Original Article

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Androgen receptor gene CAG repeat polymorphism and ovarian cancer risk: A meta-analysis

Yang Deng[1], Jue Wang[2], Ling Wang[3,4,5,*], Yan Du[2,*]

[1] *Department of Epidemiology, School of Public Health, Taishan Medical University, Taian, Shandong, China;*
[2] *Office of Clinical Epidemiology, Obstetrics and Gynecology Hospital of Fudan University, Shanghai, China;*
[3] *Laboratory for Reproductive Immunology, Hospital & Institute of Obstetrics and Gynecology, IBS, Fudan University Shanghai Medical College, Shanghai, China;*
[4] *The Academy of Integrative Medicine of Fudan University, Shanghai, China;*
[5] *Shanghai Key Laboratory of Female Reproductive Endocrine Related Diseases, Shanghai, China.*

Summary **Ovarian cancer is one of the common gynecological malignancies worldwide. It is usually diagnosed at a later stage, thus missing the best opportunity for treatment. Despite the advancement of ovarian cancer treatment, the prognosis is still poor. Androgen receptor (AR) may play a role in ovarian carcinogenesis. Previous studies regarding the association between AR CAG repeat length and ovarian cancer risk reported inconsistent results. Therefore, we conducted a meta-analysis to evaluate the association between AR CAG repeat length and ovarian cancer risk following the MOOSE guidelines. PubMed, Web of Science, EBSCO and other databases were searched up to September 15th 2016. Case control studies with clear definition of CAG repeat length and detailed genotype information were included. Two authors independently reviewed and extracted data. Pooled analysis and subgroup analysis stratified by ethnicity were performed for different genetic models. Begg's funnel plot and Egger's test were performed for publication bias estimation. Overall, there was no association between the AR CAG repeat polymorphism and ovarian cancer risk. However, short CAG repeat polymorphism was associated with increased ovarian cancer risk in African Americans and Chinese under the dominant model, whereas a reverse association was observed in Caucasians and Italians under the other three models. Our study results should be interpreted with caution. Further well-designed epidemiological and functional studies are needed to elucidate the role of AR in ovarian carcinogenesis.**

Keywords: Androgen receptor (AR), CAG polymorphism, ovarian cancer risk, meta-analysis

1. Introduction

Ovarian cancer is one of the common gynecological malignancies among women worldwide (*1*). It is the second most commonly diagnosed gynecological malignancies and second leading cause of death from gynecological malignancies. In 2012, there were about 238,700 incident cases of and 151,900 deaths due to ovarian cancer (*1*). The etiology of ovarian cancer has not been well elucidated, although previous researches have demonstrated that several factors, including family history, diet, obesity, inflammation, use of estrogen and hormone-replacement therapy, reproductive factors such as null-parity, early age at menarche, late age at menopause and oral contraceptive use, and genetic susceptibility may contribute to ovarian cancer development (*2*).

Epidemiologic and biological data have suggested that androgens and androgen receptor (AR) may play a role in the occurrence of ovarian cancer (*3,4*). The AR is

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*Address correspondence to:
Dr. Yan Du, Office of Clinical Epidemiology, Obstetrics and Gynecology Hospital of Fudan University, No. 419 Fangxie Road, Shanghai 200011, China.
E-mail: sophiedu_61@163.com

Dr. Ling Wang, Hospital and Institute of Obstetrics and Gynecology, IBS, Fudan University, 413 Zhaozhou Road, Shanghai 200011, China.
E-mail: Dr.wangling@fudan.edu.cn

a ligand-dependent transcriptional factor mediating the actions of testosterone and dihydrotesterone (*5*). Mapped to X chromosome (q11.2-12), the *AR* gene includes eight exons. In exon 1 is a trinucleotide cytosine, adenine, guanine (CAG) repeat, which encodes a polyglutamine tract with varying lengths (*5*). It is reported that different ethnicities have different CAG repeat lengths, with the shortest being reported in African-Americans (mean,20; range,10-29) and the longest in Mexican-Americans (mean,25; range,16-32) (*6*). Studies have shown that CAG repeat lengths were associated with the risks of different cancer types in various populations, such as breast cancer, prostate cancer and colorectal cancer (*7-9*). In terms of ovarian cancer, some studies have shown that long CAG repeat allele was associated with increased ovarian cancer risk (*10,11*), while other studies have reported an inverse association between CAG repeat length and ovarian cancer risk (*12,13*). Furthermore, several studies suggested no relationship between CAG repeat length and ovarian cancer (*14-17*). These conflicting results may be explained by ethnically diverse populations and different sample sizes in each publication. To the best of our knowledge, so far no meta-analysis has been conducted to investigate the association between *AR* CAG repeat polymorphism and the risk of ovarian cancer, as well as genetic heterogeneity across different ethnic groups. Therefore, we performed the present meta-analysis to evaluate the association between *AR* CAG repeat polymorphism and ovarian cancer risk following the Meta-analyses of Observational Studies in Epidemiology (MOOSE) guidelines (Supplementary Table S1, *http://www.biosciencetrends.com/action/getSupplementalData.php?ID=8*).

