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THE RELATIONSHIP OF TNFα -308 G/A POLYMORPHISM WITH THE INCIDENCE OF CERVICAL CANCER IN ASIAN WOMEN: A META ANALYSIS OBSERVATIONAL STUDY

Hubungan Polimorfisme TNFα -308G/A dengan Kejadian Kanker Serviks pada Wanita Asia: Sebuah Studi Meta Analisis Observasional

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ABSTRACT

Cervical cancer is a malignancy with high mortality rates in women, and its incidence continues to rise. The main etiological factor for cervical cancer is infection with Human Papillomavirus (HPV), which disrupts the regulation of apoptosis in cells. Several studies have shown a correlation between TNFα polymorphisms, including the -308 position (TNFα -308 G/A), and the incidence of cervical cancer.This gene have a role in proliferation of cancer cells. This study investigates the impact of TNFα-308 polymorphism on the risk of cervical cancer in Asian female populations. A meta-analysis of five sources was conducted to determine potential associations. Findings reveal that neither allele A (OR 95%CI = 1.20 [0.70-2.03], p = 0.51) nor genotype AA (OR 95%CI = 0.85 [0.37-1.91], p = 0.69) were significantly linked with an elevated risk of cervical cancer in Asian women. The same result was seen for the G allele (OR 95%CI = 0.84 [0.49-1.42], p = 0.51) and GG genotype (OR 95%CI = 0.80 [0.44-1.48], p = 0.48). The study results indicate that the TNFα-308 polymorphism is not associated with cervical cancer in Asian women. Further research is needed to investigate the role of other gene polymorphisms in cervical cancer susceptibility in Asian women.

***Keywords**: Asian women, Allele, Cervical cancer, Genotype, TNFα-308 polymorphism.*

ABSTRAK

Kanker serviks adalah salah satu kanker pada wanita dengan angka kematian yang tinggi. Jumlah penderita kanker ini juga meningkat. Penyebab utama kanker serviks adalah infeksi Human Papillomavirus (HPV) yang mengganggu pengaturan proses apotosis dalam sel. Beberapa studi menunjukkan adanya peranan polimorfisme TNFα (salah satunya adalah polimorfisme -308G/A) pada kejadian kanker serviks. Gen ini diketahui berperan dalam proliferasi sel kanker.Penelitian ini bertujuan untuk melihat peran polimorfisme TNFα -308 terhadap kejadian kanker serviks pada wanita Asia. Studi meta analisis ini dilakukan terhadap 5 referensi yang membahas tentang hubungan polimorfisme TNFα-308 dengan kejadian kanker serviks pada populasi Asia.Hasil analisis menunjukkan bahwa alel A (OR 95%CI = 1.20 [0.70-2.03], p = 0.51) dan genotipe AA genotype (OR 95%CI = 0.85 [0.37-1.91], p = 0.69) tidak berhubungan dengan kejadian kanker serviks pada wanita Asia. Hal yang sama juga terlihat pada alel G (OR 95%CI = 0.84 [0.49-1.42], p = 0.51) dan genotipe GG (OR 95%CI = 0.80 [0.44-1.48], p = 0.48).

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Hasil riset ini memperlihatkan bahwa polimorfisme TNFα-308 terlihat tidak berperan dalam kejadian kanker serviks pada wanita Asia. Perlu dilakukan penelitian lebih lanjut tentang peranan polimorfisme gen-gen lain yang berperan dalam insiden kanker serviks pada populasi wanita Asia.

Kata kunci: Alel, Genotipe, Kanker serviks, Polimorfisme TNFα-308, Wanita Asia.

INTRODUCTION

Cervical cancer is a disease characterized by the abnormal division of cervical epithelial cells in women. It is a global problem due to its high prevalence and mortality rates. In 2020, cervical cancer affected 604,127 individuals, comprising 6.5% of all cancer cases, and resulted in 341,831 deaths, accounting for approximately 7.7% of cancer cases, therefore ranking as the 4th most prevalent form of cancer and leading to patient mortality. (GLOBOCAN 2020).

In Indonesia, the incidence of cervical cancer in 2021 was 36,633 cases (17.2% of all female cancer cases), making it the second most common cancer. In addition, the mortality rate from cervical cancer was high, resulting in 21,003 deaths (19.1% of all cancer deaths) (Kementerian Kesehatan 2021). Cervical cancer has a huge socio-economic impact, which is why the Indonesian government is committed to eradicating it.

