Androgen receptor gene polymorphisms and risk of prostate cancer: a meta-analysis

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Although the association between CAG and GGN repeats in the androgen receptor gene and prostate cancer risk has been widely studied, it remains controversial from previous meta-analyses and narrative reviews. Therefore, we performed this meta-analysis to provide more precise estimates with sufficient power. A total of 51 publications with 61 studies for CAG repeats and 14 publications with 16 studies for GGN repeats were identified in the meta-analysis. The results showed that short CAG repeats (<22 repeats) carriers presented an elevated risk of prostate cancer than long CAG repeats (≥22) carriers (OR = 1.31, 95% CI 1.16 to 1.47). Prostate cancer cases presented an average fewer CAG repeats (MD = −0.85, 95% CI −1.28 to −0.42) than controls. Short GGN repeats (≤16) carriers presented an increased risk of prostate cancer than long GGN repeats (>16) carriers (OR = 1.38, 95% CI 1.05 to 1.82). In subgroup analyses, the abovementioned significant association was predominantly observed in Caucasian populations. The meta-analysis showed that short CAG and GGN repeats in androgen receptor gene were associated with increased risk of prostate cancer, especially in Caucasians.

Prostate cancer ([Mendelian Inheritance in Man 176807]) is the most commonly diagnosed nonskin malignancy and the second leading cause of cancer-related death among men in United States and first leading cause of death among Hispanics/Latinos\(^1,2\); and in Asian countries, especially in China, the incidence of prostate cancer is increasing\(^3\). Worldwide, the disease is the second most common cancer in men after lung cancer\(^4\). Prostate cancer is a complicated and multifactorial disease. The precise etiology and pathological mechanism of prostate cancer remains unclear. Age, family history, and ethnicity are the most consistently addressed risk factors associated with prostate cancer. However, age and inherited factors are estimated to be responsible for 5% to 9% percentage of prostate cancer\(^5\). Therefore, identifying a preventable cause of prostate cancer would produce an important influence of public health.

The substantial differences aforementioned in incidence of prostate cancer worldwide may be due to ethnic variation\(^6\). Therefore, certain researchers indicated that different levels of androgens across varying ethnicity may contribute to these differences\(^6,7\). The exact mechanism through which androgen is involved in the etiology of prostate cancer remains unclear. The androgen receptor gene [Mendelian Inheritance in Man 313700] is located at Xq11.2-q12, and the length of androgen receptor gene is more than 90 kb\(^8\). The androgen receptor gene is comprised of eight exons that encode four functional domains, which include the transactivation domain, the DNA binding domain, a hinge region, and the carboxyl-terminal ligand binding domain\(^9\). There are two main polymorphisms including CAG and GGN repeats in the androgen receptor gene. Moreover, CAG was associated with the transcriptional activity of the AR in response to ligand binding. Therefore, the correlation between these polymorphisms of androgen receptor and risk of prostate cancer has received much attention. Three published meta-analyses\(^6,10,11\) and several narrative reviews\(^12–15\) have addressed the association between the repeat polymorphisms and prostate cancer susceptibility. However, the conclusions of these previous meta-analyses were not consistent and the narrative reviews could not quantify the estimate. Additionally, more studies have been published since the most recent meta-analysis. Therefore, we performed the present meta-analysis aimed to provide

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a more precise and comprehensive result for the relationship between CAG and GGN repeat polymorphisms of androgen receptor gene and prostate cancer susceptibility.

Methods

Eligible criteria. For inclusion in this meta-analysis, the publication had to meet the following eligible criteria: (1) the exposure was androgen receptor gene CAG and GGN repeat polymorphisms; (2) populations were men with prostate cancer (cases) without prostate cancer (controls); (3) the outcome was incident of prostate cancer; (4) the study design was retrospective or prospective (i.e. nested) case-control study; (5) study provided distribution of genotype, odds ratio (OR) and corresponding 95% confidence interval (CI), mean difference (MD) and corresponding standard error (SE), and mean repeats in case and control groups with related SE. For duplicated publication, we included the most recent or that providing the most information. If one publication provided different groups of ethnicity, we considered the each group as a separate study. We conducted the meta-analysis according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement in reporting meta-analysis. The protocol (registration number: CRD42016036971) of the meta-analysis was published in the PROSPERO register (http://www.crd.york.ac.uk/PROSPERO/).