2. Materials and Methods

2.1. *Literature Searches*

Studies in English were searched in PubMed, Web of Science, EBSCO and Cancer Genetic Markers of Susceptibility (CGEMS), and reports in Chinese were searched in China National Knowledge Infrastructure (CNKI), the Database of Chinese Scientific and Technical Periodicals (VIP) and the China Biology Medical Literature database (CBM), from the earliest date up to September 15th 2016. The search terms included ("androgen receptor" or the gene abbreviation "*AR*") and ["CAG" or "(CAG)n" or "polymorphism" or "short tandem repeat"] and ("ovarian cancer" or "ovarian carcinoma" or "ovarian neoplasms"). Titles and abstracts of the search results were first screened, and full texts of promising articles were retrieved and evaluated in detail. References from identified articles and reviews were also examined. If the full text of an article or detailed information was not available online, we proceeded to contact the corresponding author of the article by e-mail.

2.2. *Evaluation criteria*

The following criteria were applied to select studies for inclusion in the meta-analysis: *i*) articles about *AR* CAG polymorphism and ovarian cancer risk, *ii*) clear definition of CAG_S (shorter allele), CAG_L (longer allele) and detailed genotype information, *iii*) case control studies, *iv*) if multiple publications for a single study were reported, only the latest publication with the most complete or updated data was selected. Studies did not report an adequate description of the epidemiological design, statistical analysis, or separate analyses for *AR* CAG repeat in relation to ovarian cancer risk were excluded. Case series were also excluded.

2.3. *Data extraction*

Data were extracted by two authors (Yang D. and Yan D.) independently, and any differences were resolved by consensus after discussion. The following information was extracted from each study: first author, population (ethnicity of participants), year of publication, sample size, and genotype counts for cases and controls.

2.4. *Statistical analysis*

The association between *AR* CAG repeat polymorphism and ovarian cancer risk was evaluated by odds ratios (ORs) and their 95% confidence intervals (CIs), and the ORs were calculated for the allele genetic model, additive genetic model, dominant genetic model, and recessive genetic model, respectively. The choice of using fixed or random effects model was determined by the results of the between-study heterogeneity test, which was measured using the Q test and I^2 statistic. If the test result was $I^2 \geq 50\%$ or $P_Q < 0.1$, indicating the presence of heterogeneity, the random effect model was selected; otherwise, the fixed-effects model was chosen (*18*). Subgroup analysis was performed based on the ethnicity. Begg's funnel plot and Egger's test were conducted to estimate the possible publication bias (*19*). All statistical analyses were performed using Review Manager 5.3 (The Cochrane Collaboration, Oxford, UK) and Stata 12.0 (Stata-Corp, College Station, Texas, USA).

3. Results

3.1. *Study Characteristics*

The initial search retrieved 18 potentially relevant publications (17 published in English and 1 in Chinese). Ten of these publications were excluded according to the evaluation criteria: 6 publications were not case-control studies (*20-25*), and another 4 did not provide detailed genotype or allele distribution data (*26-29*). Finally, 8 case-control studies containing 6613 cases and 7041

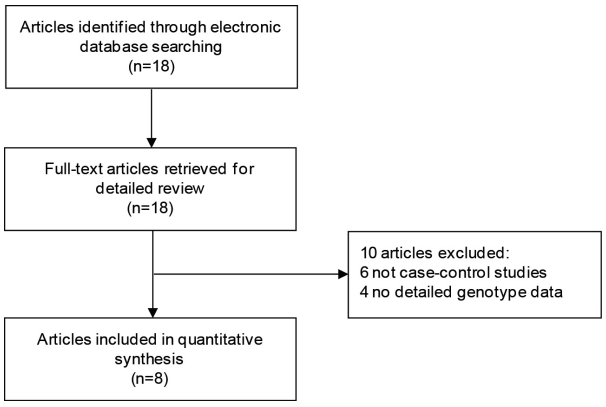

Figure 1. Flow chart of the study selection process.

controls were included in the current meta-analysis (*10-17*). A flow chart of study selection process was shown in Figure 1, and the baseline characteristics of all included studies were presented in Table 1.

3.2. *Overall analysis*

The pooled analyses of the association of *AR* CAG repeat polymorphism with ovarian cancer risk were shown in Figure 2 to Figure 5. In this study, CAG_S is referred to repeat length ≤ 21 for Chinese, Caucasians and Italians, while for African Americans CAG_S is referred to repeat length < 16. The results suggested that *AR* CAG repeat polymorphism was not associated with ovarian cancer risk under the allele, additive, dominant and recessive models (for L allele versus S allele: OR = 1.06, 95%CI = 0.87-1.31, $P = 0.56$; $I^2 = 76\%$ and $P_Q = 0.0009$ for heterogeneity; for LL versus SS: OR = 1.23, 95%CI = 0.88-1.72, $P = 0.23$; $I^2 = 62\%$ and $P_Q = 0.02$ for heterogeneity; for SL+LL versus SS: OR = 0.91, 95%CI = 0.72-1.15, $P = 0.45$; $I^2 = 83\%$ and $P_Q < 0.00001$ for heterogeneity; for LL versus SL+SS: OR = 1.16, 95%CI = 0.84-1.59, $P = 0.36$; $I^2 = 73\%$ and $P_Q = 0.003$ for heterogeneity). The existence of study heterogeneity is found in all models.

