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The association between rs1800872 polymorphism in interleukin-10 and risk of cervical cancer
A meta-analysis

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Abstract

Background: In recent years, several reports have tried to prove this connection between rs1800872 polymorphism in interleukin-10 and cervical cancer among different populations, but the results are debatable. Thus, we collected all the published literature and conducted an integrated meta-analysis, which provided better evidence-based medicine for the relationship between rs1800872 polymorphism in interleukin-10 and risk of cervical cancer.

Methods: We systematically performed our search on PubMed, EMBASE, Web of Science, WanFang database, and CNKI for all papers related to this research, published up to August 1, 2020. Summary odds ratios (OR) with 95% confidence interval (95% CI) were calculated in allelic, homozygous, heterozygous, dominant, and recessive model to appraise the association.

Results: The meta-analysis included 8 studies containing 1393 cervical cancer cases and 1307 controls. The aggregate data under heterozygous model and dominant inheritance model (OR=0.66, 95% CI: 0.55–0.80) indicated a significant association between rs1800872 and the low risk of cervical cancer in the entire population. And the aggregated data under the dominant inheritance model shows that rs1800872 is significantly associated with the reduction in the risk of cervical tumors in the entire population.

Conclusion: Our conclusion is that the AC/AA+AC variant of Rs1800872 indicates a protective effect in the development of cervical cancer.

Abbreviations: CI = confidence interval, HWE = Hardy–Weinberg Equilibrium, NOS = Newcastle–Ottawa Scale, OR = odds ratio, SNP = single nucleotide polymorphism.

Keywords: meta-analysis, Interleukin-10, polymorphism, rs1800872, cervical cancer

1. Introduction

Cervical cancer is a major challenge to global health, ranking fourth in the global female malignant tumors.[1] Early cervical cancer is usually asymptomatic and is often diagnosed by routine screening or pelvic examination. Bleeding after sexual intercourse

or abnormal vaginal bleeding is the main symptom of cervical cancer.[2] A large amount of foul-smelling vaginal discharge may also be one of its symptoms, but it rarely appears alone.[3] Diagnosis is established by histopathological examination that relies on cervical biopsy. The most common histological subtypes of cervical cancer are squamous cell carcinoma and adenocarcinoma, accounting for 70% and 25%, respectively.[4] Although the prevention, screening, diagnosis, and treatment of cancer have made rapid progress in the past decade, there are huge regional differences in the evolution and outcome of cervical cancer. In 2015, 270,000 people worldwide died of cervical cancer. About 90% of them occur in low- and middle-income countries, and the death rate is nearly 18 times that of developed countries.[5] In 2018, an estimated 569,847 new cases of cervical cancer were diagnosed globally and 311,365 patients died.[1] There are many causes of uterine cervical neoplasms, among which genetic polymorphisms can affect its susceptibility. As the main member of the IL-10 cytokine family,[6] IL-10 plays an important role in regulating the proliferation and differentiation of various immune cells.[7] It has been reported that the IL-10 promoter region polymorphism affects the transcription and translation of *IL-10* gene, leading to abnormal cell proliferation and intervening in the development of tumors.[8] In recent years, several reports have tried to prove this connection between rs1800872 polymorphism in interleukin-10 and cervical cancer among different populations, but the results are debatable. Given that interleukin-10 plays a decisive role in cancer, it is important

to understand the relationship between rs1800872 polymorphism and the risk of cervical cancer. The study collected all the published literature and conducted a integrated meta-analysis, which provided better evidence-based medicine for the relationship between rs1800872 polymorphism in interleukin-10 and risk of cervical cancer.