Search strategy. A comprehensively literature search was performed in PubMed, Embase, CBM, CNKI and Wanfang databases up to March, 2016, without restriction to regions, publication types, or languages. The search strategy was as following: (“polymorphism” AND “prostate cancer” AND “androgen receptor”). In addition, references in the recent reviews or meta-analysis and included articles were identified for any further potential related studies.

Data extraction. Data from the included studies were extracted and summarized independently by two authors (HW and XT-Z). Any disagreement was resolved by discussion of which data should be extracted. The following information was extracted: last name of first author, publication year, country of study, ethnicity, study design, control status, sample size, age of the cases and controls, percentage of advanced prostate cancer cases (T3-T4, M0; T0-T4, M1), the repeat cutpoint of polymorphisms, mean number of repeats in case and control groups with related SE, dichotomous data (short versus long repeats), and estimate with corresponding 95% CI (including OR for dichotomous data and continuous data). We defined the long CAG and GGN repeats as ≥22 and >16 repeats as previously published⁶, respectively. Otherwise, <22 and ≤16 were short CAG and GGN repeats, respectively.

Statistical analysis. We calculated ORs and 95% CIs for short CAG repeats (<22) versus long CAG repeats (≥22) and short GGN repeats (≤16) versus long GGN repeats (>16) using dichotomous data⁶. We summarized ORs and corresponding 95% CIs for per decrement of CAG and GGN repeats. We also summarized the
MDs in number of repeats between cases and controls. In this meta-analysis, all pooled analyses were performed with random-effects model using the method of DerSimonian-Laird, with the estimate of heterogeneity being taken from the Mantel-Haenszel model. Subgroup analyses were also performed according to ethnicity.

Figure 2. Sample size of the CAG repeat polymorphism.
(Caucasian, Asian, Africa, or Hispanic), study design (prospective, i.e. nested or retrospective case-control study),
control status, and histology grade of prostate cancer (localized and advanced). In addition, meta-regression anal-
ysis was also performed for interaction of between-group. Sensitivity analysis was performed by removing each
study at a time. Publication bias was detected using contour-enhanced funnel plot and Egger’s linear regression
method. Statistical analysis was performed using Stata 12.0 software. A two-sided P value of 0.05 was used, except
for heterogeneity test (0.1).

Results

Study characteristics. A total of 717 relevant publications were identified from the electronic liter-
ature search. The PRISMA flow diagram was presented in Fig. 1, which shows the detail of inclusion and
exclusion of studies. Ultimately, 51 publications16–66 were included in the meta-analysis, in which 51 publica-
tions16–66 with 61 case-control studies (14 803 cases and 18 888 controls, Fig. 2) for CAG repeats and 14 publi-
cations16,18,20,21,23,24,32,33,35,47,53,54,56,57 with 16 case-control studies (2986 cases and 3705 controls, Fig. 3) for GGN
repeats. The characteristics of included studies were shown in Table 1.

Association between CAG repeats polymorphism and prostate cancer risk. Fifty-one case-control
studies conveyed data on the short versus long CAG repeats. The pooled analysis showed that men with short
CAG repeats carried higher risk of prostate cancer than long CAG repeats (OR = 1.31, 95% CI 1.16 to 1.47;
I² = 74.9%, P for heterogeneity < 0.01; Fig. 4). Thirty-three case-control studies presented the data for per one
CAG decrement and the summarized OR was 1.04 (95% CI 1.02 to 1.07; I² = 83.4%, P for heterogeneity < 0.01;
Fig. 5) for men with per one CAG decrement. The aggregated analysis suggested that prostate cancer cases seemed
to have on average 0.85 fewer CAG repeat length than controls (MD = −0.85, 95% CI −1.28 to −0.42; I² = 88.7%,
P for heterogeneity < 0.01; Fig. 6) with 23 case-control studies.