3.3. *Subgroup analysis*

The results of subgroup analysis showed significant positive associations of long CAG repeat allele with ovarian cancer risk among Caucasians (L allele versus S allele: OR = 1.12, 95%CI = 1.02-1.23, $P = 0.02$; $I^2 = 0\%$ and $P_Q = 0.88$ for heterogeneity) and Italians (L allele versus S allele: OR = 1.45, 95%CI = 1.03-1.23, $P = 0.03$; $I^2 = 19\%$ and $P_Q = 0.27$ for heterogeneity) under the allele model, but a significantly decreased ovarian cancer risk was found among African Americans with long CAG repeat allele (OR = 0.42, 95%CI = 0.26-0.68, $P = 0.0004$) under the allele model. The details were presented in Figure 2.

The subgroup analysis of the additive model of *AR*

Table 1. Characteristics of studies of androgen receptor gene CAG polymorphism and ovarian cancer susceptibility

Author	Population	Year	Short SS[a]		Any long SL and LL		Case			Control			OR(95%CI)			
			Case	Control	Case	Control	SS	SL	LL	SS	SL	LL	Allele	Additive	Dominant	Recessive
Spurdle *et al. (16)*	Australian Caucasians	2000	75	128	244	425	75	149	95	128	281	144	1.07 (0.88,1.30)	1.13 (0.77,1.65)	0.98 (0.71,1.36)	1.20 (0.89,1.64)
Menin *et al. (14)*	Italians	2001	18	32	32	69	18	20	12	32	57	12	1.17 (0.72,1.91)	1.78 (0.66,4.77)	0.82 (0.40,1.68)	2.34 (0.97,5.68)
Santarosa *et al. (11)*	Italians	2002	27	35	94	65	27	57	37	35	47	18	1.66 (1.14,2.43)	2.66 (1.25,5.67)	1.87 (1.04,3.39)	2.01 (1.06,3.81)
Terry *et al. (10)*	American Caucasians	2005	212	249	693	727	212	432	261	249	488	239	1.14 (1.00,1.29)	1.28 (1.00,1.65)	1.12 (0.91,1.38)	1.25 (1.02,1.53)
Schildkraut *et al. (15)*	American Caucasians	2007	163	198	321	324	163	237	84	198	240	84	1.12 (0.94,1.34)	1.21 (0.84,1.75)	1.20 (0.93,1.56)	1.09 (0.79,1.53)
	African-Americans		11	5	88	136	11	28	60	5	25	111	0.42 (0.26,0.68)	0.25 (0.08,0.74)	0.29 (0.10,0.88)	0.42 (0.24,0.74)
Liu *et al. (17)*	Chinese	2011	2	4	38	44									1.73 (0.30,9.96)	
Zhu *et al. (12)*	Chinese	2016	673	509	1127	1291									0.66 (0.57,0.76)	
Meng *et al. (13)*	Chinese	2016	1048	818	1747	1982									0.69 (0.62,0.77)	

[a]CAG_S is referred to repeat length ≤ 21 for Chinese, Caucasians and Italians, while for African Americans CAG_S is referred to repeat length < 16.