2. Materials and methods

2.1. Literature search strategy

We systematically performed our search on PubMed, EMBASE, Web of Science, WanFang database, and CNKI (China National Knowledge Infrastructure electronic databases) for all papers related to this research, published up to August 1, 2020. Using the Medical Subject Headings (MeSH) and free words: (Polymorphisms, Genetic OR Genetic Polymorphisms OR Genetic Polymorphism OR Polymorphism OR Polymorphisms OR "Polymorphism, Genetic"[Mesh]) AND (Cervical Neoplasm, Uterine OR Cervical Neoplasms, Uterine OR Cervical Cancer OR Cancer of the Cervix OR Cancer of the Uterine Cervix OR Cervix Neoplasm OR "Uterine Cervical Neoplasms"[Mesh]) AND (Interleukin 10 OR IL10 OR IL-10 OR CSIF-10 OR Cytokine Synthesis Inhibitory Factor OR "Interleukin-10"[Mesh]). Through a comprehensive review of the literature, we had identified all relevant studies. Then, to ensure that no relevant studies were excluded, we reviewed all the included literature again. Two authors independently completed a literature search. We also conducted a manual search of the literature for possible potential research. The meta-analysis did not involve data related to patient personal information and therefore does not require ethical approval.

2.2. Inclusion and exclusion criteria

Inclusion criteria were published research on the relevance of rs1800872 in the interleukin-10 and cervical cancer, all studies were either case–control studies, and these studies have enough data to calculate OR and 95% CI. Exclusion criteria were comments, letters, conferences reports, correspondences, simple case studies, and case reports, and repeated research and incomplete research, and the literature with less than 6 NOS score, and studies without useable genotype frequencies.

2.3. Methodological quality assessment

Two authors, KXW and ZJ, used Newcastle–Ottawa scale (NOS) to estimate the methodological quality of the inclusion studies. the selection of cases and controls, the comparability of cases and controls, and the determination of exposures or results of interest in case–control studies. The disagreement was resolved by the opinion of the third author.

2.4. Data extraction

All data used standardized tables and were independently extracted by two authors (Kexin Wang and Jing Lu). We extracted the following information from each study: first author, publication year, country, sample size, ethnicity, and genotype frequencies.

2.5. Statistical analysis

ORs with 95% CI were used as a vehicle for assess the strength of association between rs1800872 polymorphism in interleukin-10 and cervical cancer risk. The pooled ORs were performed for interleukin-10 rs1800872 polymorphism under the allelic model (A vs C), homozygous model (AA vs CC), recessive genetic models (AA vs CC + AC), heterozygous model (AC vs CC), and dominant inheritance model (AA + AC vs CC), respectively. The consequence of the pooled OR was analyzed by the Z test, and $P < .05$ was considered statistically significant. The data analysis was performed using Review Manager 5.3 software.

2.6. Heterogeneity and publication bias

Q statistical test and I^2 test were used to assess the heterogeneity of included studies, which test result was $I^2 \geq 50\%$ and $P < .1$ indicated the existence of heterogeneity. The random-effect model was used when there was no significant heterogeneity between studies. Instead, the fixed-effect model was used. For models with heterogeneity, we would conduct a stratified analysis based on ethnicity to determine the potential source of heterogeneity. Funnel plot was used to detect publication bias, and an asymmetric plot indicates that there may be publication bias. The stability of the results was evaluated by sensitivity analysis.

3. Results

3.1. Basic condition of research data

According to the criteria, 8 articles in total were selected, including 3 from Caucasian population and 5 from Asian population, with 1393 patients in the case group and 1307 normal people in the control group. The specific screening process was shown in the flow diagram. The characteristics of each study and the distribution of genotypes reported in this study are summarized in Table 1.[9–16]

Table 1

Main characteristics of included studies and genotype frequencies of cases and controls.

Study	Year	Country	Ethnicity	Sample size	Case					Control					HWE	NOS score
					A	C	AA	AC	CC	A	C	AA	AC	CC		
Bai et al[9]	2016	China	Asian	165/165	208	122	63	82	20	220	110	70	80	15	0.24	8
Poveda et al[10]	2012	Mexico	Caucasian	204/166	203	205	49	105	50	130	202	30	136	66	0.13	8
Roh et al[11]	2002	Korea	Asian	144/179	210	78	77	56	11	251	107	87	77	15	0.72	7
Shekari et al[12]	2012	Iran	Asian	200/200	272	128	88	96	16	264	136	81	102	17	0.05	8
Singhal et al[13]	2014	India	Asian	256/250	191	321	37	117	102	257	243	67	123	60	0.81	7
Sotirija et al(a)[14]	2020	Macedonia	Caucasian	134/113	48	220	4	40	90	62	164	5	52	56	0.10	8
Sotirija et al(b)[14]	2020	Macedonia	Caucasian	94/113	32	156	4	24	66	62	164	5	52	56	0.10	8
Sotirija et al(c)[14]	2020	Macedonia	Caucasian	40/113	16	64	0	16	24	62	164	5	52	56	0.10	8
xiong et al[15]	2010	China	Asian	70/108	93	47	35	23	12	146	70	51	44	13	0.08	7
Zidi et al[16]	2015	Tunisia	Caucasian	86/126	51	122	9	32	45	73	178	5	64	57	0.01	8

