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CTLA-4 rs5742909 polymorphism and cervical cancer risk

A meta-analysis

ShiWan Hu, MD, Dan Pu, MD, XueYi Xia, MD, BeiXi Guo, MD, ChuanLi Zhang, MD*

Abstract

Background: Number of studies have been performed to evaluate the relationship between the cytotoxic T-lymphocyte associated antigen-4 (CTLA-4) gene variant rs5742909 polymorphism and cervical cancer risk, but the sample size was small and the results were conflicting. This meta-analysis was conducted to comprehensively evaluate the overall association.

Methods: PubMed, Web of Science, Embase, China Biology Medical Literature database, China National Knowledge Infrastructure, WanFang, and Weipu databases were searched before July 31, 2018. The strength of associations was assessed using odds ratios (ORs) and 95% confidence intervals (CIs). All of the statistical analyses were conducted using Review Manager 5.3 and Stata 14.0.

Results: Eleven studies involved 3899 cases and 4608 controls. Overall, significant association was observed between the *CTLA*-4 gene variant rs5742909 polymorphism and cervical cancer (T vs C: OR = 1.40, 95% CI = 1.12–1.76; TT vs CC: OR = 2.22, 95% CI = 1.13–4.37; TT vs CT+CC: OR = 1.96, 95% CI = 1.03–3.74; TT+CT vs CC: OR = 1.47, 95% CI = 1.14–1.90). In subgroup analysis by ethnic group, a statistically significant association was observed in Asians (T vs C: OR = 1.56, 95% CI = 1.22–1.99), but not in Caucasians (T vs C: OR = 1.19, 95% CI = 0.87–1.62). The sensitivity analysis confirmed the reliability and stability of the meta-analysis.

Conclusion: our meta-analysis supports that the *CTLA-4* gene variant rs5742909 polymorphism might contribute to individual susceptibility to cervical cancer in Asians.

Abbreviations: CI = confidence interval, CTLA-4 = cytotoxic T-lymphocyte associated antigen-4, HWE = Hardy–Weinberg equilibrium, NOS = Newcastle–Ottawa scale, OR = odds ratio, PCR = polymerase chain reaction, PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism, SNP = single nucleotide polymorphism.

Keywords: cervical cancer, cytotoxic T-lymphocyte associated antigen-4, meta-analysis, polymorphism

1. Introduction

Cervical cancer, the fourth most frequently-diagnosed cancer in women worldwide, is the major cause of cancer-related mortality for women in developing countries.[1,2] The United States estimates suggested that approximately 12,820 new cervical cancer cases were diagnosed, and 4210 patients died of cervical cancer in 2017.[3] At present, the etiology of cervical cancer is well known, multiple factors such as human papilloma virus infection, smoking, alcoholic consumption, genetic mutation, family history, and occupational exposure to carcinogens are risk factors for cervical cancer, and play essential roles in the pathogenesis and progression of cervical cancer.[4–9]

The human *cytotoxic T-lymphocyte associated antigen-4* (*CTLA-4*) gene, located in chromosome 2q33, is associated with susceptibility to tumor immunity and autoimmunity.[10–12] CTLA-4 is an inhibitory molecule, involved in downregulation of T-cell response and peripheral tolerance.[13,14] CTL4 is playing a major role in the immune system. Multiple polymorphisms in *CTLA-4* gene are associated with susceptibility to autoimmune diseases and malignancy susceptibility.[15,16] The *CTLA-4* gene variant rs5742909, one of the most frequently studied polymorphism, was recently identified as a risk factor for cervical cancer.[17]

Although a number of studies have focused on *CTLA-4* gene variant rs5742909 polymorphism with respect to cervical cancer, they have small sample sizes and yielded contradictory results. Therefore, we perform this updated meta-analysis on all published case–control studies to derive a more precise estimation of *CTLA-4* gene variant rs5742909 polymorphism with cervical cancer risk.

2. Materials and methods

2.1. Publication search

The databases of PubMed, Web of Science, Embase, China Biology Medical Literature, China National Knowledge

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Infrastructure, WanFang, and Weipu databases were searched for studies examining the relation between CTLA-4 gene variant rs5742909 polymorphism and cervical cancer risk up to July 31, 2018. The search terms were as follows: "cytotoxic T-lymphocyte associated antigen-4," "CTLA-4," "rs5742909," "cervical cancer," "cervical carcinoma," "cervical tumor," and "cervical neoplasm." In addition, the references lists of relevant studies were also reviewed to identify other potential studies missed by the initial search. All analyses were based on previous published studies, thus no ethical approval and patient consent are required.

2.2. Inclusion and exclusion criteria

Only studies meeting the following inclusive selection criteria were eligible: case–control study investigating the association of *CTLA-4* gene variant rs5742909 polymorphism and cervical cancer susceptibility; the genotypes in cases and controls were available; sufficient raw data to calculate odds ratio (OR) with 95% confidence interval (CI). Exclusion criteria: study with incomplete data; editorial articles, review articles, case reports, and meeting abstracts; or duplicate publications with overlapping data.