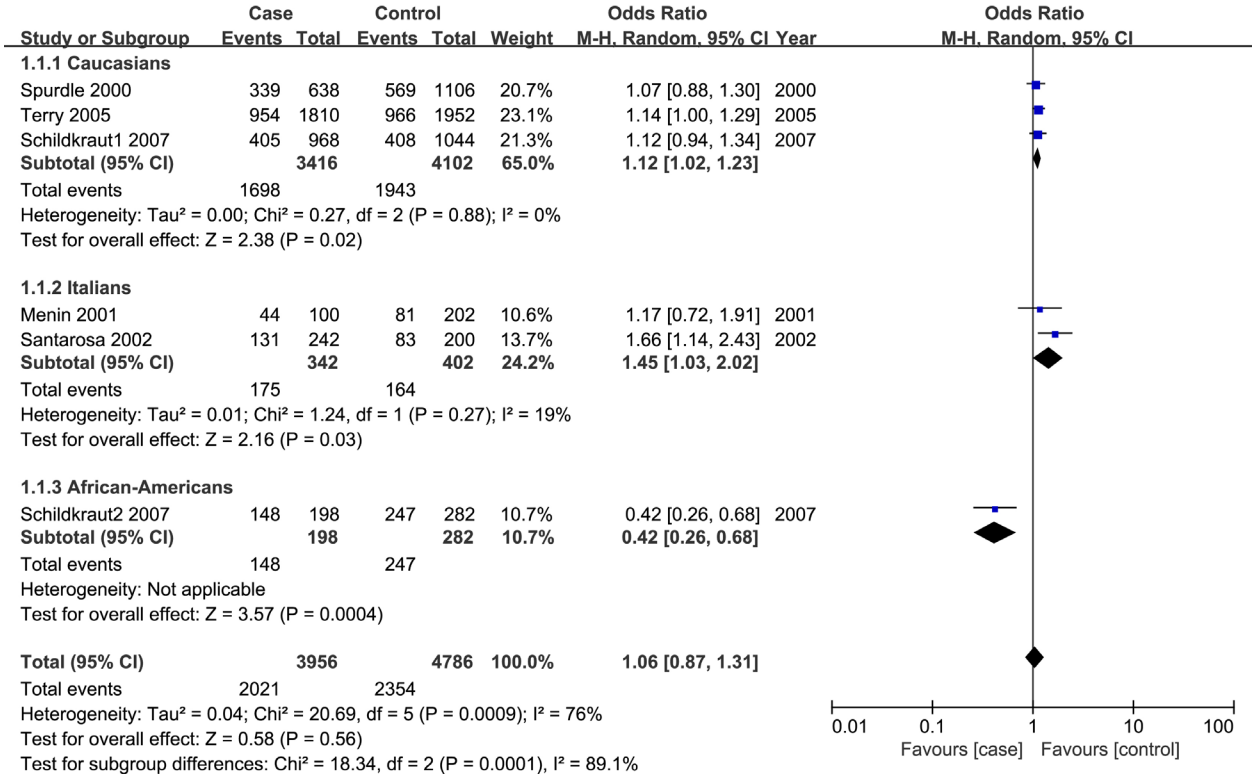

Figure 2. Forest plot of the association between the *AR* CAG repeat polymorphism and ovarian cancer risk under the allele model. Each study is shown by an OR and the 95%CI.

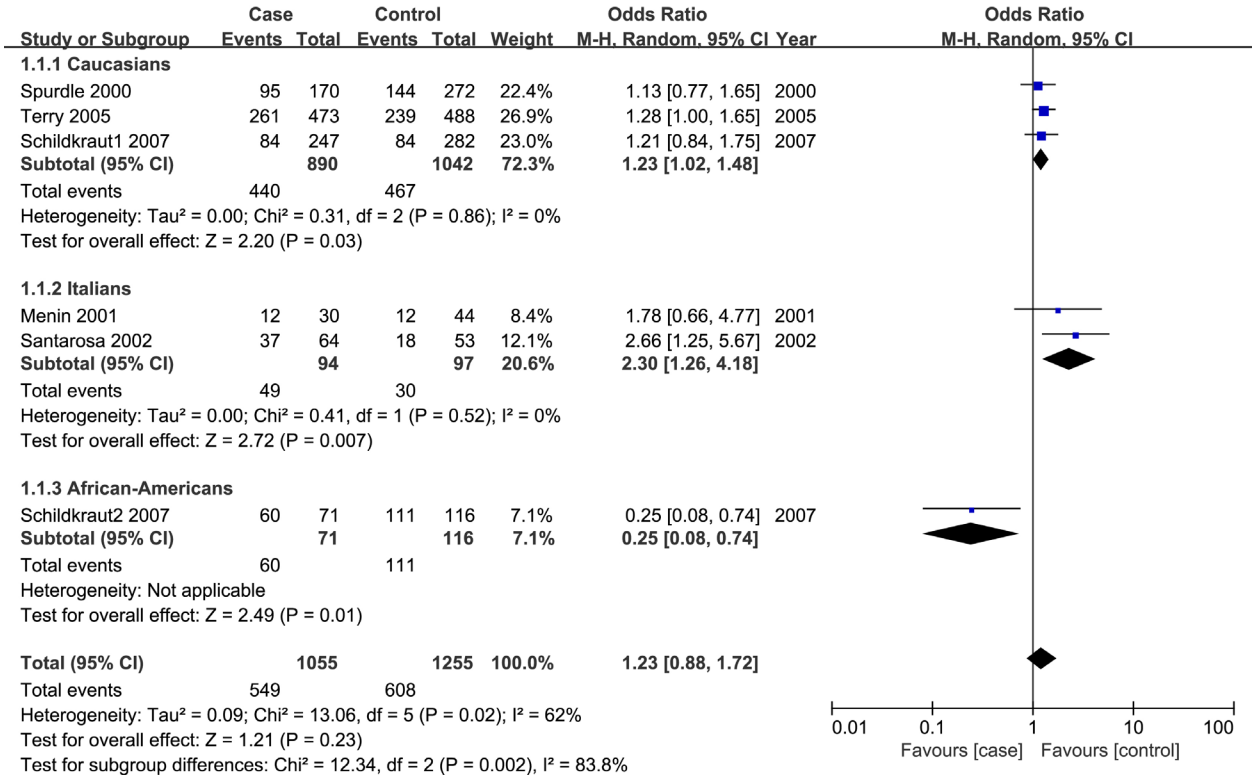

Figure 3. Forest plot of the association between the *AR* CAG repeat polymorphism and ovarian cancer risk under additive model. Each study is shown by an OR and the 95%CI.

