

## Original Article

# IFN- $\gamma$ +874 T/A polymorphisms contributes to cervical cancer susceptibility: a meta-analysis

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**Abstract:** Interferon gamma (IFN- $\gamma$ ) is a potent proinflammatory cytokine which plays an important role in the antiviral, antiproliferative, and antitumor activities. So our meta-analysis was conducted to evaluate the correlations between common genetic polymorphisms in the IFN- $\gamma$  gene and susceptibility to cervical cancer. The +874 polymorphism in IFN gene region reportedly affects cancer risk. In order to derive a more precise estimation of the association, eight clinical case-control studies met all the inclusion criteria and were included in this meta-analysis. A total of 2,375 cancer cases and 2,106 controls were involved in this meta-analysis. Overall, no significant association was detected in allelic model (A allele vs. T allele OR=0.97, 95% CI, 0.73~1.28), homozygote comparison (AA vs. TT OR=1.12, 95% CI, 0.68~1.85), heterozygote comparison (AT vs. TT OR=1.43, 95% CI, 0.97~1.61), dominant model (AA+AT vs. TT OR=1.19, 95% CI, 0.87~1.63), nor recessive model (AA vs. AT+TT OR=0.95, 95% CI, 0.64~1.40). Subgroup analysis based on ethnicity, genotyping method, and Hardy-Weinberg equilibrium status. Ethnicity suggested that genetic polymorphisms in the IFN- $\gamma$  gene were closely correlated with increased cervical cancer risk among Asians (allelic model: OR=1.11, 95% CI=0.61~2.02, P<0.001; recessive model: OR=0.98, 95% CI=0.36~2.96, P<0.001; homozygous model: OR=1.43, 95% CI=0.56~3.65, P=0.001; respectively), but not among Mixed (all P>0.05). In conclusion, the current meta-analysis supported that IFN- $\gamma$  genetic polymorphism may contribute to cervical cancer susceptibility, and further well-designed studies with large sample size are warranted to validate our conclusion.

**Keywords:** IFN- $\gamma$ , genetic polymorphism, susceptibility, cervical cancer, meta-analysis

## Introduction

Cervical cancer is the second most common malignancy in women worldwide [1], with approximately 80% of cases arising in developing countries. Innate immune deficiency, environmental aggravation, and genetic mutation have been considered as important pathogenesis factors.

The genetic polymorphisms in cytokine genes have been investigated widely, which could influence cancer predisposition and prognosis by altering the expression level [2, 3]. The gene that encodes IFN- $\gamma$  is located on chromosome 12q24 spanning approximately 5.4 kb and consists of four exons with three intervening regions [4]. The human IFN- $\gamma$  gene shows the presence of a variable-length CA repeat within the first intron of the gene ranging from 12 to

15 repeats [5]. IFN- $\gamma$  is a pleiotropic cytokine secreted by type-1 helper (Th1) T cells, cytotoxic T cells, and stimulated natural killer cells in response to antigenic stimulation and involved in activation of macrophages and endothelial cells [6]. It can produce various immune cells such as activated CD4+ T cells, cytotoxic CD8+ cells, and activated natural killer cells [7, 8]. On one hand, IFN- $\gamma$  can exert direct anti-proliferative and anti-metabolic effects on a wide variety of tumor cells [9-13]; on the other hand, IFN- $\gamma$  can inhibit angiogenesis in the tumor [14, 15]. Pravica [16] et al. noted a novel single nucleotide polymorphism (SNP), T to A, located at the +874 position from translation start site in the first intron of IFN- $\gamma$  gene, which coincides with a putative NF- $\kappa$ B binding site that could play a fundamental role in the induction of constitutively high IFN- $\gamma$  production. Therefore, a meta-analysis of the published studies was per-

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**Table 1.** Characteristics of eligible studies included in the meta-analysis