2.3. Data extraction

Two authors extracted the relevant data using a standardized data extraction form independently. Discrepancies were resolved by discussion with a third investigator. The following information was extracted from each study: first author, year of publication, country, ethnicity, genotyping method, sample size, and genotype frequencies of *CTLA-4* gene variant rs5742909 polymorphism.

2.4. Quality assessment

The Newcastle–Ottawa scale was used to assess the quality of included studies by 2 authors.[18] This scale assesses the quality of case–control studies included 3 areas: selection, comparability, and exposure. A star rating system was used to judge methodological quality. Scores range from 0 stars (worst) to 9 stars (best), and studies with a score ≥7 were defined as high quality. Discrepant opinions were resolved by discussion and consensus.

2.5. Statistical analysis

ORs with 95% CI were used to assess the strength of association between *CTLA-4* gene variant rs5742909 polymorphism and cervical cancer risk. The pooled ORs were performed for *CTLA-4* gene variant rs5742909 polymorphism under the allele comparison model (T vs C), additive model (TT vs CC), recessive model (TT vs CT+CC), and dominant model (TT+CT vs CC), respectively. The significance of the pooled OR was analyzed by the Z test, and $P < .05$ was considered statistically significant. The Chi-square-based Q test and I^2 statistics were used to calculate heterogeneity among included studies. The $P > .05$ for Q test or $I^2 < 50\%$ indicated a statistically significant degree of heterogeneity among studies. Random effect model was used to summarize all the studies. All statistical analyses were performed by using Review Manager 5.3 and Stata 14.0. Publication bias was investigated with the funnel plot, Begg test, and Egger test. Sensitivity analysis was conducted to assess the stability of the results by sequentially omitted individual studies.

3. Results

3.1. Description of included studies

A total of 385 results were retrieved after first search in the selected databases, as shown in Figure 1. Of these studies, after the first screening, 374 studies were excluded based on inclusion and exclusion criteria. Finally, 11 case–control studies considering 3899 cases and 4608 controls were included in the meta-analysis.[10,17,19–27] The publication years of the assessed studies ranged from 2007 to 2018. Of these, there were 3 studies of Caucasian descendants and 8 studies of Asian descendants. The characteristics of each of the included studies are shown in Table 1.

3.2. Meta-analysis of CTLA-4 gene variant rs5742909 polymorphism in cervical cancer susceptibility

Eleven studies involving a total of 8507 individuals evaluated the influence of the *CTLA-4* gene variant rs5742909 polymorphism on the risk of cervical cancer. Figures 2–5 show the meta-analysis results for the allele model, additive model, recessive model, and dominant model, for which the I^2 value was 71%, 32%, 49%, and 64%, respectively. The random effect model was used to synthesize the data. Overall, pooled risk estimates indicated that CTLA-4 gene variant rs5742909 polymorphism was associated with an increased risk of cervical cancer (T vs C: OR = 1.40, 95% CI = 1.12–1.76; TT vs CC: OR = 2.22, 95% CI = 1.13–4.37; TT vs CT+CC: OR = 1.96, 95% CI = 1.03–3.74; TT+CT vs CC: OR = 1.47, 95% CI = 1.14–1.90).

Subgroup analysis based on ethnicity indicated that the *CTLA-4* gene variant rs5742909 polymorphism was associated with increased susceptibility to cervical cancer in Asians (T vs C: OR = 1.56, 95% CI = 1.22–1.99; TT vs CC: OR = 3.55, 95% CI = 1.75–7.18; TT vs CT+CC: OR = 1.60, 95% CI = 1.22–2.11; TT +CT vs CC: OR = 3.13, 95% CI = 1.55–6.33); however, no association was found between *CTLA-4* gene variant rs5742909 polymorphism and cervical cancer risk in Caucasians (T vs C: OR = 1.19, 95% CI = 0.87–1.62; TT vs CC: OR = 1.28, 95% CI = 0.49–3.32; TT vs CT+CC: OR = 1.24, 95% CI = 0.72–2.15; TT+CT vs CC: OR = 1.03, 95% CI = 0.77–1.39) (Table 2).

3.3. Publication bias and sensitivity

Funnel plot, Begg test, and Egger test were used to analyze the publication bias. No significant publication bias was observed under all the genetic models, as shown in Figure 6 and Table 3. The sensitivity analyses were performed to assess the effect of each individual study on the pooled ORs by sequentially excluding individual studies, and the results showed no individual study influenced the overall pooled ORs (Fig. 7), indicating that the results of this meta-analysis are relatively stable.