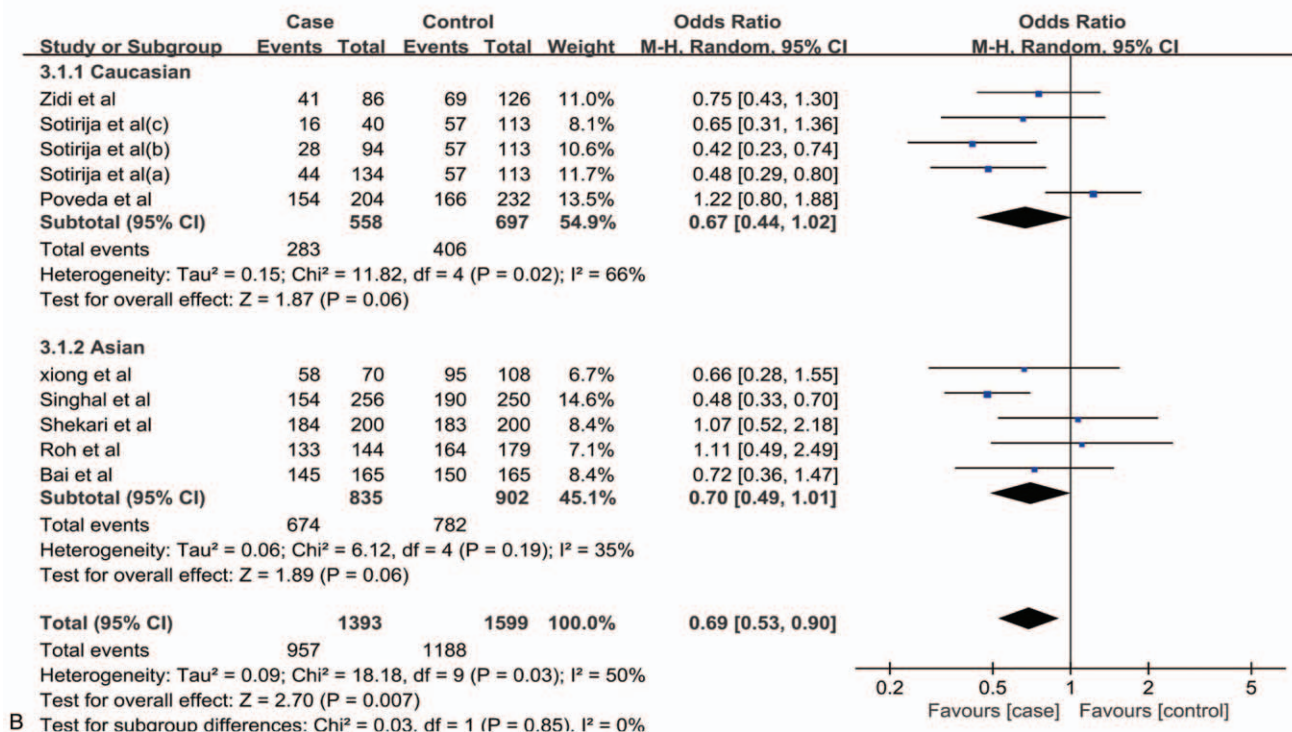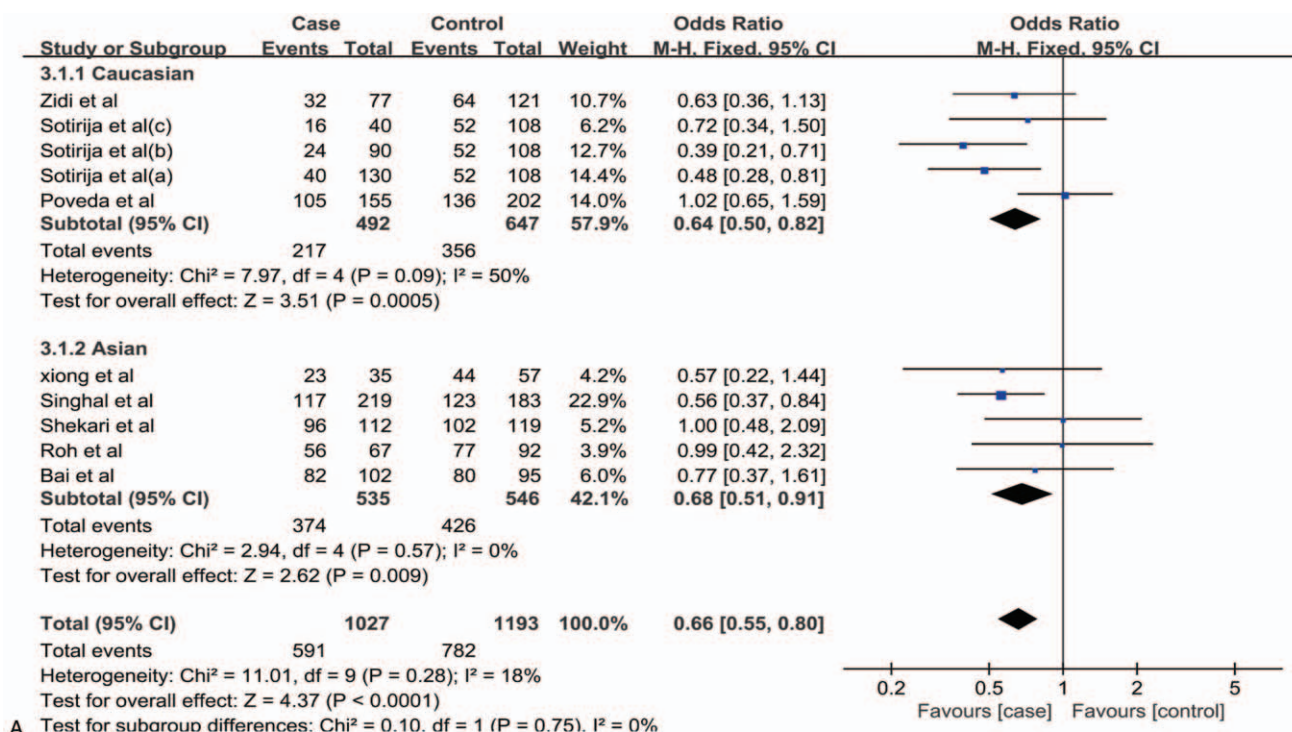HWE = Hardy–Weinberg Equilibrium, NOS = Newcastle–Ottawa Scale.

