzalez et al[12]	Caucasian	155	102		270	123	

Notes: SS, women carrying two shorter alleles; SL, women carrying at least one long allele; LL, women carrying two long alleles.

Heterogeneity

Obvious heterogeneity was detected in each of the comparison models. A meta-regression revealed that ethnicity, publication year, sample size, and source of control subjects did not contribute to the heterogeneity (data not shown).

Publication bias

To assess the publication bias, a funnel plot and Begg's test were performed. No publication bias was detected in the overall analysis (Figure 5). Additionally, no publication bias was found in the Caucasian and Asian subgroup analyses

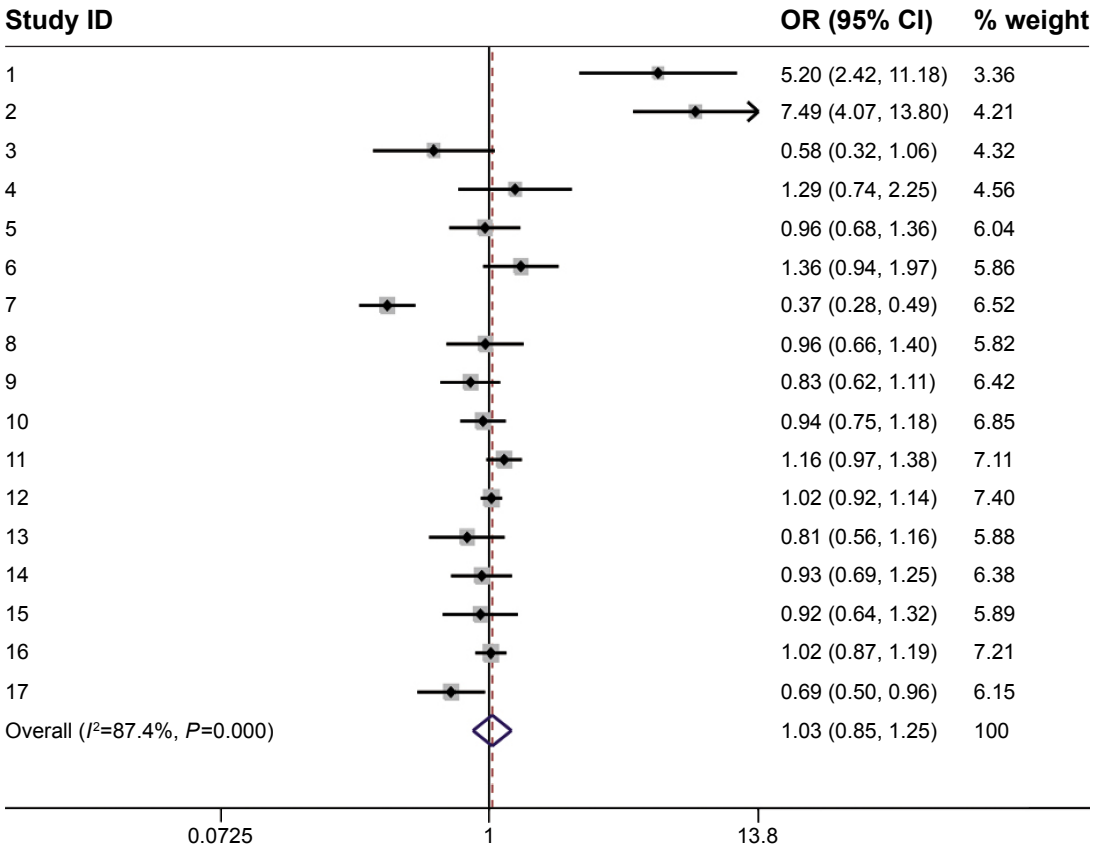

Figure 2 (*Continued*)