4. Discussion

This meta-analysis was conducted to provide a clear understanding of *CTLA-4* gene variant rs5742909 polymorphism and risk of cervical cancer. Our results of this meta-analysis suggest that

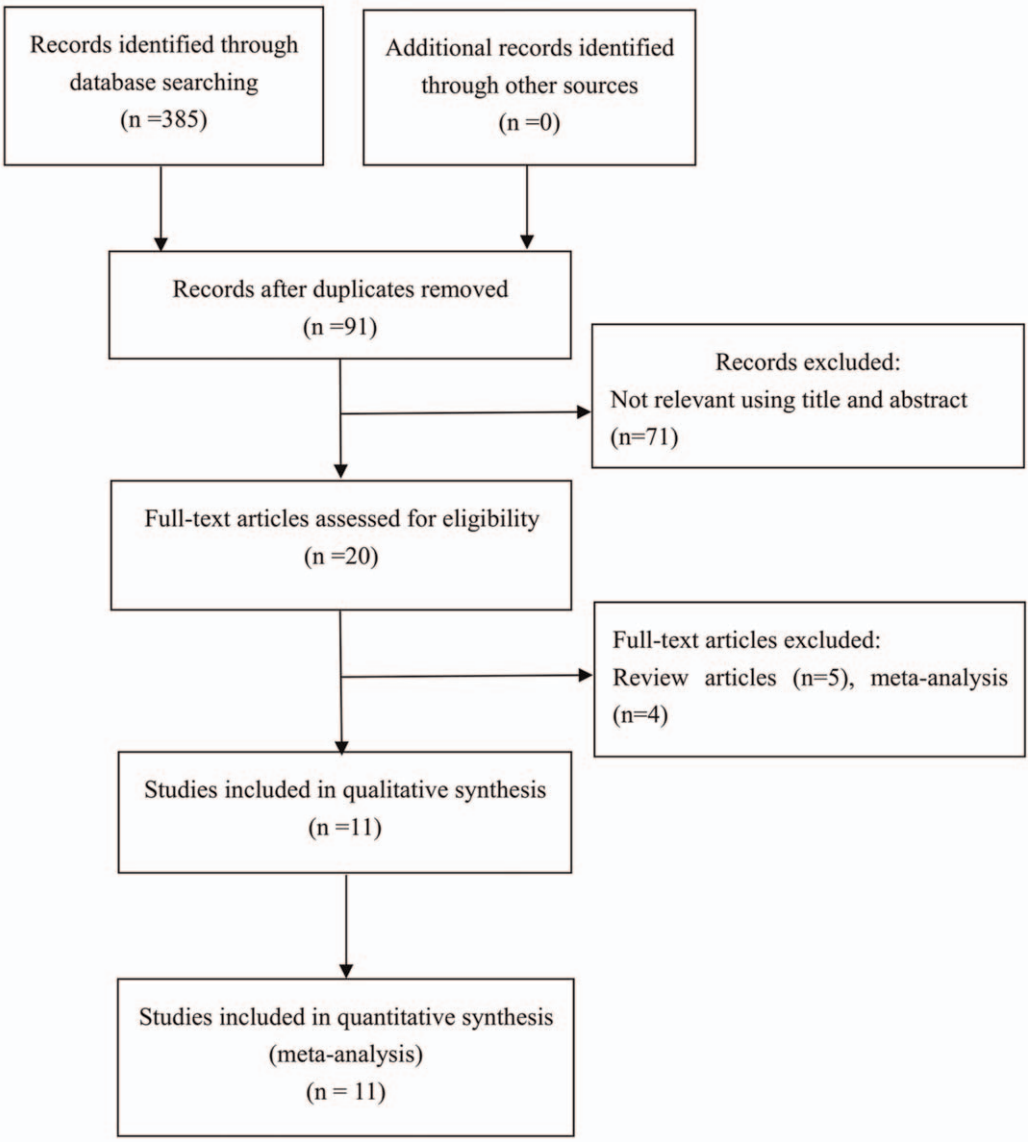

Figure 1. Flowchart showing the study selection.

Table 1

Characteristics of studies included in meta-analysis.

References	Region	Ethnicity	Genotyping method	Case	Control	Case			Control			HWE	NOS
						CC	CT	TT	CC	CT	TT		
[23]	Sweden	Caucasian	PCR	948	1700	5	124	819	6	223	1471	>0.05	8
[24]	China	Asian	PCR	350	350	222	115	13	258	89	3	>0.05	5
[17]	Indian	Asian	PCR-RFLP	100	101	93	7	0	94	7	0	>0.05	6
[10]	Sweden	Caucasian	TaqMan	1306	811	1044	228	9	666	138	4	>0.05	7
[25]	China	Asian	Sequenom MassARRAY	100	100	75	24	1	92	8	0	>0.05	7
[20]	Poland	Caucasian	TaqMan	147	225	99	38	3	180	35	1	>0.05	8
[19]	Iran	Asian	PCR-ARMS	55	110	51	3	0	89	20	1	>0.05	8
[22]	Taiwan	Asian	PCR-RFLP	144	378	105	38	1	306	67	5	>0.05	8
[27]	Indian	Asian	NA	92	57	90	2	0	56	1	0	>0.05	7
[26]	China	Asian	PCR	292	355	183	97	12	266	85	4	>0.05	7
[21]	China	Asian	Sequencing	365	421	232	127	6	316	104	1	<0.05	8

HWE = Hardy–Weinberg equilibrium, NA = not acquired, NOS = Newcastle–Ottawa scale, PCR = polymerase chain reaction, PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism.