Author	Year	Country	Ethnicity	Cancer types	Genotyping methods	Case			Control			HWE
						TT	AT	AA	TT	AT	AA	
do Carmo	2012	Brazil	Mixed	Cervical cancer	PCR-SSP	2	3	4	13	46	17	Yes
Wang	2011	China	Asian	Cervical cancer	PCR-SSP	21	84	81	38	96	66	Yes
Ivansson	2010	Sweden	Caucasian	Cervical cancer	TaqMan	286	650	354	157	371	274	Yes
Gangwar	2009	India	Asian	Cervical cancer	PCR-ARMS	23	91	86	45	115	70	Yes
Kordi	2008	India	Asian	Cervical cancer	PCR-ARMS	24	125	51	25	75	100	Yes
Govan 1	2003	South Africa	African	Cervical cancer	PCR-ARMS	5	30	61	7	31	102	No
Govan 2	2003	South Africa	Mixed	Cervical cancer	PCR-ARMS	14	66	85	26	81	158	No
Guzman	2008	Brazil	Mixed	Cervical cancer	PCR-SSP	130	99	126	67	67	67	Yes

**Table 2.** Detailed association of IFNG +874 T/A polymorphism with cancer risk in each individual study

Author	Ethnicity	Cancer types	A vs. T allele	AA vs. TT	AT vs. TT	AA+AT vs. TT	AA vs. AT+TT
			OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
do Carmo	Mixed	Cervical cancer	1.41 (0.52, 3.84)	1.53 (0.24, 9.67)	0.42 (0.06, 2.81)	0.72 (0.13, 3.88)	2.78 (0.67, 11.5)
Wang	Asian	Cervical cancer	1.47 (1.10, 1.97) <sup>b</sup>	2.22 (1.19, 4.15) <sup>b</sup>	1.58 (0.86, 2.91)	1.84 (1.04, 3.28) <sup>b</sup>	1.57 (1.04, 2.37) <sup>b</sup>
Ivansson	Caucasian	Cervical cancer	0.83 (0.73, 0.94) <sup>a</sup>	0.71 (0.55, 0.91) <sup>a</sup>	0.96 (0.76, 1.21)	0.85 (0.69, 1.06)	0.73 (0.60, 0.88) <sup>a</sup>
Gangwar	Asian	Cervical cancer	1.54 (1.17, 2.04) <sup>b</sup>	2.40 (1.33, 4.35) <sup>b</sup>	1.55 (0.87, 2.75)	0.81 (0.46, 1.44)	1.72 (1.16, 2.56) <sup>b</sup>
Govan 1	African	Cervical cancer	0.73 (0.45, 1.17)	0.84 (0.26, 2.75)	1.36 (0.39, 4.74)	0.96 (0.30, 3.11)	0.65 (0.37, 1.14)
Govan 2	Mixed	Cervical cancer	0.84 (0.62, 1.15)	1.00 (0.50, 2.01)	1.51 (0.73, 3.13)	1.17 (0.59, 2.32)	0.72 (0.49, 1.07)
Kordi	Asian	Cervical cancer	0.60 (0.45, 0.80)	0.53 (0.28, 1.02)	1.74 (0.93, 3.26)	1.05 (0.58, 1.91)	0.34 (0.22, 0.52)
Guzman	Mixed	Cervical cancer	- <sup>c</sup>	- <sup>c</sup>	- <sup>c</sup>	- <sup>c</sup>	1.43 (0.97, 2.13)

<sup>a</sup>Significantly associated with decreased cancer risk. <sup>b</sup>Significantly associated with increased cancer risk. <sup>c</sup>Cannot be calculated.

formed, with the aim to clarify the relationship between the IFN- $\gamma$  polymorphism and cervical cancer risk.

## Materials and methods

### Identification of eligible studies

PubMed, Embase and Web of Science database searches were performed in our meta-analysis. In order to search as many related studies as possible, we used different combinations of the following MeSH terms and keywords: 'Interferon' or 'IFN', 'polymorphism' or 'SNP', 'cervical cancer' or 'cervical tumor' (the last search was updated 1 August 2014). The search was limited to English language papers. All reference lists of reviews and retrieved articles were manually screened for further potential studies.

### Inclusion and exclusion criteria

The following criteria were used to decision inclusion eligibility: (1) must be a study focused on the correlation of IFN- $\gamma$  genetic polymorphisms with cervical cancer susceptibility; (2)

clinical case-control studies; and (3) providing sufficient data to calculate the odds ratio (OR) and its corresponding 95% confidence interval (CI). Furthermore, studies that did not meet our inclusion criteria were excluded.