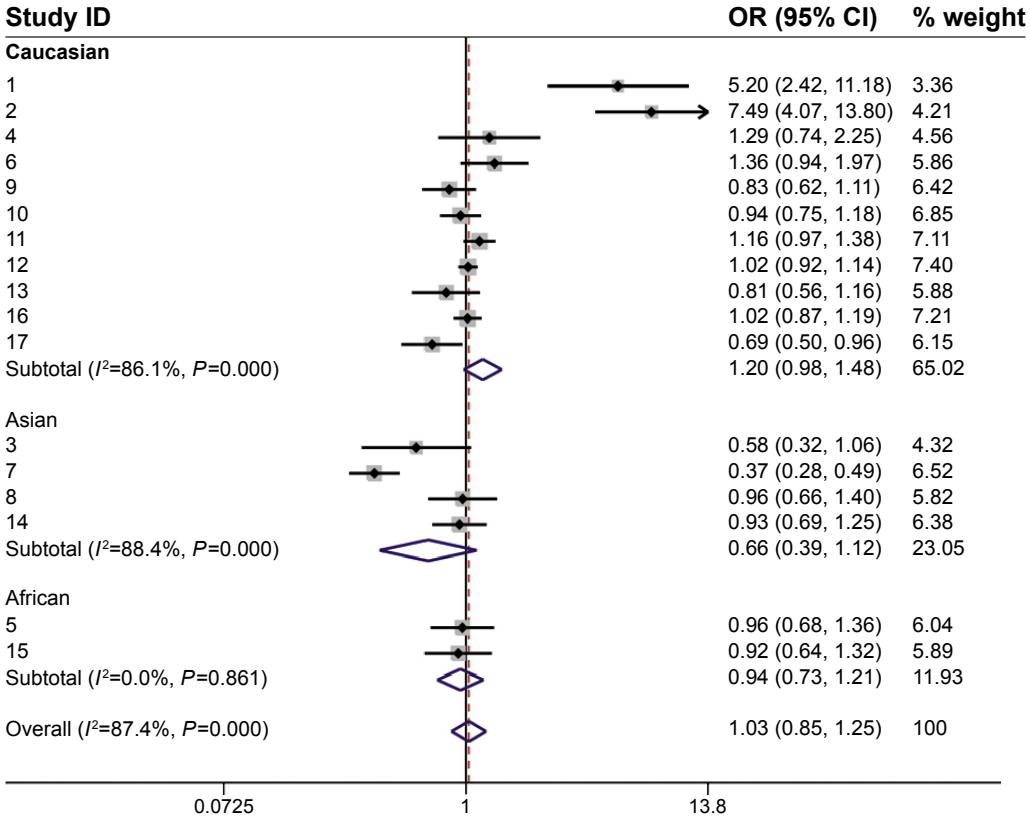

Figure 2 Forest plot of SS versus all SL-LL and Forest plot of the subgroup analysis (SS versus all SL-LL).
Notes: Weights are from random effects analysis; SS, women carrying two shorter alleles; SL, women carrying at least one long allele; LL, women carrying two long alleles.
Abbreviations: OR, odds ratio; CI, confidence interval.