Association between GGN repeats polymorphism and prostate cancer risk. Sixteen case-control
studies provided data on the short versus long GGN repeats. The pooled results showed that men with short GGN
repeats carried higher risk of prostate cancer than long GGN repeats (OR = 1.38, 95% CI 1.05 to 1.82; I² = 69.1%,
P for heterogeneity < 0.01; Fig. 7). Six case-control studies presented the data for per one GGN decrement and
the summarized OR was 1.04 (95% CI 1.02 to 1.07; I² = 83.4%, P for heterogeneity < 0.01; Fig. 5) for men with per one GGN decrement. The aggregated analysis suggested that prostate cancer cases seemed to have on average 0.85 fewer CAG repeat length than controls (MD = −0.85, 95% CI −1.28 to −0.42; I² = 88.7%, P for heterogeneity < 0.01; Fig. 6) with 23 case-control studies.

Haplotype analysis of CAG and GGN repeat polymorphisms. Six case-control studies provided data
for haplotype analysis. The estimated ORs were 2.06 (95% CI 1.29 to 3.29; I² = 69.3%, P for heterogeneity = 0.006),
1.79 (95% CI 1.08 to 2.96; I² = 75.8%, P for heterogeneity = 0.00), and 1.21 (95% CI 0.94 to 1.56; I² = 0, P for
heterogeneity = 0.99) for haplotypes CAG <22/GGN ≤16, CAG <22/GGN >16, and CAG ≥22/GGN ≤16 com-
pared with CAG ≥22/GGN >16 (Fig. 10).

Subgroup, meta-regression and sensitivity analysis. Subgroup analyses were conducted according
to ethnicity, study design, control status, and histology grade of prostate cancer. The results of subgroup analyses
showed that the elevated risk of prostate cancer in both CAG and GGN repeat polymorphisms were more pre-
dominant among Caucasian populations (Tables 2, 3 and 4) and the increased risk of prostate cancer of long GGN
repeats were more predominant in advanced prostate cancer cases (Fig. 11). Meta-regression analysis did not