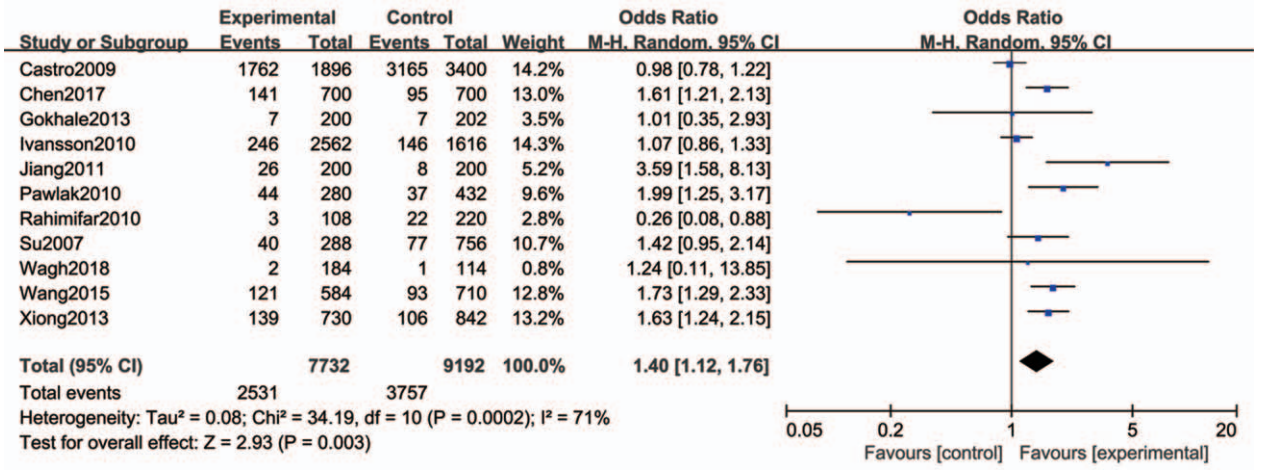

Figure 2. Forest plot of studies assessing association between *CTLA-4* gene variant rs5742909 polymorphism and cervical cancer (allelic model: T vs C). CI = confidence interval, CTLA-4 = cytotoxic T-lymphocyte associated antigen-4.

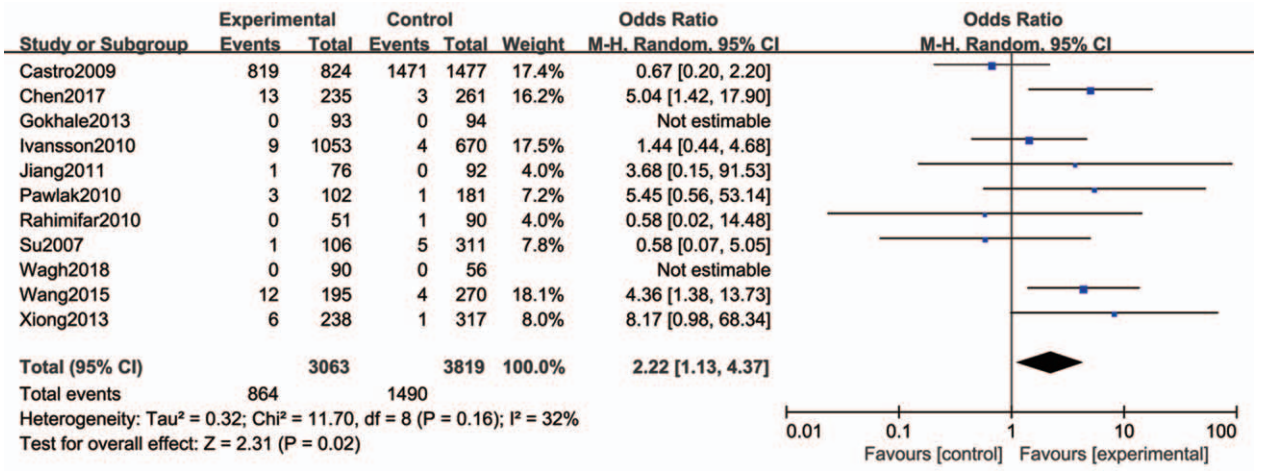

Figure 3. Forest plot of studies assessing association between *CTLA-4* gene variant rs5742909 polymorphism and cervical cancer (additive model: TT vs CC). CI = confidence interval, CTLA-4 = cytotoxic T-lymphocyte associated antigen-4.