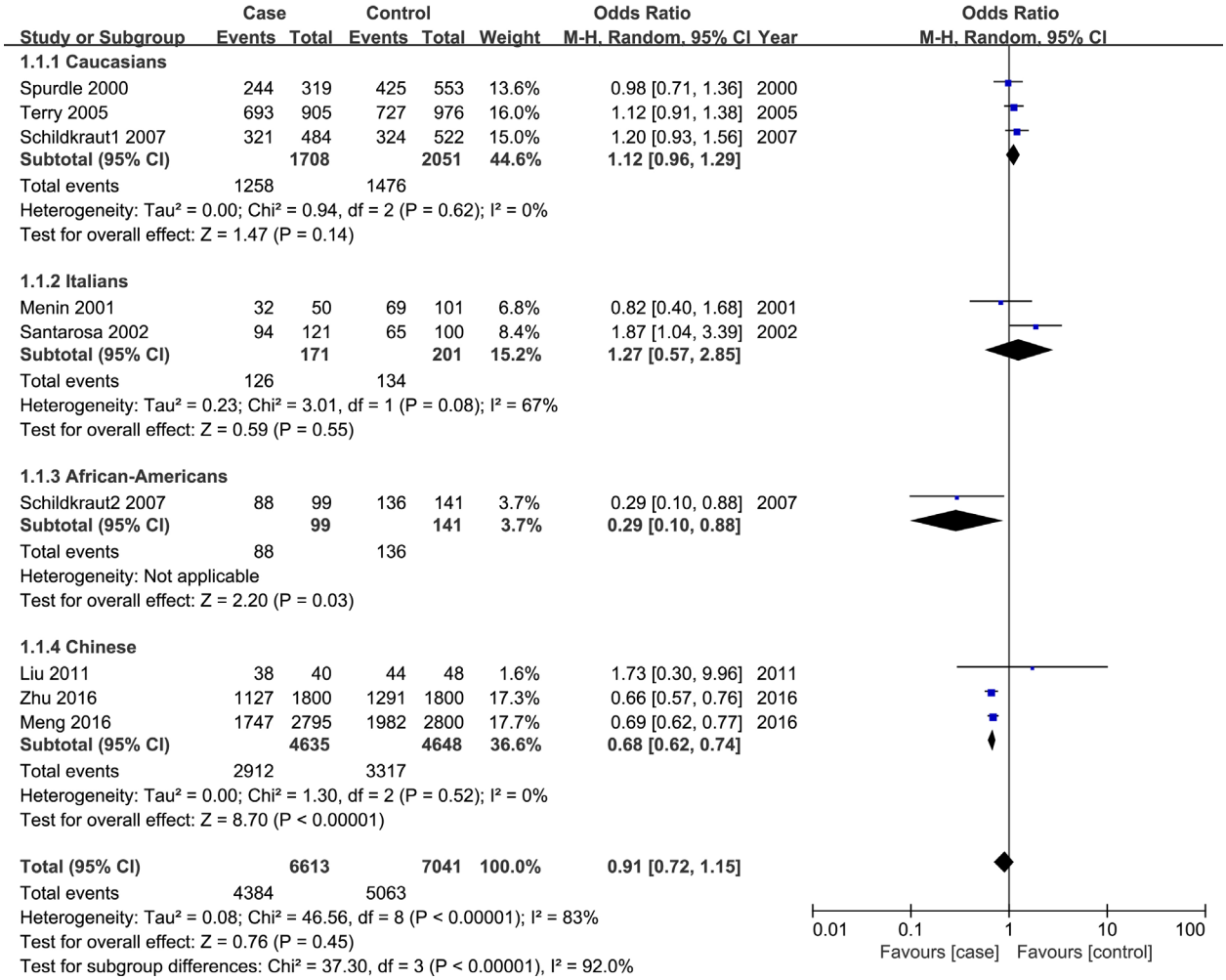

Figure 4. Forest plot of the association between the *AR* CAG repeat polymorphism and ovarian cancer risk under dominant model. Each study is shown by an OR and the 95%CI.