Figure 3. Sample size of the GGN repeat polymorphism.
| Reference | Country | Race | Study design | Control status | Age, yr (ca/co) | Advanced cases (%) | Sample size | Repeat cutpoint |
|-----------|---------|------|-------------|----------------|---------------|--------------------|-------------|----------------|
| Irvine et al. 1995 (a) | US | Caucasian | Retrospective | Healthy | 57.8/NR | 46 | 57 | 39 | 22 |
| Irvine et al. 1995 (b) | US | African | Retrospective | Healthy | 57.8/NR | 46 | 57 | 44 | 22 |
| Irvine et al. 1995 (c) | US | Asian | Retrospective | Healthy | 57.8/NR | 46 | 57 | 39 | 22 |
| Giovannucci et al. 1997 | US | Caucasian | Prospective | Healthy | NR | 30.7 | 587 | 588 | 22 |
| Hakimi et al. 1997 | US | Caucasian | Retrospective | Healthy | 62.1/NR | 42.4 | 59 | 370 | 17 |
| Ingles et al. 1997 | US | Caucasian | Retrospective | Healthy | 57.8/NR | 46 | 57 | 46 | 22 |
| Stanford et al. 1997 | US | Caucasian | Retrospective | Healthy | 54.9/54 | 45.9 | 281 | 266 | 22 |
| Platz et al. 1998 | US | Caucasian | Prospective | Healthy | 62/NR | 46.6 | 582 | 794 | 23 |
| Bratt et al. 1999 | Sweden | Caucasian | Retrospective | Healthy | 70.2/NR | 1.6 | 160 | 186 | 22 |
| Correa-Cerro et al. 1999 | Germany | Caucasian | Retrospective | Healthy | 68.2/71.2 | NR | 132 | 105 | 22 |
| Edwards et al. 1999 | UK | Caucasian | Retrospective | Healthy | 68.1/NR | 75.3 | 162 | 390 | 22 |
| Lange et al. 2000 | US | Caucasian | Retrospective | Healthy | 64/NR | NR | 133 | 305 | 22 |
| Xue et al. 2000 | US | Caucasian | Retrospective | Healthy | 57.8/58.2 | 46 | 57 | 156 | 20 |
| Belin et al. 2001 | Australia | Caucasian | Retrospective | Healthy | 67/66.6 | 39.2 | 448 | 456 | 22 |
| Latil et al. 2001 | France | Caucasian | Prospective | Healthy | 70.5/71.7 | 69.8 | 226 | 156 | 23 |
| Modugno et al. 2001 | US | Caucasian | Retrospective | Healthy | 68.9/73.6 | NR | 88 | 241 | 23 |
| Panz et al. 2001 (a) | Israel | Caucasian | Retrospective | Healthy | 76/NR | 30 | 20 | 20 | 22 |
| Panz et al. 2001 (b) | South Africa | African | Retrospective | Healthy | 68/NR | 30 | 20 | 20 | 22 |
| Balic et al. 2002 | US | Hispanic | Retrospective | Healthy | 64/57 | NR | 82 | 145 | 18 |
| Chang et al. 2002 | US | Caucasian | Retrospective | Healthy | 60.9/58 | NR | 210 | 180 | 22 |
| Chen et al. 2002 | US | Caucasian | Prospective | Healthy | 61.2/60.8 | 11.5 | 300 | 300 | 22 |
| Gaur et al. 2002 | Australia | Caucasian | Retrospective | BPH | 65.9/66.5 | NR | 190 | 190 | 22 |
| Hsing et al. 2002 | China | Asian | Retrospective | Healthy | 72.2/71.9 | 62.6 | 190 | 300 | 22 |
| Mononen et al. 2002 (a) | Finland | Caucasian | Retrospective | Healthy | 68.1/NR | 48.1 | 461 | 574 | 18 |
| Mononen et al. 2002 (b) | Finland | Caucasian | Retrospective | BPH | 68.1/NR | 48.1 | 461 | 223 | 18 |
| Huang et al. 2003 | China | Asian | Retrospective | Healthy | 71.5/71.7 | 40.9 | 66 | 104 | 22 |
| Li et al. 2003 (a) | Sweden | Caucasian | Retrospective | BPH | 69/67 | NR | 59 | 38 | 22 |
| Li et al. 2003 (b) | Japan | Asian | Retrospective | BPH | 71/NR | NR | 34 | 33 | 22 |
| dos Santos et al. 2003 (a) | Brazil | Caucasian | Retrospective | Healthy | 65/58 | NR | 97 | 100 | 21 |
| dos Santos et al. 2003 (b) | Brazil | African | Retrospective | Healthy | 65/58 | NR | 32 | 100 | NR |
| Gilligan et al. 2004 | US | African | Retrospective | Healthy | 66.7/55.5 | 24.5 | 118 | 576 | 22 |
| Visvanathan et al. 2004 | US | Caucasian | Prospective | Healthy | 66.1/66 | 45.8 | 164 | 324 | 22 |
| Guhnmir et al. 2004 | China | Asian | Retrospective | Healthy | 67.5/66.3 | NR | 31 | 80 | 22 |
| Li et al. 2004 | China | Asian | Retrospective | Healthy | 67.9/67.1 | 60 | 105 | 190 | 22 |
| Freedman et al. 2005 | US | Mixed | Prospective | Healthy | 45.75 | NR | 2160 | 2036 | 22 |
| Mishra et al. 2005 | India | Caucasian | Retrospective | Healthy | 65.6/63.7 | NR | 113 | 133 | 22 |
| Platz et al. 2005 | US | Caucasian | Prospective | Healthy | NR | NR | 448 | 448 | 22 |
| Salinas et al. 2005 | US | Caucasian | Retrospective | Healthy | NR | 33.8 | 553 | 523 | 22 |
| Anderson et al. 2006 | Sweden | Caucasian | Retrospective | Healthy | 76.2/NR | NR | 137 | 125 | 23 |
| Vijayakrishnai et al. 2006 | India | Caucasian | Retrospective | Mixed# | 67.5/66 | NR | 87 | 120 | 22 |
| Lindstrom et al. 2006 | Sweden | Caucasian | Retrospective | Healthy | NR | 48 | 1461 | 796 | 22 |
| Okugi et al. 2006 | Japan | Asian | Retrospective | Healthy | 69.9/71 | NR | 102 | 117 | 22 |
| Sieh et al. 2006 (a) | US | Caucasian | Prospective | Healthy | 77.1/NR | 31.9 | 160 | 320 | 22 |
| Sieh et al. 2006 (b) | US | African | Prospective | Healthy | 74.9/NR | 45.5 | 33 | 71 | 22 |
| Du et al. 2006 | China | Asian | Retrospective | Healthy | NR | NR | 35 | 15 | NR |
| Mittal et al. 2007 | India | Caucasian | Retrospective | Healthy | 66.2/64.1 | NR | 135 | 142 | 22 |
| Das et al. 2007 (a) | Singapore | Asian | Retrospective | Healthy | 66/69 | NR | 47 | 46 | 22 |
| Das et al. 2007 (b) | Singapore | Asian | Retrospective | BPH | 66/67 | NR | 47 | 130 | 22 |
| Lange et al. 2007 | US | African | Retrospective | Healthy | 40–79 | NR | 180 | 840 | 22 |
| Neto et al. 2008 | Brazil | Caucasian | Retrospective | Healthy | 64/59 | NR | 49 | 51 | 21 |
| Nicolaiew et al. 2009 | France | Caucasian | Retrospective | Healthy | 67/63 | NR | 1045 | 814 | 17 |
| Kuasne et al. 2010 | Brazil | Caucasian | Retrospective | Healthy | 65.3/63.8 | 38.8 | 160 | 160 | 20 |
| Price et al. 2010 (a) | US | Caucasian | Prospective | Healthy | 63.4/63.6 | NR | 1082 | 1080 | 19 |
| Price et al. 2010 (b) | US | African | Prospective | Healthy | 63.4/63.6 | NR | 47 | 128 | 19 |