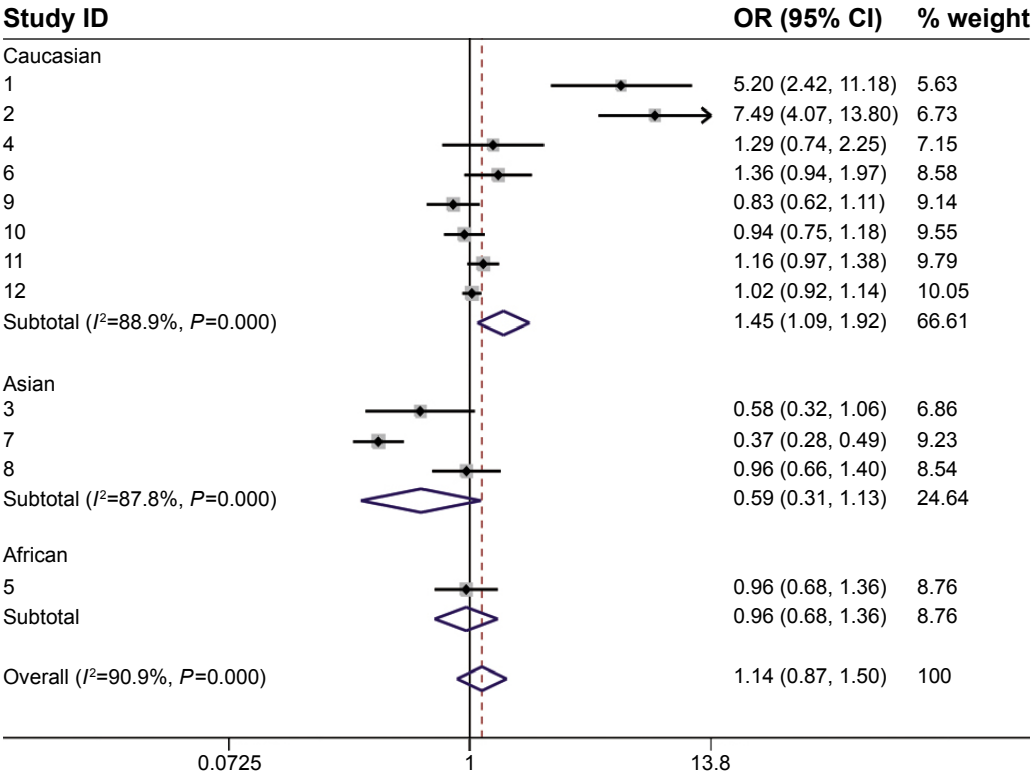

Figure 3 Forest plot of the subgroup analysis (SS versus SL-LL).
Notes: Weights are from random effects analysis; SS, women carrying two shorter alleles; SL, women carrying at least one long allele; LL, women carrying two long alleles.
Abbreviations: OR, odds ratio; CI, confidence interval.

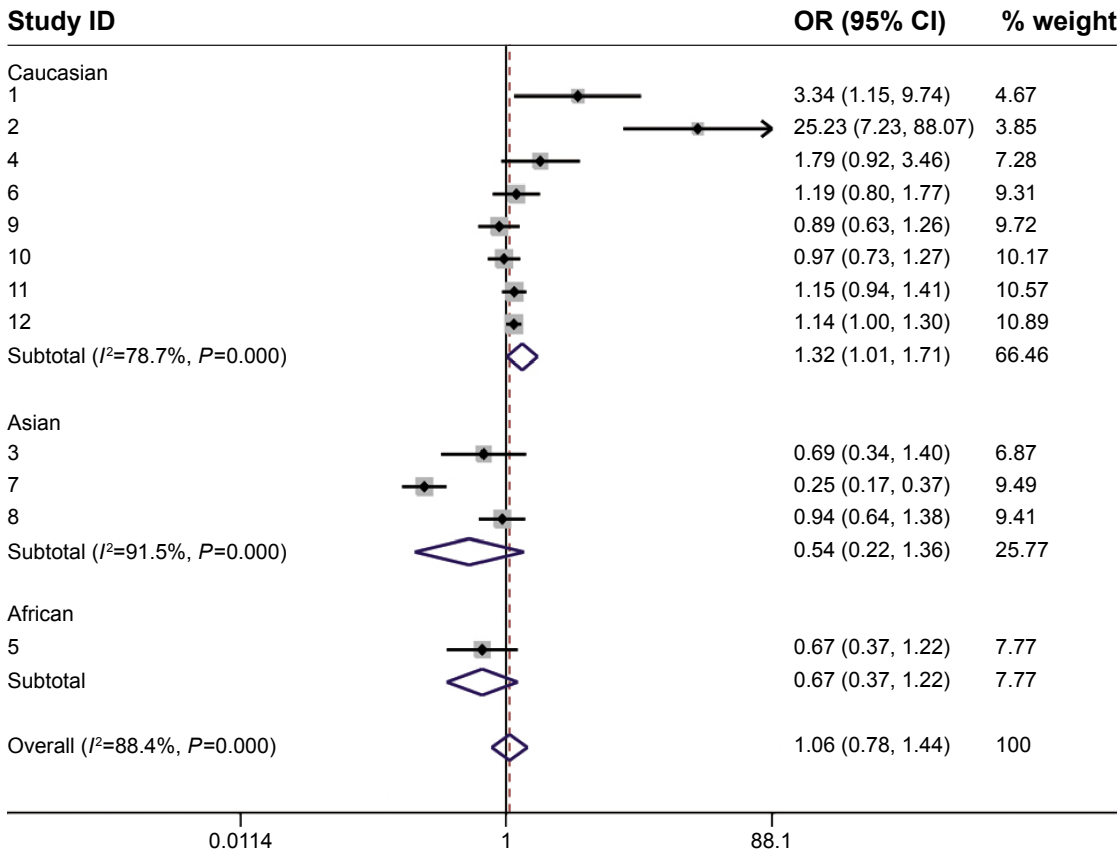

Figure 4 Forest plot of the subgroup analysis (SS versus LL).
Notes: Weights are from random effects analysis; SS, women carrying two shorter alleles; SL, women carrying at least one long allele; LL, women carrying two long alleles.