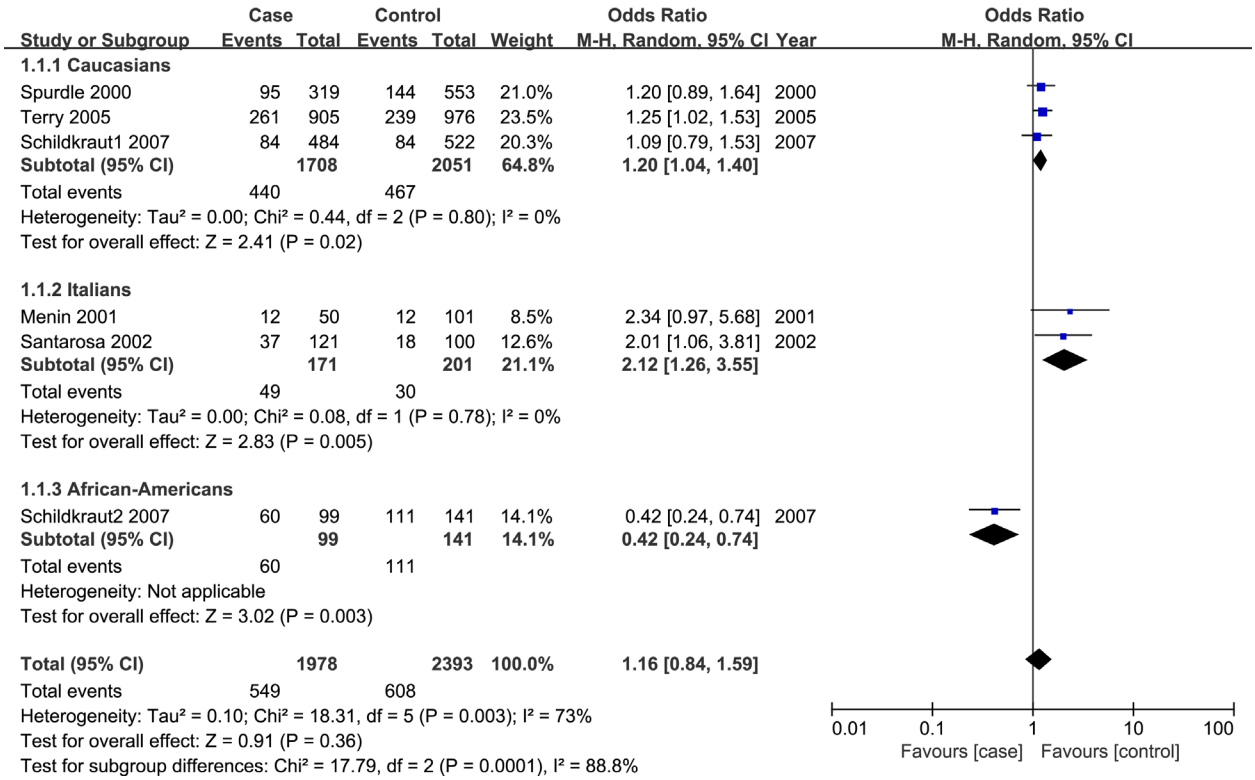

Figure 5. Forest plot of the association between the *AR* CAG repeat polymorphism and ovarian cancer risk under recessive model. Each study is shown by an OR and the 95%CI.