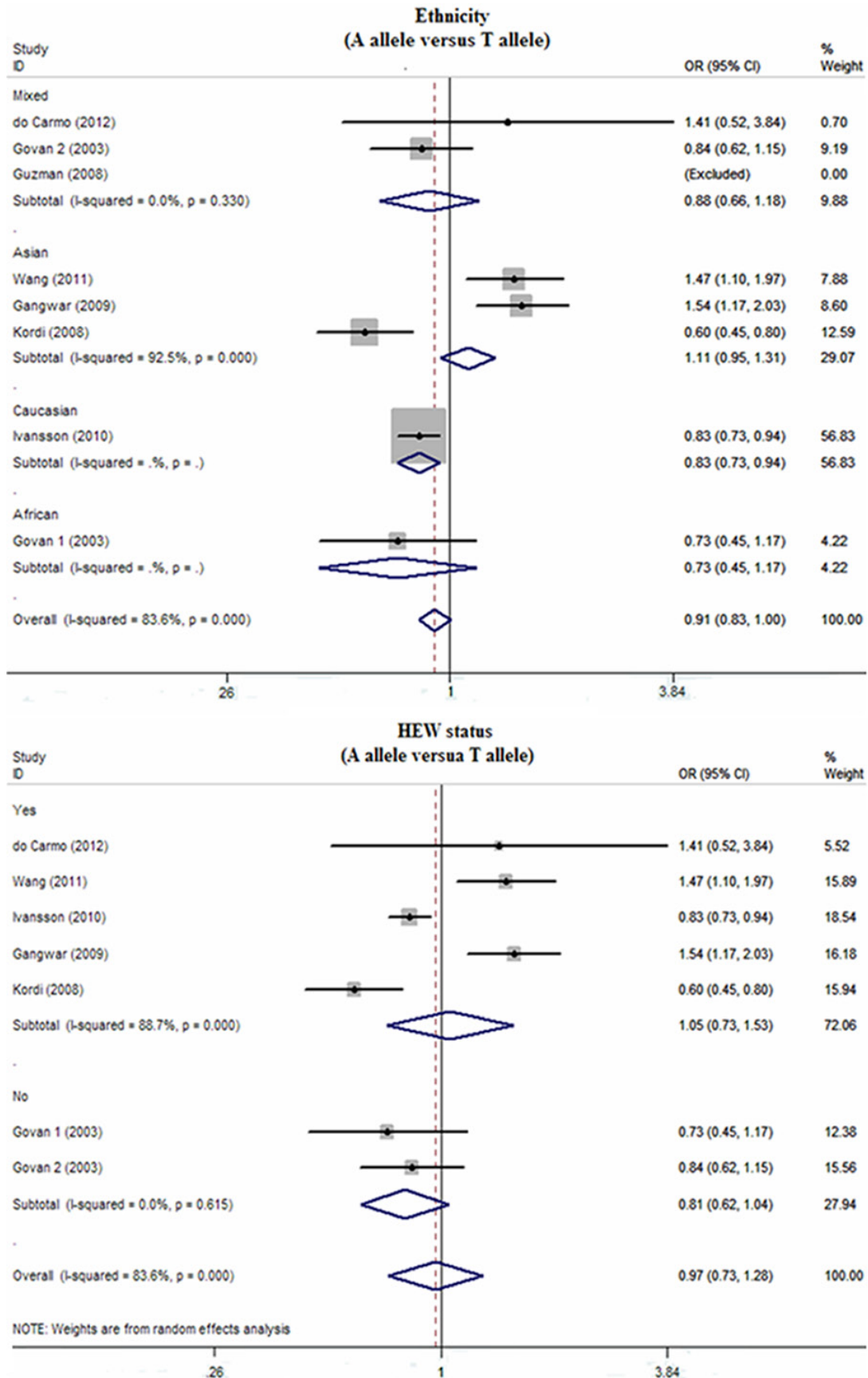
### Data extraction

Data of eligible studies were extracted by two authors independently and in duplicate according to the predesigned data-collection form. For each article, extracted information contained the following: the first author's name, publication year, country of origin, the patients' ethnicities, genotyping method, numbers of cases and controls, and evidence of HWE. The different ethnic descents were categorized as African, Asian, Caucasian and Mixed.