($P_{Caucasian}$=0.072 and P_{Asian}=0.656). Two studies showed Hardy-Weinberg disequilibrium.[11,26]

Discussion

Breast cancer is a known sex steroid hormone-related disease. Sex steroid hormones exert their biological effects by binding to nuclear receptors, including the AR. The AR mediates the effects of androgen and plays a complex role in breast carcinogenesis. Androgen binding to the AR activates the androgen signaling pathway and inhibits the proliferation of breast cancer.[3] Polymorphic variations in sex hormone receptor-encoding genes, such as CAG polymorphisms in the AR, may therefore alter the activity of the receptor molecules and, in turn, the susceptibility to breast cancer.[28–31]

Previous conclusions regarding CAG polymorphism and breast cancer risk have been conflicting and inconsistent. Gonzalez et al,[12] Liede et al[22] and Wang et al[13] proposed that a long CAG allele would increase the risk of breast cancer, and a study by Haiman et al[21] demonstrated that long AR repeat alleles might increase the breast cancer risk among women with a first-degree

Table 3 Meta-analysis results regarding the length of CAG repeats and breast cancer risk

	Comparison (SS versus any SL-LL)			Homozygote comparison (SS versus LL)			Recessive model (SS-SL versus LL)			Dominant model (SS versus SL-LL)		
	Studies	OR (95% CI)	P_{het}	Studies	OR (95% CI)	P_{het}	Studies	OR (95% CI)	P_{het}	Studies	OR (95% CI)	P_{het}
Overall	17	1.031 (0.855–1.245)	<0.01	12	1.062 (0.784–1.439)	<0.01	12	0.994 (0.819–1.207)	<0.01	12	1.142 (0.871–1.498)	<0.01
Caucasian	11	1.201 (0.977–1.477)	<0.01	8	1.315 (1.014–1.707)*	<0.01	8	1.126 (0.948–1.338)	<0.01	8	1.447 (1.089–1.992)*	<0.01
Asian	4	0.665 (0.393–1.124)	<0.01	3	0.540 (0.215–1.357)	<0.01	3	0.721 (0.384–1.352)	<0.01	3	0.589 (0.307–1.129)	<0.01
African	2	0.942 (0.733–1.210)	0.861	2	0.671 (0.370–1.219)	–	2	0.656 (0.370–1.162)	–	2	0.962 (0.681–1.358)	–

Notes: P_{het}, *P*-value of heterogeneity; *significant difference; SS, women carrying two shorter alleles; SL, women carrying at least one long allele; LL, women carrying two long alleles.
Abbreviations: OR, odds radio; CI, confidence interval.

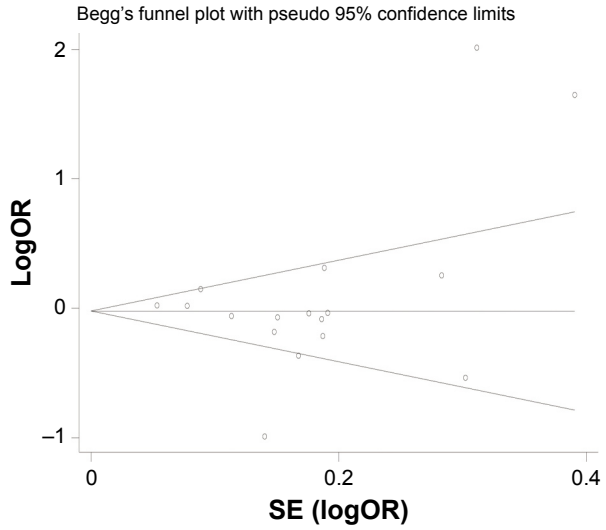

Figure 5 Begg's test for publication bias.
Abbreviation: SE (logOR), standard error for log odds ratio.

family history of breast cancer. However, no associations were found in studies by Slattery et al[24] or Spurdle et al.[25] In contrast, some investigations have shown that short CAG repeats are associated with breast carcinoma in women.[9,10]

In the present meta-analysis, we found that CAG repeats longer than 22 units increased the risk of breast cancer in Caucasian women (SL-LL versus SS, OR 1.447, 95% CI 1.089–1.992). An increased breast cancer risk was also found in Caucasian women in the homozygote comparison model (SS versus LL, OR 1.315, 95% CI 1.014–1.707).