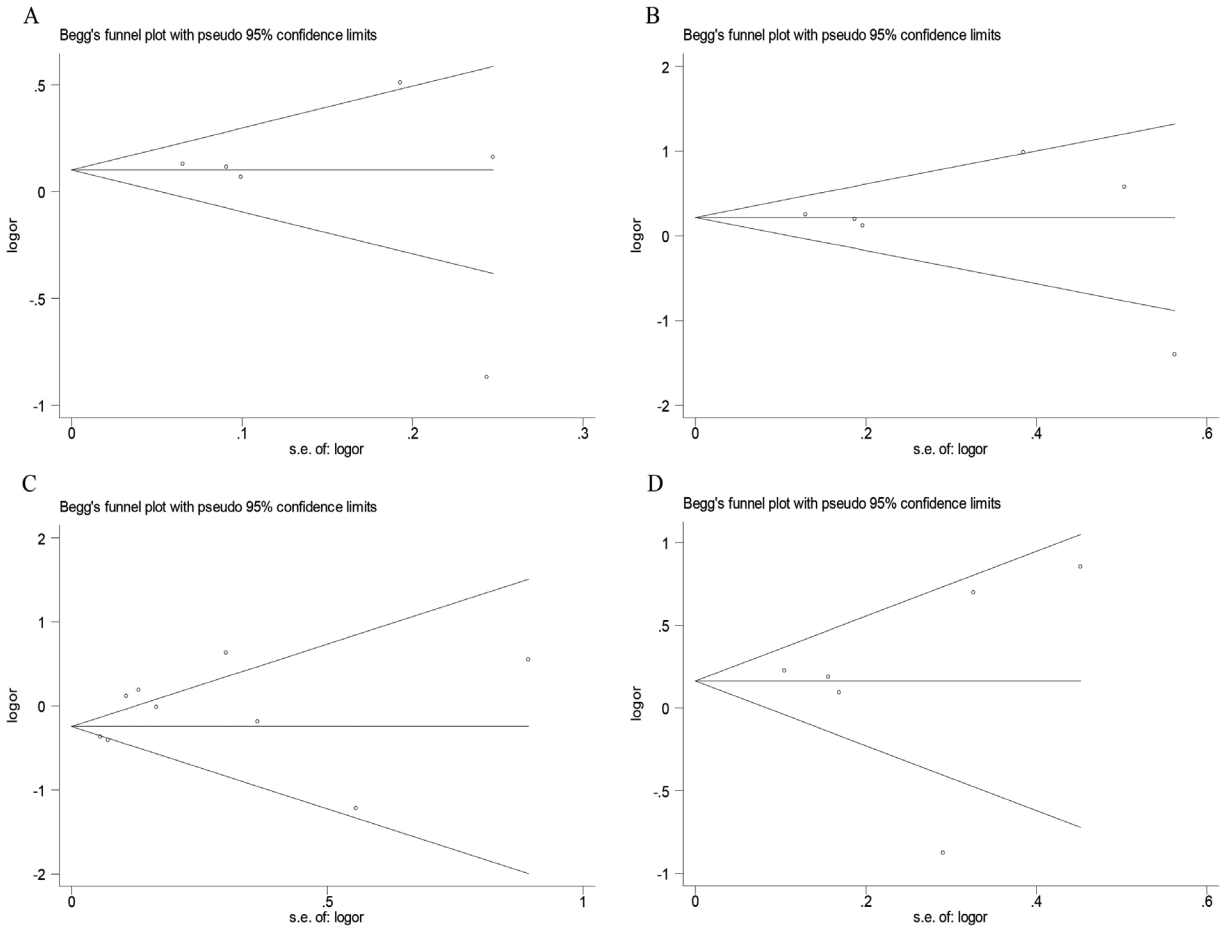

Figure 6. Begg's funnel plot analysis to detect publication bias. Each point represents a separate study for the indicated association. (A), allele model; **(B)**, additive model; **(C)**, dominant model; **(D)**, recessive model.

CAG repeat polymorphism was shown in Figure 3. For the additive model, significantly increased ovarian cancer risk was found among Caucasians and Italians with long CAG repeat allele (LL versus SS: OR = 1.23, 95%CI = 1.02-1.48, P = 0.03; I^2 = 0% and P_Q = 0.86 for heterogeneity; OR = 2.30, 95%CI = 1.26-4.18, P = 0.007; I^2 = 0% and P_Q = 0.52 for heterogeneity), and a significant negative association among African Americans with long CAG repeat allele (LL versus SS: OR = 0.25, 95%CI = 0.08-0.74, P = 0.01).

For the dominant model of *AR* CAG repeat polymorphism, there was a significant negative association of long CAG repeat allele and ovarian cancer risk among African Americans and Chinese (SL+LL versus SS: OR = 0.29, 95%CI = 0.10-0.88, P = 0.03; OR = 0.68, 95%CI = 0.62-0.74, P < 0.00001; I^2 = 0% and P_Q = 0.52 for heterogeneity). No significant association was found among Caucasians and Italians (OR=1.12, 95%CI = 0.96-1.29, P = 0.14; I^2 = 0% and P_Q = 0.62 for heterogeneity; OR = 1.27, 95%CI = 0.57-2.85, P = 0.55; I^2 = 67% and P_Q = 0.08 for heterogeneity). The details were shown in Figure 4.

The results of subgroup analysis showed that a significant positive association of long CAG repeat allele with ovarian cancer risk among Caucasians and Italians under the recessive model (OR = 1.20, 95%CI = 1.04-1.40, P = 0.02; I^2 = 0% and P_Q = 0.80 for heterogeneity; OR = 2.12, 95%CI = 1.26-3.55, P = 0.005; I^2 = 0% and P_Q = 0.78 for heterogeneity), and a significant negative association was found among African Americans (OR = 0.42, 95%CI = 0.24-0.74, P = 0.003). The details were shown in Figure 5. We did not calculated the association of CAG repeat polymorphism with ovarian cancer risk among Chinese under the allele, additive and recessive model due to the lack of detailed allele information in these models.

3.4. *Publication bias*

Begg's funnel plot did not indicate evidence of publication bias in the pooled analyses of the association between AR CAG repeat polymorphism and ovarian cancer risk under the allele, additive, dominant and recessive models (Figure 6). Egger's test also suggested no obvious publication bias in overall models (P = 0.586 for L allele versus S allele; P = 0.787 for LL versus SS; P = 0.225 for SL+LL versus SS; P = 0.960 for LL versus SL+SS).

4. Discussion

The present meta-analysis, including 6613 cases and 7401 controls from 8 case control studies, evaluated the association between the *AR* CAG repeat polymorphism and ovarian cancer risk. Our overall analysis results showed no association between *AR* CAG repeat polymorphism and ovarian cancer risk. However, in subgroup analysis stratifying by ethnic groups, CAG_L was significantly associated with increased ovarian cancer risk among Caucasians and Italians under the allele model, additive model, and recessive model. In contrary, a negative association was observed of the CAG_L and ovarian cancer risk among African Americans under all models (allele, additive, dominant, and recessive models). In addition, a negative association was shown between CAG_L and ovarian cancer risk among Chinese under the dominant model. Furthermore, no obvious publication bias was detected in the pooled analyses of the association of *AR* CAG repeat polymorphism with ovarian cancer risk under the allele, additive, dominant and recessive models, suggesting that the result was relatively stable.