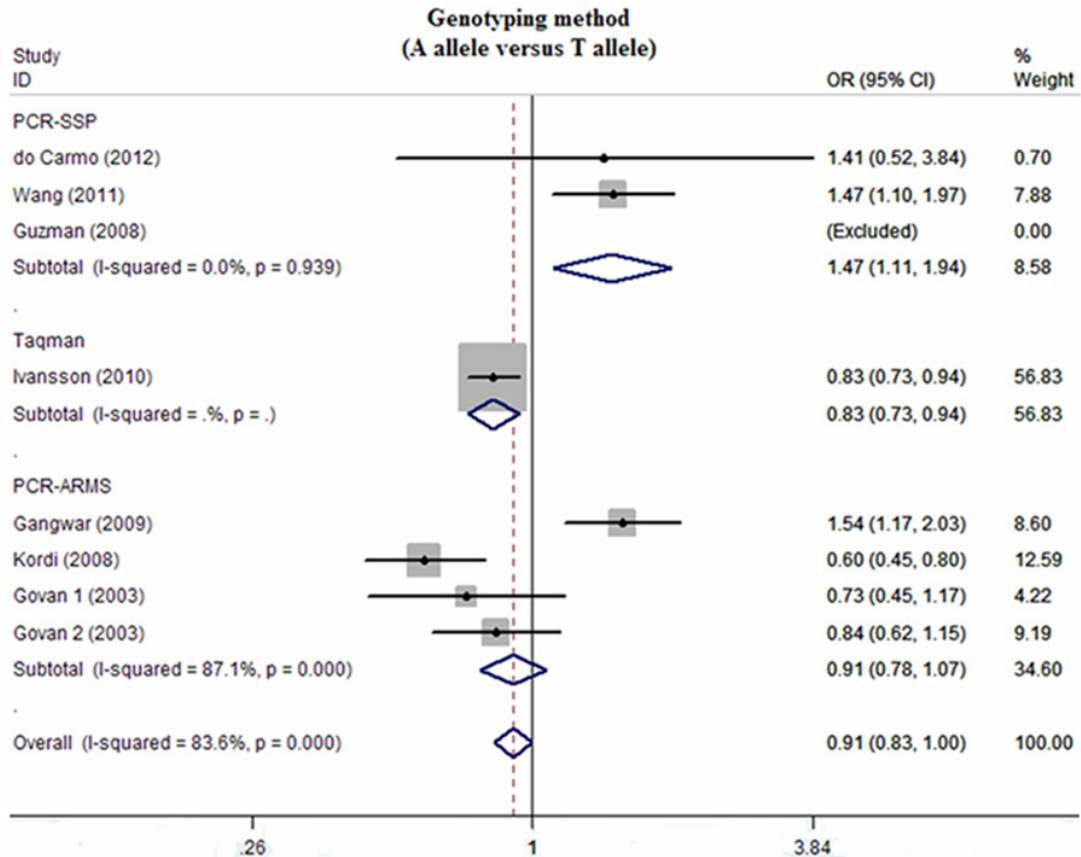
### Statistic analysis

Meta-analysis was performed using the STATA statistical software (Version 12.0, Stata Corporation, College Station, TX, USA). The strength of the association between IFNG +874 T/A polymorphism and the risk of cancer was calculated by Odds ratios (OR) with 95% confi-

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**Figure 1.** Subgroup analyses by ethnicity, genotyping method, and HEW status of relationships between IFN- $\gamma$  genetic polymorphisms and susceptibility to cervical cancer.

dence interval (95% CI) in the following five genetic models: allelic model (A allele vs. T allele), homozygote comparison (AA vs. TT), heterozygote comparison (AT vs. TT), dominant model (AA+AT vs. TT), and recessive model (AA vs. AT+TT). The statistical significance of the pooled OR was assessed with the Z test and a  $P$  value of  $<0.05$  was considered significant. Chi-square-based  $Q$  test was conducted to measure the heterogeneity between eligible studies, and the existence of heterogeneity was considered significant if  $P < 0.10$  [17]. When the between-study heterogeneity was absent, a fixed-effect model (the Mantel-Haenszel method) was used to pool the data from different studies [18]; otherwise, a random-effect model (the DerSimonian and Laird method) was applied [19]. To explore the source of heterogeneity among variables such as ethnicity, and HWE status, both subgroup analyses and logistic met regression analyses were performed [20]. Funnel plots and Egger's linear regression

test were applied to investigate publication bias [21].

## Results

### Study selection and description

For cervical cancer susceptibility related to the IFN- $\gamma$  +874 T/A polymorphism, 8 studies with 2,375 cancer cases and 2,106 controls were included in the current meta-analysis. We summarized the study characteristics and methodological quality in **Table 1**. Among these 8 eligible studies, 3 of them were Asian descendants, 1 Caucasian, 1 African, and the remaining 3 studies were conducted in mixed populations.