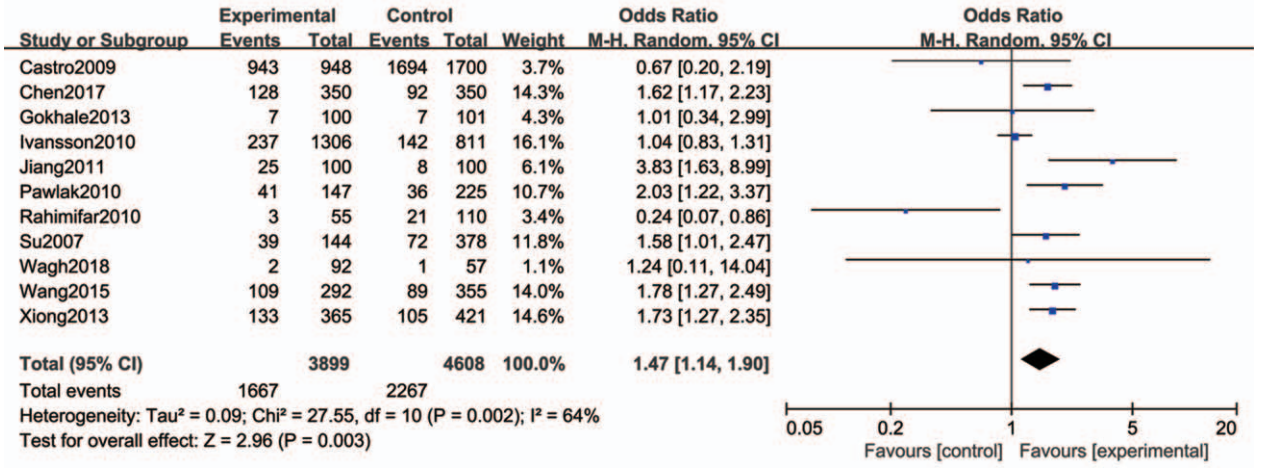

Figure 4. Forest plot of studies assessing association between *CTLA-4* gene variant rs5742909 polymorphism and cervical cancer (dominant model: TT+CT vs CC). CI = confidence interval, CTLA-4 = cytotoxic T-lymphocyte associated antigen-4.

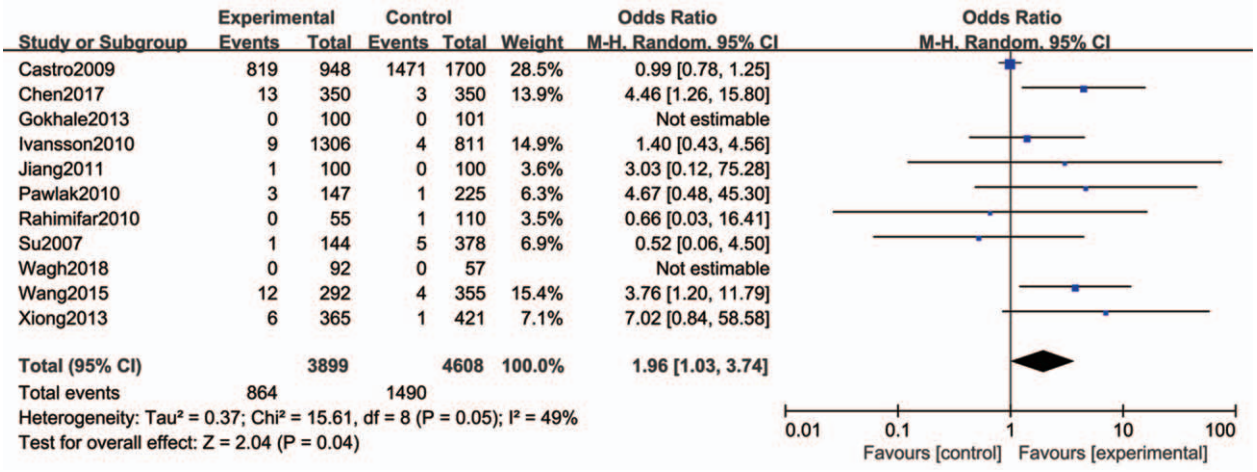

Figure 5. Forest plot of studies assessing association between *CTLA-4* gene variant rs5742909 polymorphism and cervical cancer (recessive model: TT vs CT +CC). CI = confidence interval, CTLA-4 = cytotoxic T-lymphocyte associated antigen-4.

Table 2

Meta-analysis of association of cytotoxic T-lymphocyte associated antigen-4 gene variant rs5742909 polymorphism with cervical cancer.

CTLA-4 rs5742909	N	T vs C (OR, 95% CI)	TT vs CC (OR, 95% CI)	TT+CT vs CC (OR, 95% CI)	TT vs CT+CC (OR, 95% CI)
Caucasian	3	1.19 [0.87, 1.62]	1.28 [0.49, 3.32]	1.24 [0.72, 2.15]	1.03 [0.77, 1.39]
Asian	8	1.56 [1.22, 1.99]	3.55 [1.75, 7.18]	1.60 [1.22, 2.11]	3.13 [1.55, 6.33]
Overall	11	1.40 [1.12, 1.76]	2.22 [1.13, 4.37]	1.47 [1.14, 1.90]	1.96 [1.03, 3.74]

CI = confidence interval, CTLA-4 = cytotoxic T-lymphocyte associated antigen-4, N = number, OR = odds ratio.

genetic variations of *CTLA-4* gene variant rs5742909 polymorphism may contribute to susceptibility to cervical cancer in Asians, but not in Caucasians.