In a meta-analysis conducted by Hao et al 4 years ago,[32] long CAG repeats had a protective effect on breast cancer in the dominant comparison. However, many studies have been published in the past 4 years, and more studies have investigated the Asian and African populations. Thus, different and comprehensive conclusions are presented in this meta-analysis. Initially, we considered that long CAG repeats might increase the susceptibility to breast cancer in Caucasian women. However, we analyzed the data from all investigations collected in this meta-analysis. The outcome showed no association between CAG polymorphisms and breast cancer in women; this result differs from that of a previous meta-analysis. Taking ethnic differences into consideration, we conducted a subgroup analysis by race. In the Caucasian subgroup, a significant correlation was observed between CAG polymorphisms and breast cancer risk. These results were consistent with the conclusions of Gonzalez et al and Wang et al. Androgen might play a protective role in breast cancer development.[12] Long CAG repeats were correlated with decreased efficacy in inducing androgen activity. Long CAG repeats could contribute to the risk of breast cancer in women by decreasing the AR transcriptional efficiency in breast cells and hence producing a decreased response to circulating androgens. Conversely, there was a different trend in the Asian subgroup. The long CAG repeat polymorphisms showed a trend of reducing the risk of breast cancer in women. However, strictly speaking, no statistically significant correlation was identified for CAG repeat length in the Asian population because the upper limit of the 95% CI was greater than 1. This opposite trend might result from many factors. The variation ranges of CAG repeats in the Asian population were shorter than those in the Caucasian population. Thus, the median of the CAG repeat length might be different in the Asian population than the Caucasian population. This discrepancy between races might have led to the inconsistent results. Moreover, only three studies included a subgroup analysis of the Asian population. The sample size was too small. More studies are needed to determine the correlation between the CAG polymorphism length and breast cancer in the Asian population. There was no positive result in the African subgroup.

As mentioned previously, the heterogeneity of this meta-analysis was not satisfactory. After dividing the subjects into three subgroups, heterogeneity still existed. A meta-regression was necessary to identify the heterogeneity. We analyzed the ethnicity, source of control subjects, publication year, study type, age of the population and official language of the population. The results of the official language analysis suggested that the heterogeneity of the OR was derived from studies by Tsezou et al,[10] Mehdipour et al[23] and De Abreu et al.[20] We then reviewed the articles again, and we found no obvious difference in the populations in these three articles and those in the other studies. Therefore, we propose that the heterogeneity of the OR may be derived from other factors that were not mentioned in the studies.

The strengths of our study include a large sample size and no indication of publication bias. However, some limitations should be considered. Physiological factors, environmental factors and other unknown risks may play a role in the interaction of AR genetic variations and breast cancer risk in women.[33–36] Moreover, due to a relatively small sample size or lack of necessary information in some studies, we were unable to perform further subgroup analyses. Thus, further investigations should be performed to identify the association between the length of CAG repeat polymorphisms and breast cancer in women.

Conclusion

In this meta-analysis, we reviewed previous findings regarding the association between AR CAG repeat polymorphisms and breast cancer risk. We discovered that long CAG

repeats might increase the susceptibility to breast cancer in the Caucasian population. Further studies are required to analyze the relationship between the length of CAG repeat polymorphisms and breast cancer in women.

Acknowledgments

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Disclosure

The authors declare that they have no conflicts of interest in this work.

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Supplementary material

Table S1 PRISMA checklist

Section	#	Check item	Reported on page
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (eg, Web address), and, if available, provide registration information including registration number.	3–4
Eligibility criteria	6	Specify study characteristics (eg, PICOS, length of follow-up) and report characteristics (eg, years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (eg, databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (ie, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (eg, piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (eg, PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4
Summary measures	13	State the principal summary measures (eg, risk ratio, difference in means).	4
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (eg, I2) for each meta-analysis.	4–5
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (eg, publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (eg, sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5
Study characteristics	18	For each study, present characteristics for which data were extracted (eg, study size, PICOS, follow-up period) and provide the citations.	5
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	5
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	5
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	5–6
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see item 15).	6
Additional analysis	23	Give results of additional analyses, if done (eg, sensitivity or subgroup analyses, meta-regression [see item 16]).	6
Discussion			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (eg, health care providers, users, and policy makers).	6
Limitations	25	Discuss limitations at study and outcome level (eg, risk of bias), and at review-level (eg, incomplete retrieval of identified research, reporting bias).	7
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	8
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (eg, supply of data); role of funders for the systematic review.	8

Abbreviations: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PICOS, participants, interventions, comparators, outcomes, and study design.