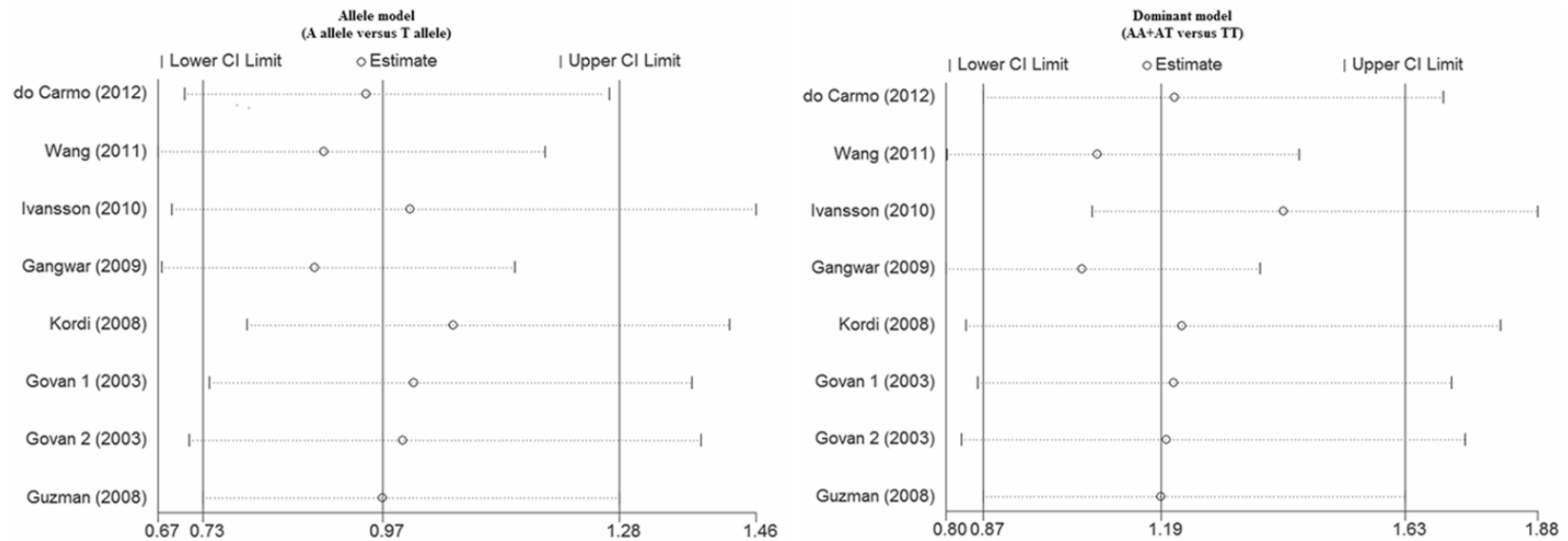
### Quantitative data synthesis

A total of 8 studies were identified and analyzed, a summary of the meta-analysis findings on the correlations between IFN- $\gamma$  polymorphisms and the risk of cervical cancer in each

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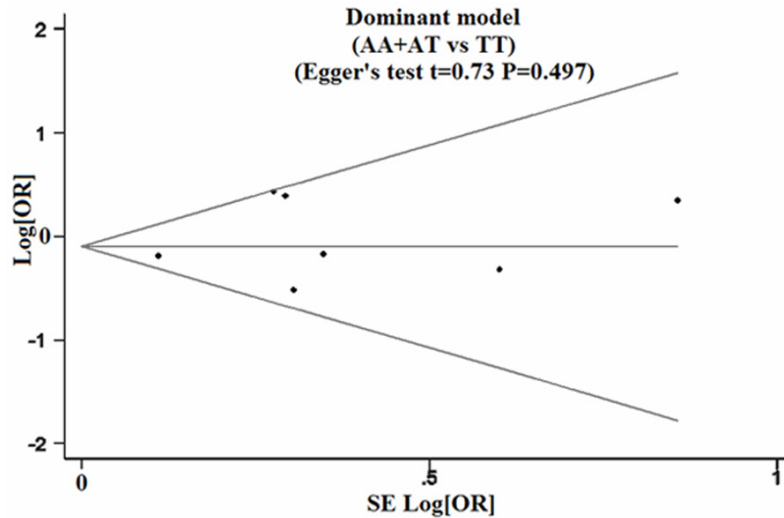
**Table 3.** Stratification analysis of genetic susceptibility of IFNG +874 T/A polymorphism to cancer risk