The etiology of cervical cancer is complicated, and several risk factors are involved in the development and progression.[28] In addition to environmental and lifestyle risk factors, genetic causes, such as single gene mutations, also play essential roles in cervical cancer.[29,30] The rs5742909 polymorphism is one of the most commonly investigated single nucleotide polymorphisms (SNPs) in the *CTLA-4* gene, which is located in chromosome 2q33.[22] The SNP influences the promoter activity of the *CTLA-4* gene, which is associated with suppression of antitumor

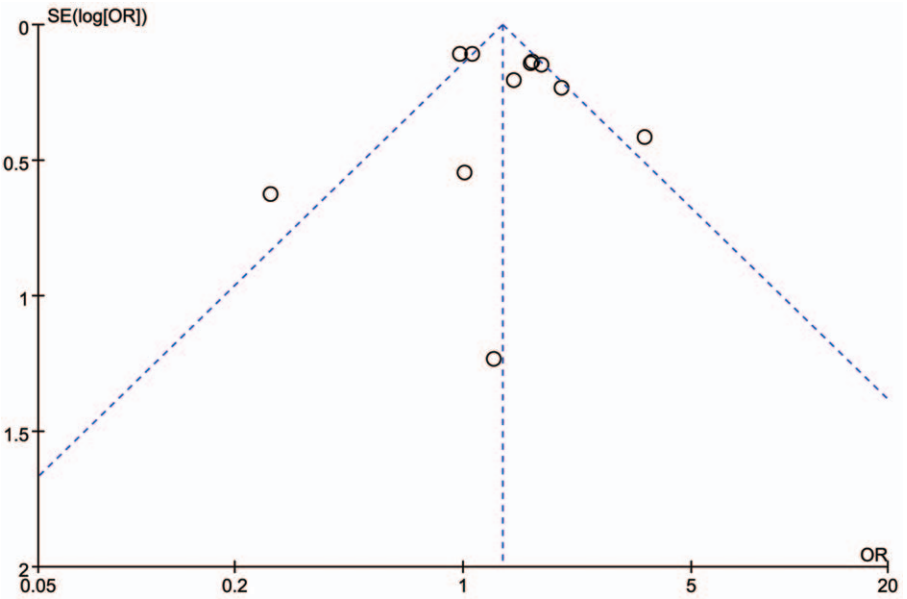

Figure 6. Funnel plots for *CTLA-4* gene variant rs5742909 polymorphism and cervical cancer risk (allelic model: T vs C). CTLA-4 = cytotoxic T-lymphocyte associated antigen-4, OR = odds ratio.

Table 3

Publication bias test for cytotoxic T-lymphocyte associated antigen-4 gene variant rs5742909 polymorphism.

Comparisons	Egger test			Begg test
	Coefficient	*P*	95% CI	*P*
CTLA-4 rs5742909				
T vs C	0.493	.681	−2.137–3.124	.876
TT vs CC	0.084	.946	−2.782–2.952	.466
TT+CT vs CC	−0.157	.877	−2.403–2.087	.640
TT vs CT+CC	1.101	.059	−0.055–2.257	.754

CI = confidence interval, CTLA-4 = cytotoxic T-lymphocyte associated antigen-4.

immunity.[31] In the present study, the overall results showed that *CTLA-4* gene variant rs5742909 polymorphism could increase the risk of cervical cancer (T vs C: OR = 1.40, 95% CI = 1.12–1.76; TT vs CC: OR = 2.22, 95% CI = 1.13–4.37; TT vs CT+CC: OR = 1.96, 95% CI = 1.03–3.74; TT+CT vs CC: OR = 1.47, 95% CI = 1.14–1.90). It reveals that individuals with the variant T allele may have a higher risk for cervical cancer than those carrying C homozygote. Nevertheless, in the subgroup analysis of ethnicity, we found that *CTLA-4* gene variant rs5742909 polymorphism had an effect on increase in the cervical cancer risk in Asians, while the susceptibility to cervical cancer was not observed in Caucasian population.

There is an increasing evidence investigating the association between *CTLA-4* gene variant rs5742909 polymorphism and risk of different type of cancers. Several studies have evaluated the relationship of *CTLA-4* gene variant rs5742909 polymorphism and cervical cancer, and the results remain inconclusive rather than consistent. Ivansson et al[10] reported that *CTLA-4* gene variant rs5742909 polymorphism confirmed high risk for cervical cancer in Swedish population. Similarly, a case–control study conducted by Pawlak et al[20] found the *CTLA-4* gene variant rs5742909 polymorphism is associated with risk of cervical cancer in Polish population. However, Gokhale et al[17] reported that no association was observed between *CTLA-4* gene variant rs5742909 polymorphism and cervical cancer in Indian women. The difference between the studies could arise from race, geography, or genetic background of the study population. In the present study, significant association was observed between *CTLA-4* gene variant rs5742909 polymorphism and cervical cancer in the overall population. In a subgroup analysis based on nationality, we have found a significant association between the *CTLA-4* gene variant rs5742909 polymorphism and cervical cancer risk in Asians, but not in Caucasian population. Only 3 studies reported the relationship between the *CTLA-4* gene variant rs5742909 polymorphism and cervical cancer risk in Caucasians and 8 studies for Asian population were included in the present meta-analysis. The sample size was small; thus, studies with larger sample sizes are needed to further investigate the potential relationships of *CTLA-4* gene variant rs5742909 polymorphism with cervical cancer risk.