Continued
Table 1. Characteristics of included studies in the meta-analysis. NR, not report.

| Study design | Case status | Age, yr (ca/co) | Advanced cases (%) | Sample size | Repeat cutpoint |
|--------------|-------------|-----------------|-------------------|-------------|-----------------|
| Retrospective | Healthy | NR | NR | 110 | 100 | 21 |
| Prospective | Healthy | 60.4/NR | NR | 195 | 1344 | 19 |
| Healthy | Healthy | 66/63.2 | 7.9 | 291 | 1221 | 22 |
| Healthy | Healthy | 67/67.9 | 38.2 | 68 | 60 | 22 |
| Healthy | Healthy | NR | NR | 70 | 70 | 18 |
| Healthy | Healthy | 64/58 | NR | 95 | 98 | 22 |
| Retrospective | Healthy | NR | NR | 70 | 70 | 18 |
| Retrospective | Healthy | NR | NR | 95 | 98 | 22 |

Table 2. The results of overall and subgroup analyses of the association between CAG repeats and prostate cancer risk. BPH, benign prostatic hyperplasia; OR, odds ratio; CI, confidence interval; NA, not available.
detect any significant difference between subgroups (Tables 2, 3 and 4). Subgroup analysis showed that the result of CAG repeat length and risk of prostate cancer was robust (Fig. 12).

**Publication bias.** Publication bias was detected using contour-enhanced funnel plot and Egger’s linear regression method. Contour-enhanced funnel plots showed that publication bias might exist for the short versus long CAG repeat polymorphism (Fig. 13) and no publication bias existed in the short versus long GGN repeat polymorphism (Fig. 14). Egger’s linear regression method supported the aforementioned conclusion (P = 0.004 for CAG repeats; P = 0.07 for GGN repeats).