Worldwide, ovarian cancer is the seventh most common and the eighth leading cause of cancer death in females (*1*). Despite the advances in ovarian cancer treatment, the five-year survival rate is still below 45% (*30*). Although epidemiological studies have identified a number of ovarian cancer risk factors, the etiology of ovarian carcinogenesis is far from clear. Host genetic susceptibility plays an important role in ovarian cancer development. Mutations in genes such as *BRCA1*, *BRCA2*, *BRIP1* and *RAD51*, as well as more than 20 low-risk susceptibility loci located in *CHEK2*, *WNT4*, *TERT* and *ABO* have been suggested to contribute to ovarian cancer risk (*31-33*). The *AR* gene, more than 90 kb long, codes for a protein which functions as a steroid-hormone activated transcription factor. The receptor dissociates from accessory proteins upon binding the hormone ligand, then translocates into the nucleus, dimerizes, and further stimulates transcription of androgen responsive genes. The protein contains 3 main functional domains: the N-terminal domain, DNA-binding domain, and androgen-binding domain. There are 2 polymorphic trinucleotide repeat segments in the N-terminal transactivation domain of the AR protein. The exon 1 of *AR* gene contains a polymorphic CAG repeat, and the length of CAG repeats ranges from 6 to 39 among people of different ethnicity (*6*). The abnormal range of CAG repeat length is usually associated with the risk of developing different cancer types including ovarian cancer (*7-11*). However, previous studies of the association between *AR* CAG repeat polymorphism and ovarian cancer risk have shown inconsistent results (*10-17*). In this meta-analysis, we performed a comprehensive evaluation of the relationship between *AR* CAG repeat polymorphism and ovarian cancer risk under the allele, additive, dominant and recessive models.

AR CAG repeat lengths vary among different ethnicities, and African Americans have shorter CAG repeat lengths than Caucasians and Italians (*6*). The association between CAG repeat length and cancer risk has been studied extensively in recent years. A study conducted in Brazil has reported that shorter CAG repeat length was associated with lower disease-free survival and higher risk of recurrence or metastasis in head and neck cancer among the general population (*34*). A meta-analysis revealed that long (> 22) CAG repeat length was a protective factor against breast cancer risk under the dominant model (*35*). However, studies from Taiwan showed the association between CAG repeat length and the risk of hepatocellular carcinoma (HCC) was sex dependent. Shorter CAG repeat length was associated with increased risk of HCC in men, but was associated with less susceptibility in women (*36,37*), suggesting different mechanisms are involved in the HCC development regarding men and women. The shorter CAG repeat length is associated with an increased risk of hyperandrogenic manifestations including hirsutism, annovulation, and acne in women and baldness and prostatic hyperplasia in men, perhaps because shorter length may facilitate chronic androgen stimulation which can result in enhanced proliferative activity (*5,13*). Compared to healthy women, patients with ovarian cancer have high levels of circulating androgen before the disease diagnosis, and ARs are usually detected in most ovarian cancer patients (38). A study about the association of *AR* gene polymorphism and polycystic ovary syndrome (PCOS) revealed that shorter CAG repeat length was associated with the higher risk of PCOS (*39*). Moreover, women with PCOS under 54 years of age had an increased risk of developing ovarian cancer (OR = 2.52, 95%CI = 1.08-5.89) (*40*), suggesting that abnormal CAG repeat length might contribute to ovarian cancer through inducing PCOS. Interestingly, our meta-analysis suggest longer CAG repeat length was associated with increased ovarian cancer risk among Caucasians and Italian women, but was protective among African Americans and Chinese. Our results need to be interpreted with caution, since only a relatively small number of available studies have been included.

There are some limitations, which are common in the meta-analysis of genetic polymorphism and disease risk. First, as mentioned above, our meta-analysis only involved eight studies including two studies in American Caucasians, one study in Australian Caucasians, two studies in Italians, three studies in Chinese and only one in African-Americans. Moreover, detailed allele information was insufficient in the studies of Chinese. The number of study in each ethnic population is limited and the conclusion is perhaps partial for lacking enough evidences to estimate the association between

CAG repeat length and ovarian cancer risk. Second, the existence of heterogeneity in overall analyses may affect the accuracy of results. Heterogeneity is often caused by different environmental and ethnic background of population enrolled in each study, and it is inevitable in pooled analysis of included studies. Third, the etiology of ovarian cancer is complicated, including genetic and environmental factors, and their complex interactions. Lack of information of other physiological or environmental factors such as diet, obesity, inflammation status, and use of estrogen and hormone-replacement therapy has prevented us from further evaluating the association between the CAG repeat polymorphism and ovarian cancer risk.

In summary, our meta-analysis suggested that there was no association between the *AR* CAG repeat polymorphism and ovarian cancer risk in overall populations. The short CAG repeat polymorphism was associated with increased ovarian cancer risk in African Americans and Chinese under the dominant model. Whereas the long CAG repeat polymorphism was associated with increased ovarian cancer risk in Caucasians and Italians under the allele, additive and recessive models. Our study results suggest the association between *AR* CAG repeat polymorphism and ovarian cancer risk may differ by different ethnic groups. However, only a few studies are available to be included in this meta-analysis, therefore our study results need to be interpreted with caution. Future well-designed epidemiological studies with adequate sample size and appropriately chosen controls among different ethnic groups especially minority groups should be performed to more accurately estimate the association between CAG repeat polymorphism and ovarian cancer risk. Furthermore, functional studies are needed to elucidate the exact mechanism of *AR* gene in ovarian cancer so as to provide more information for effective prevention and treatment strategies in specific and to improve women's health in general.

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