Category	A allele vs. T allele			AA vs. TT			AT vs. TT			AA+AT vs. TT			AA vs. AT+TT		
	N	OR (95% CI)	P	N	OR (95% CI)	P	N	OR (95% CI)	P	N	OR (95% CI)	P	N	OR (95% CI)	P
Total	7	0.97 (0.73, 1.28)	<0.001	7	1.12 (0.68, 1.85)	<0.001	7	1.25 (0.97, 1.61)	0.263	7	1.19 (0.87, 1.63)	0.068	8	0.95 (0.64, 1.40)	<0.001
Ethnicity															
Asian	3	1.11 (0.61, 2.02)	<0.001	3	1.43 (0.56, 3.65)	0.001	3	1.61 (1.14, 2.29)	0.963	3	1.56 (1.08, 2.24)	0.292	3	0.98 (0.35, 2.69)	<0.001
Caucasian	1	0.83 (0.73, 0.94)	-	1	0.71 (0.55, 0.91)	-	1	0.96 (0.76, 1.21)	-	1	0.85 (0.69, 1.06)	-	1	0.73 (0.60, 0.88)	-
African	1	0.73 (0.45, 1.17)	-	1	0.84 (0.26, 2.75)	-	1	1.36 (0.38, 4.74)	-	1	0.96 (0.30, 3.11)	-	1	0.65 (0.37, 1.13) <sup>c</sup>	-
Mixed	2	0.88 (0.66, 1.18)	0.330	2	1.02 (0.64, 1.62)	0.672	2	1.09 (0.37, 3.25)	0.218	2	1.20 (0.58, 2.06)	0.600	3	1.17 (0.62, 2.22)	0.021
Genotyping method															
PCR-SSP	2	1.47 (1.11, 1.94)	0.939	2	2.14 (1.18, 3.86)	0.707	2	1.13 (0.36, 3.49)	0.194	2	1.63 (0.88, 3.03)	0.301	3	1.53 (1.16, 2.03)	0.672
TaqMan	1	0.83 (0.73, 0.94)	-	1	0.71 (0.55, 0.91)	-	1	0.96 (0.76, 1.21)	-	1	0.85 (0.69, 1.06)	-	1	0.73 (0.60, 0.88)	-
PCR-ARMS	4	0.87 (0.56, 1.37)	<0.001	4	1.05 (0.50, 2.17)	0.008	4	1.58 (1.11, 2.24)	0.983	4	1.19 (0.87, 1.85)	0.464	4	0.73 (0.36, 1.46)	<0.001
HWE status															
Yes	6	1.05 (0.73, 1.53)	<0.001	6	1.20 (0.61, 2.34)	<0.001	6	1.26 (0.91, 1.76)	0.136	6	1.23 (0.81, 1.87)	0.021	6	1.07 (0.64, 1.79)	<0.001
No	2	0.81 (0.62, 1.04)	0.615	2	1.11 (0.68, 1.85)	0.802	2	1.47 (0.78, 2.76)	0.881	2	1.19 (0.87, 1.63)	0.77	10	0.70 (0.51, 0.96)	0.768



**Figure 2.** Sensitivity analysis of the summary odds ratio coefficients on the relationships between IFN- $\gamma$  genetic polymorphisms and susceptibility to cervical cancer.





**Figure 3.** Funnel plot of publication biases on the relationships between IFN- $\gamma$  genetic polymorphisms and susceptibility to cervical cancer.

individual study was presented in **Table 2**, and the summary results were summarized in **Table 3**. In our meta-analysis the random-effects model was performed. The results declared that IFN- $\gamma$  genetic polymorphisms might be significantly associated with an increased risk of cervical cancer (allele model: OR=0.97, 95% CI=0.73~1.28,  $P<0.001$ ; recessive model: OR=0.95, 95% CI=0.64~1.40,  $P<0.001$ ; homozygous model: OR=1.12, 95% CI=0.68~1.85,  $P<0.001$ ; respectively).