When interpreting the results of the present study, there are still several limitations that should be taken with cause. First, only 11 studies were included in the meta-analysis, the sample size of included published articles was small, and so sufficient data was unavailable. Second, subgroup analysis was not conducted based on pathological patterns, due to the lack of information. Third, we did not estimate the potential interactions among gene–gene, gene–environment, as the studies enrolled lacked of information. Finally, its OR values were unadjusted data, due to the lack of data of smoking, alcoholic consumption, family history, age, and other environmental exposure factors.

5. Conclusions

This meta-analysis result suggests that the *CTLA-4* gene variant rs5742909 polymorphism may increase the risk of cervical cancer, especially in Asians. However, large sample size, well-designed, and population-based studies are necessary to comprehensively verify the association between *CTLA-4* gene variant rs5742909 polymorphism and cervical cancer risk.

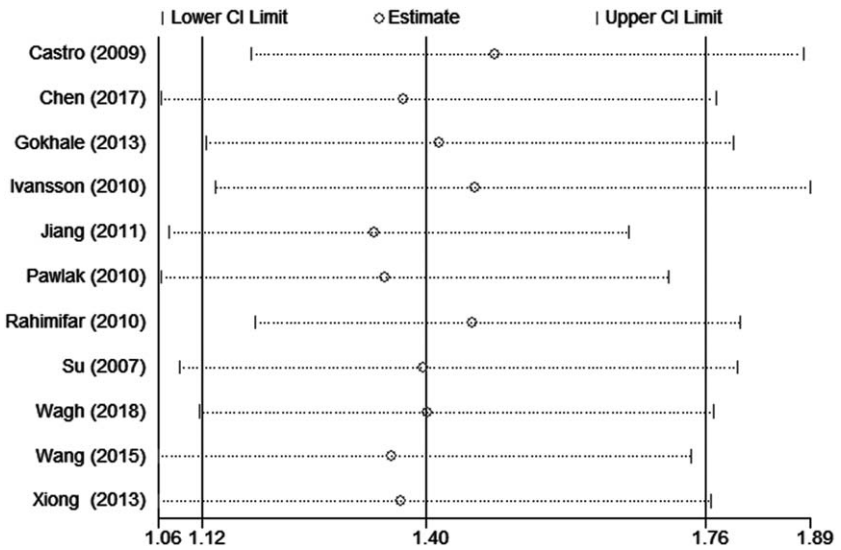

Figure 7. Sensitivity analysis diagram for each study used to assess relative risk estimates for *CTLA-4* gene variant rs5742909 polymorphism and cervical cancer in all included studies (allelic model: T vs C). CI = confidence interval, CTLA-4 = cytotoxic T-lymphocyte associated antigen-4.

Author contributions

Conceptualization: ChuanLi Zhang, ShiWan Hu.
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Formal analysis: ShiWan Hu.
Methodology: Dan Pu, XueYi Xia.
Software: XueYi Xia.
Supervision: BeiXi Guo.
Writing – original draft: ShiWan Hu.
Writing – review & editing: ChuanLi Zhang, BeiXi Guo.