**Discussion**

The present meta-analysis summarizes the evidence to date regarding the association between CAG and GGN repeat polymorphisms of androgen receptor and the risk of prostate cancer. The results suggested that short CAG and GGN repeats in the androgen receptor gene were associated with increased risk of prostate cancer, especially in Caucasians.
Figure 5. Forest plot of per one CAG repeat decrement and risk of prostate cancer risk.

| Study ID |
|----------|

| Length of CAG repeat | No. studies | MD (95% CI) | P_{MD} | I^2 | P_{heterogeneity} | P_{interaction} |
|----------------------|-------------|-------------|--------|-----|-----------------|-----------------|
| Ethnicity            |             |             |        |     |                 |                 |
| Caucasian            | 14          | −1.09 (−1.65 to −0.53) | <0.01  | 92.9 | <0.01           |                 |
| Asian                | 8           | −0.32 (−0.86 to 0.22)  | 0.25   | 32.1 | 0.17            |                 |
| African              | 1           | −0.40 (−1.69 to 0.89)  | 0.55   | NA   | NA              |                 |
| Study design         |             |             |        |     |                 |                 |
| Retrospective        | 20          | −1.06 (−1.60 to −0.51) | <0.01  | 88.2 | <0.01           |                 |
| Prospective          | 3           | 0.14 (−0.06 to 0.34)   | 0.17   | 0.0  | 0.88            |                 |
| Control status       |             |             |        |     |                 |                 |
| Healthy              | 19          | −0.72 (−1.15 to −0.29) | <0.01  | 85.8 | <0.01           |                 |
| BPH                  | 4           | −1.40 (−3.19 to 0.38)  | 0.12   | 94.5 | <0.01           |                 |

Table 3. Results of length of CAG repeats and risk of prostate cancer. BPH, benign prostatic hyperplasia; MD, mead difference; CI, confidence interval; NA, not available.
The short CAG repeats (<22) and short GGN repeats (≤16) carry a roughly 1.31- and 1.38-fold higher risk of developing prostate cancer compared with subjects with long CAG (≥22) repeats and long GGN repeats (>16), respectively. Each decrement in CAG repeat presented 1.04-fold higher risk of developing prostate cancer. Prostate cancer cases presented an average 0.85 fewer CAG repeats than controls. In Caucasians, the aforementioned elevated risk was increased. This could be due to that more studies conducted in Caucasians, which provided greater statistical power for detecting small gene effect. Specifically, the prostate cancer cases in Caucasian population carried an average 1.09 fewer CAG repeats than controls. This difference might yield certain measurable biological impact in prostate carcinogenesis, such as early diagnosis and gene therapy.

Figure 6. Forest plot of difference in number of CAG repeat length between cases and controls.

| Study ID | No. studies | OR (95% CI) | P_H | I² | P_heterogeneity | P_interaction |
|----------|-------------|-------------|-----|----|-----------------|---------------|
| Short versus long | 16 | 1.38 (1.05 to 1.82) | 0.02 | 69.1 | <0.01 |
| Ethnicity | | | 0.52 |
| Caucasian | 12 | 1.24 (1.01 to 1.52) | 0.04 | 38 | 0.09 |
| Asian | 2 | 8.96 (0.25 to 318.05) | 0.51 | 86.6 | 0.01 |
| African | 2 | 2.02 (0.25 to 16.24) | 0.23 | 94 | <0.01 |
| Study design | | | 0.37 |
| Retrospective | 14 | 1.46 (1.09 to 1.97) | 0.01 | 71.8 | <0.01 |
| Prospective | 2 | 0.70 (0.17 to 2.80) | 0.61 | 49.9 | 0.16 |
| Control status | | | 0.57 |
| Healthy | 15 | 1.44 (1.07 to 1.93) | 0.02 | 70.5 | <0.01 |
| Mixed | 1 | 0.91 (0.52 to 1.58) | 0.73 | NA | NA |

Table 4. Results of the association between GGN repeats and prostate cancer. OR, odds ratio; CI, confidence interval; NA, not available.
An interaction between CAG and GGN repeat polymorphisms in increasing the prostate cancer susceptibility was documented by our meta-analysis. Haplotype analysis showed that short CAG and short GGN repeats carriers presented 2.06-fold higher risk of developing prostate cancer compared with long CAG and long GGN repeats.