Figure 1. Forest plot for the association between rs1800872 polymorphism in interleukin-10 and risk of cervical cancer (A: Heterozygote model; B: Dominant model).

3.2. Meta-analysis and subgroup-analysis

The aggregate data under heterozygous model (AC vs CC, OR = 0.66, 95% CI: 0.55–0.80, $P < .0001$; Fig. 1) indicated a significant association between rs1800872 and the low risk of cervical cancer in the entire population. The genotype AC of heterozygote model, compared with genotype CC, was $I^2 = 18\%$, $P > .10$, indicating no statistical significance in heterogeneity among studies, and fixed effect model was applied. The aggregated data under the dominant inheritance model shows that rs1800872 is significantly associated with the reduction in

The pooled ORs and 95% CIs for the association between rs1800872 polymorphism in interleukin-10 and risk of cervical cancer susceptibility.

Comparison	Association			Effect model	Heterogeneity	
	OR	95% CI	P		I^2 (%)	P
Overall						
A vs C	0.86	0.67–1.10	.22	R	77%	<.1
AA vs CC	0.87	0.52–1.44	.58	R	69%	<.1
AC vs CC	0.66	0.55–0.80	<.01	F	18%	.3
AC+AA vs CC	0.69	0.53–0.90	<.01	R	50%	<.1
AA vs CC+AC	1.05	0.74–1.50	.77	R	66%	<.1
Asian						
A vs C	0.88	0.66–1.18	.40	R	76%	<.1
AA vs CC	0.71	0.41–1.23	.22	R	65%	<.1
AC vs CC	0.68	0.51–0.91	<.01	F	0%	.6
AC+AA vs CC	0.70	0.49–1.01	.06	R	35%	.2
AA vs CC+AC	0.90	0.63–1.29	.57	R	68%	<.1
Caucasian						
A vs C	0.82	0.52–1.29	.39	R	82%	<.1
AA vs CC	1.18	0.56–2.51	.67	R	47%	<.1
AC vs CC	0.64	0.50–0.82	<.01	F	50%	.1
AC+AA vs CC	0.67	0.44–1.02	.06	R	66%	<.1
AA vs CC+AC	1.52	0.82–2.79	.18	R	31%	.2

CI = confidence interval, F = fixed-effect model, OR = odds ratio, R = random-effect model.

the risk of cervical tumors in the entire population. The genotype AC+AA of dominant inheritance model, compared with genotype CC, was $I^2 = 50\%$, $P < .10$, which suggested that the heterogeneity among studies was statistically significant, and random effect model was applied. However, allelic model, recessive genetic models, and homozygous model were not significantly correlated (Table 2).

We conduct subgroup analysis of 5 genetic models of different races, and the results showed that in the heterozygous model, rs1800872 maintains a low-risk correlation with Caucasian population (OR = 0.64, 95% CI: 0.50–0.82, $P = .0005$) and Asian population (OR = 0.68, 95% CI: 0.51–0.91, $P = .009$) cervical cancer. However, in the subgroup analysis of the dominant inheritance model, there was no significant correlation between rs12807809 and the risk of uterine cervical neoplasms in Caucasian population and Asian population. See Figure 1 for the forest map.

3.3. Sensitivity analysis

Individual studies were excluded in turn to conduct sensitivity analysis to evaluate the impact of a single study on the combined ORs. The results showed that no single study affected the combined ORs, which indicates that the results of this meta-analysis are relatively stable.

3.4. Publication bias

A funnel plot was used to assess whether the included studies had publication bias. The shape of the funnel plot has no obvious asymmetry. It can be considered that the included studies have no publication bias (Fig. 2).

4. Discussion

In this meta-analysis, we retrieved all the literature on rs1800872 and cervical cancer through multiple databases, and included the
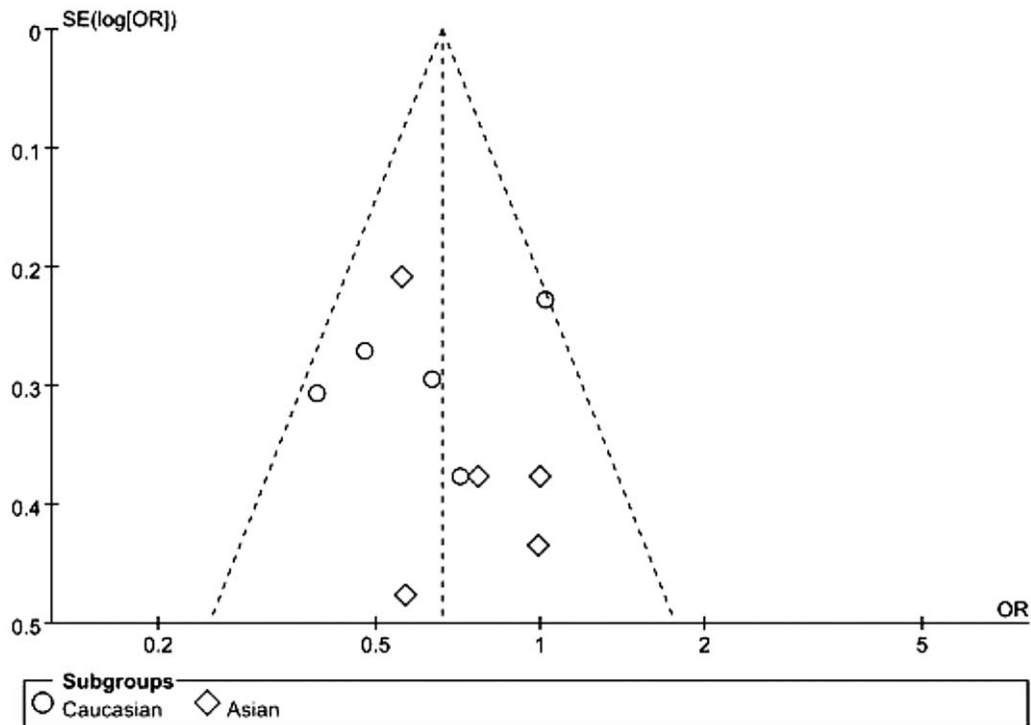