References

[1] Denny L. Cervical cancer: prevention and treatment. Discov Med 2012;14:125–31.
[2] Ginsburg O, Bray F, Coleman MP, et al. The global burden of women's cancers: a grand challenge in global health. Lancet 2017; 389:847–60.
[3] Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. CA Cancer J Clin 2017;67:7–30.
[4] Wright TC, Stoler MH, Behrens CM, et al. Primary cervical cancer screening with human papillomavirus: end of study results from the ATHENA Study using HPV as the first-line screening test. Obstet Gynecol Surv 2015;70:321–2.
[5] Sugawara Y, Tsuji I, Mizoue T, et al. Research Group for the Development and Evaluation of Cancer Prevention Strategies in JapanCigarette smoking and cervical cancer risk: an evaluation based on a systematic review and meta-analysis among Japanese women. Jpn J Clin Oncol 2019;49:77–86.
[6] Bagnardi V, Rota M, Botteri E, et al. Alcohol consumption and site-specific cancer risk: a comprehensive dose-response meta-analysis. Br J Cancer 2015;112:580–93.
[7] Boffetta P, Dosemeci M, Gridley G, et al. Occupational exposure to diesel engine emissions and risk of cancer in Swedish men and women. Cancer Causes Control 2001;12:365–74.
[8] Mwaka AD, Orach CG, Were EM, et al. Awareness of cervical cancer risk factors and symptoms: cross-sectional community survey in post-conflict northern Uganda. Health Expect 2016;19:854–67.
[9] Lai HC, Chu CM, Lin YW, et al. Matrix metalloproteinase 1 gene polymorphism as a prognostic predictor of invasive cervical cancer. Gynecol Oncol 2005;96:314–9.
[10] Ivansson EL, Juko-Pecirep I, Gyllensten UB. Interaction of immunological genes on chromosome 2q33 and IFNG in susceptibility to cervical cancer. Gynecol Oncol 2010;116:544–8.
[11] Rudd CE, Taylor A, Schneider H. CD28 and CTLA-4 coreceptor expression and signal transduction. Immunol Rev 2009;229:12–26.
[12] Sun T, Zhou Y, Yang M, et al. Functional genetic variations in cytotoxic T-lymphocyte antigen 4 and susceptibility to multiple types of cancer. Cancer Res 2008;68:7025–34.
[13] Wing K, Yamaguchi T, Sakaguchi S. Cell-autonomous and -non-autonomous roles of CTLA-4 in immune regulation. Trends Immunol 2011;32:428–33.
[14] Wolchok JD, Saenger Y. The mechanism of anti-CTLA-4 activity and the negative regulation of T-Cell activation. Oncologist 2008;13(Suppl 4):2–9.
[15] Min WK, Kim S, Sung SK, et al. Allelic discrimination of the Restorer-of-fertility gene and its inheritance in peppers (Capsicum annuum L.). Theor Appl Genet 2009;119:1289–99.
[16] Fernandez-Mestre M, Sanchez K, Balbas O, et al. Influence of CTLA-4 gene polymorphism in autoimmune and infectious diseases. Hum Immunol 2009;70:532–5.
[17] Gokhale P, Kerkar S, Tongaonkar H, et al. CTLA-4 gene polymorphism at position+49 A > G in exon 1: a risk factor for cervical cancer in Indian women. Cancer Genet 2013;206:154–61.
[18] Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010;25:603–5.
[19] Rahimifar S, Erfani N, Sarraf Z, Ghaderi A. ctla-4 gene variations may influence cervical cancer susceptibility. Gynecol Oncol 2010;119:136–9.
[20] Pawlak E, Karabon L, Wlodarska-Polinska I, et al. Influence of CTLA-4/CD28/ICOS gene polymorphisms on the susceptibility to cervical squamous cell carcinoma and stage of differentiation in the Polish population. Hum Immunol 2010;71:195–200.
[21] Xiong YH, He L, Fei J. Genetic variations in cytotoxic T-lymphocyte antigen-4 and susceptibility to cervical cancer. Int Immunopharmacol 2014;18:71–6.
[22] Su TH, Chang TY, Lee YJ, et al. CTLA-4 gene and susceptibility to human papillomavirus-16-associated cervical squamous cell carcinoma in Taiwanese women. Carcinogenesis 2007;28:1237–40.
[23] Castro FA, Haimila K, Sareneva I, et al. Association of HLA-DRB1, interleukin-6 and cyclin D1 polymorphisms with cervical cancer in the Swedish population: a candidate gene approach. Int J Cancer 2009;125:1851–8.
[24] Chen X, Qian Q. The association between polymorphism of ctla-4 gene and susceptibility to cervical cancer. Chin J Gerontol 2017;37:4207–9.
[25] Jiang L, Luo R, Zhang W, et al. Single nucleotide polymorphisms of CTLA4 gene and their association with human cervical cancer. Chin J Med Genet 2011;28:313–7.
[26] Wang J, Zhong J, Zhang J, et al. Correlation analysis of genetic polymorphism of cytotoxic T-lymphocyte-associated antigen-4 and susceptibility to cervical cancer. Chin J Clin Lab Sci 2015;33:119–23.
[27] Wagh P, Kulkarni P, Kerkar S, et al. Polymorphisms in cytotoxic T-lymphocyte associated antigen 4 gene does not affect scytotoxic T-lymphocyte associated antigen 4 levels in human papillomavirus-infected women with or without cervical cancer. Indian J Med Microbiol 2018;36:207–10.
[28] Castellsague X. Natural history and epidemiology of HPV infection and cervical cancer. Gynecol Oncol 2008;110(3 Suppl 2):S4–7.
[29] Ding B, Sun W, Han S, et al. Cytochrome P450 1A1 gene polymorphisms and cervical cancer risk: a systematic review and meta-analysis. Medicine (Baltimore) 2018;97:e0210.
[30] Ye F, Wang H, Liu J, et al. Genetic polymorphism (rs246079) of the DNA repair gene uracil N-glycosylase is associated with increased risk of cervical carcinoma in a Chinese population. Medicine 2018;97:e13694.
[31] Antczak A, Pastuszak-Lewandoska D, Gorski P, et al. Ctla-4 expression and polymorphisms in lung tissue of patients with diagnosed non-small-cell lung cancer. Biomed Res Int 2013;2013:576486.