Figure 7. Forest plot of short GGN repeats versus long GGN repeats.

Figure 8. Forest plot of per one GGN repeat decrement and risk of prostate cancer risk.
Figure 9. Forest plot of difference in number of GGN repeat length between cases and controls.

Figure 10. Haplotype analysis of CAG and GGN repeat polymorphisms and risk of prostate cancer.
Figure 11. Subgroup analysis of histology grade of prostate cancer.

Figure 12. Sensitivity analysis of CAG repeat decrement and risk of prostate cancer risk.
repeats carriers. Moreover, the short CAG repeats and long GGN repeats carriers presented 1.79-fold higher risk of developing prostate cancer compared with long CAG and long GGN repeats carriers.

In 2004, Zeegers et al. published the first meta-analysis regarding the association between CAG and GGN repeat length polymorphisms in the androgen receptor gene and prostate cancer risk, in which included 23 articles with 19 retrospective case-control studies and 5 prospective case-control studies, comprising a total of 4274 cases and 5275 controls. They found that the presence of shorter repeats seemed to be modestly associated with prostate cancer risk. However, they did not found any significant difference in number of repeats between cases and controls. In 2012, Gu et al. aggregated 27 articles to evaluate the relationship between CAG repeat polymorphism and prostate cancer risk. Their meta-analysis demonstrated that the CAG repeat polymorphism in androgen receptor gene with more than 20 repeats might confer a protective effect among the prostate cancer cases among men 45 years or older only. In 2013, Sun et al. carried out another meta-analysis regarding the association between CAG repeat polymorphism and prostate cancer risk, which included 47 studies with 13,346 cases and 15,172 controls. They suggested that a short CAG repeat polymorphism might increase the risk of prostate cancer compared with the longer CAG repeat, especially in Caucasians and Asians. Compared with the previous meta-analysis, our meta-analysis was more comprehensively searched and our meta-analysis included 51 case-control studies (14,803 cases and 18,888 controls) for CAG repeats and 16 case-control studies (2986 cases and 3705 controls) for GGN repeats. In addition, our meta-analysis performed haplotype analysis and suggested that there exists an interaction between CAG and GGN repeat polymorphisms in increasing the prostate cancer susceptibility. Moreover, we found a significant difference in number of CAG repeat length between cases and controls, and the absolute difference in more than 1 repeat in Caucasians.

The present retrospective analysis has some limitations. First, the evidence of between study heterogeneity was apparent, and the heterogeneity might distort the conclusion of the current meta-analysis. Additionally, the meta-regression analysis failed to identify the source of heterogeneity. Second, the standard of cutpoint of repeat length polymorphisms varied in different studies. This might in part contribute to the between study heterogeneity. Third, the screening policy of prostate cancer also varies between countries. Especially in United States, the prostate-specific antigen screening of the general population is more commonly used than other countries. These different screening policies might also be responsible for the between study heterogeneity. Fourth, the publication bias was detected in the present meta-analysis for the association between CAG repeat polymorphism and risk of prostate cancer. The existing publication bias indicated that certain studies with negative results for the association between CAG repeat polymorphism and prostate cancer risk are under-represented in the literature.
publication bias also might distort the conclusion of the present meta-analysis. Ultimately, the meta-analysis is a secondary analysis; therefore, we could not handle the problem of between study heterogeneity. In summary, our meta-analysis indicated that short CAG and GGN repeats in androgen receptor gene were associated with increased risk of prostate cancer, especially in Caucasians.

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Author Contributions
H.W. and X.T.Z. designed this study; H.W. and S.L. searched databases and collected full-text papers; H.W., J.Y.H., Z.Q.H., X.Y.M., Y.C. and C.F. extracted and analyzed data; H.W. and X.T.Z. wrote the manuscript, all the authors reviewed the manuscript.

Additional Information
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