Figure 2. Funnel plot of rs1800872 polymorphism and risk of cervical cancer.

documents that meet the inclusion and exclusion criteria into this meta-analysis study, using 5 genetic models and subgroup analysis divided by ethnicity were used to comprehensively compare and analyze the gene distribution results of 1393 cases of cervical cancer patients and 1307 normal people. Comprehensive analysis shows that rs1800872 is significantly related to the reduction of cervical cancer risk in the entire population.

A total of 8 articles were included in this study, including 5 from Asian population and 3 from Caucasian population. The results showed that the allelic model, homozygous model, and recessive genetic models, were not statistically different in the overall comparison of the entire population. There are statistically significant differences between the heterozygous model and the dominant inheritance model in the overall comparison of the entire population. The analysis results of Asian population showed that the combined OR of the heterozygous model was 0.68, and the difference was statistically significant, while the difference in the dominant inheritance model was not statistically significant. The analysis of the Caucasian population showed that the combined OR of the heterozygous model was 0.64, and the difference was statistically significant, while the difference in the dominant inheritance model was not statistically significant. The combined OR of the dominant inheritance model in the entire population was 0.66, which was statistically significant, but there was no statistically significant difference in the subgroup analysis of the Asian population and the Caucasian population. This may be caused by the insufficient sample size of the two populations. As for the results of publication bias, the funnel plot of the heterozygous model is basically symmetrical, which indicates that the difference is not significant, so it can be regarded as no publication bias. The results of the sensitivity analysis showed that no single study affected the overall combined ORs, indicating that the results of this meta-analysis were relatively stable.

A meta-analysis by Jing et al[17] in 2013 suggested that the A genetic polymorphism in the Rs1800872 allele is a risk factor for cervical cancer, especially for Asians, but the Rs1800872 polymorphism in the heterozygous model and the dominant inheritance model has nothing to do with the risk of cervical cancer. This is not the same as the results of our study. We did not find a significant correlation between the rs1800872 allele and the risk of cervical cancer. And our research found that the genetic polymorphism of AC in the heterozygous model and the genetic polymorphism of AC+AA in the dominant inheritance model are statistically significant in the overall comparison of the population. The reason for the difference in conclusion may be the difference in the included literature. In the study of Jing et al,[17] 5 articles from 2013 and before were included for integrated analysis, and our study included updated articles. The 2020 study by Duvlis et al[14] concluded that the AA variant of rs1800872 has a protective effect in the development of cervical cancer, which is consistent with our research results.

For sure, there were some limitations in the study. The included studies are still relatively limited, mainly in some countries in Asia, Europe, and America, and there is still some heterogeneity in each study, even after the analysis of ethnic subgroups, and the impact of gene linkage and gene-environment interaction on all populations has not been analyzed. In general, the Interleukin-10 polymorphism has a weak correlation with cervical cancer. AC and AC+AA genotypes can reduce the risk of cervical cancer.

Therefore, considering that this study has certain limitations, such as sensitivity, lack of consideration of the interaction between genes and genes, and genes and the environment, more in-depth research is needed on a larger scale.

5. Conclusion

Our conclusion is that the AC/AA+AC variant of Rs1800872 indicates a protective effect in the development of cervical cancer.

Author contributions

Conceptualization: Hongxiang Chen.
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