A subgroup analysis was carried out to evaluate the impact of the IFN- $\gamma$  polymorphism on the risk of cervical cancer. Ethnicity stratified analysis indicated that the genetic polymorphisms in the IFN- $\gamma$  gene were closely linked to the pathogenesis of cervical cancer among Asian populations (allele model: OR=1.11, 95% CI=0.61~2.02,  $P<0.001$ ; dominant model: OR=1.56, 95% CI=1.08~2.24,  $P=0.292$ ; heterozygous model: OR=1.61, 95% CI=1.14~2.29,  $P=0.963$ ; homozygous model: OR=1.43, 95% CI=0.56~3.65,  $P=0.001$ ; respectively), but not among Mixed (all  $P>0.05$ ) (**Figure 1**). We also performed subgroup analyses based on genotyping method and HWE status. Their results indicate that IFN- $\gamma$  genetic polymorphisms might be implicated in the risk of cervical cancer in the majority of subgroups, except the PCR-SSP and no HWE status subgroups.

Sensitivity analysis suggested that no single study could influence the pooled OR (**Figure 2**).

Funnel plots demonstrated evidence of obvious asymmetry (**Figure 3**). Egger's test displayed strong statistical evidence of publication bias.

### Discussion

Cervical cancer is one of the most dangerous causes of health deficiency and death worldwide. Some SNPs of IFN- $\gamma$  have been reported. The cytokine IFN- $\gamma$ , an acid-labile protein plays a key role in cervical cancer [8, 22-29] and other cancers [30, 31]. Among different polymorphisms of IFN- $\gamma$ , the +874 T/A polymorphism is one of the most widely studied. In

our meta-analysis, we evaluated the hypothesis that IFN- $\gamma$  genetic polymorphisms contribute to susceptibility to cervical cancer. We found that genetic polymorphisms in the IFN- $\gamma$  gene were significantly correlated with an increased risk of cervical cancer.

This meta-analysis, based on 8 studies, explored the association between IFN- $\gamma$  +874 T/A and cervical cancer risk, involving about 2,375 cancer cases and 2,106 controls.

To further investigate the relationship between IFN- $\gamma$  genetic variations and the pathogenesis of cervical cancer, we conducted subgroup analyses based on ethnicity, genotyping method, and HWE status. A stratified analysis by ethnicity was conducted, the findings revealed that there were significant associations between IFN- $\gamma$  genetic polymorphisms and cervical cancer risk among Asians, but not among Mixed, indicating that ethnic differences may be a potential factor affecting individual's susceptibility to cervical cancer. Subsequently, we conducted subgroup analysis based on genotyping method revealed that IFN- $\gamma$  genetic polymorphisms were related to an increased risk of cervical cancer in the PCR-ARMS array subgroups, while no associations were detected in the PCR-SSP subgroups. In the further stratification analysis by HWE status, our results illustrated a positive correlation between IFN- $\gamma$  genetic polymorphisms and susceptibility to cervical cancer in the HWE status subgroup, but not in the any HWE status size subgroup.

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In summary, our findings were consistent with previous studies that IFN- $\gamma$  genetic polymorphisms may be potential risk factors in the development of cervical cancer, suggesting that these polymorphisms may be of great value for the early diagnosis of cervical cancer.

The current meta-analysis has several limitations that should be pointed out. The first limitation was that the small number of studies was short of sufficient statistical power to assess the correlations between IFN- $\gamma$  genetic polymorphisms and the pathogenesis of cervical cancer. The second limitation in our meta-analysis failed to obtain original data from the included articles, which may have limited further evaluation of the potential roles of IFN- $\gamma$  genetic polymorphisms in the development and progression of cervical cancer.

Although our study has several limitations, this is the first meta-analysis focusing on the relationships between IFN- $\gamma$  genetic polymorphisms and the risk of cervical cancer. Furthermore, we performed a highly sensitive literature search strategy of electronic databases, a manual search of reference lists from relevant studies, and the selection process of eligible articles was based on strict inclusion and exclusion criteria. Importantly, rigorous statistical analysis provided a basis for pooling of information from individual studies.

In conclusion, a strong association was observed between IFN- $\gamma$  genetic polymorphisms and cervical cancer, and therefore IFN- $\gamma$  genetic polymorphisms may be valuable as a biomarker. Considering that the quality and quantity of the reviewed articles were limited, larger and well-designed studies should be employed in the future for further confirmation of the association between IFN- $\gamma$  genetic polymorphisms and cervical cancer.

### Disclosure of conflict of interest

None.

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