Preventive measures against cervical cancer are available. These include vaccination and screening. Vaccination against cervical cancer is recommended on a large scale. It helps prevent infection with the Human Papillomavirus (HPV), which is the primary cause of cervical cancer. Screening, on the other hand, aids in the early detection of cancer, improving the effectiveness of the treatment process and enhancing patient recovery. However, coverage remains inadequate, particularly in developing and lower-income countries, resulting in high mortality and morbidity rates of cervical cancer in this region. According to Globocan 2020 data, Asia is known to be the region with the highest cervical cancer mortality and morbidity rates (58.5% and 58.2%, respectively) due to low vaccination and screening coverage (Salehaniya et al. 2021; Zhao et al. 2021; Momenimovahed et al. 2023; Singh et al. 2023).

Cervical cancer is caused by infection with the Human Papillomavirus (HPV), with HPV 16 and 18 being the most common HPV subtypes found in cervical cancer patients (~70%). This infection can cause changes in the cervical epithelial cells that can lead to cancer if left untreated. Studies have shown that HPV proteins play an important role in these changes. Initially, these cell changes can be overcome by the individual's immune response. However, if not treated properly, these cell changes will lead to cancer. These cell changes will occur gradually from pre-cancerous conditions to cancer. Cervical Intraepithelial Neoplasia (CIN) is a term used to describe pre-cancerous conditions. CIN can be categorized into several groups based on their severity.

Approximately 10% of women with HPV infection will develop chronic cervical cancer. There is concern that not all women with HPV infection will progress to cancer. One of the risk factors for this cancer is genetic factors, such as gene mutations that affect the immune response. This type of mutation is thought to be one of the causes of cervical cancer, such as mutations in the TNFα gene.

Tumour necrosis factor-alpha (TNFα) is a cytokine that plays a role in inflammation, protection against infection, cell apoptosis and metastasis. In some cancers, TNFα expression appears to be increased (Li et al. 2018a). This cytokine is encoded by the TNFα gene on chromosome 6p21 (Traore et al. 2020). Several studies have shown a relationship between polymorphisms of the TNFα gene at position -308 and the incidence of cervical cancer (Li et al. 2018a; Li et al. 2018b; Du et al. 2019; Thakre et al. 2019). However, the mechanism by which the TNFα-308 polymorphism causes cervical cancer remains unclear. Large-scale studies with various populations are needed to unravel this mystery. Under-

standing the role of TNFα gene polymorphisms in cervical cancer incidence may help to control the occurrence of this disease. In addition, this knowledge can be used to study the prognosis of cervical cancer, which may help guide patient treatment.

This meta-analysis study will investigate the association between TNFα -308G/A polymorphisms and cervical cancer susceptibility in Asian women, a region with high cervical cancer incidence and mortality. Understanding this relationship can improve our knowledge of how women are susceptible to cervical cancer, leading to better guidance for prevention, treatment, and prognosis.

MATERIAL AND METHODS

Location and Time

This study was conducted in June-December 2022 at Universitas Esa Unggul, using several references that match with the inclusion criteria

Study Design

We conducted this study by collecting data from Pubmed, Google Scholar, Web of Science and Cochrane. These data are used to calculate the odds ratio (OR) and the 95% confidence interval using the random or fixed model. We used a Preferred Reporting Item for Systematic Review and Meta-Analysis (PRISMA) checklist to help us report the results of the analyses.

Eligibility Criteria

We used several criteria to include and exclude the reference population used in this study. The inclusion criteria used were (1) the reference topic examined the association between the TNFα -308G/A polymorphism and the incidence of cervical cancer; (2) the availability of data allowed the calculation of the OR value with a 95% CI; and (3) a case-control study. The exclusion criteria were (1) a review study or meta-analysis; (2) using subjects from non-Asian women; and (3) having a deviation from the Hardy-Weinberg equilibrium value (as indicated by the value $X^2 > 3.84$).

Sources and Search Strategy

We searched for studies that investigated the association between the TNFα -308G>A polymorphism and the incidence of cervical cancer. Cervical cancer and (TNF polymorphism or TNFα-308 polymorphism) were used as search terms to identify publications that met the inclusion criteria. Publication sources were Pubmed, Cochrane, Google Scholar, and Web of Science collected from May to July 2022. Only English language publications were used for ease of analysis.

The selected studies were case-control studies conducted on Asian women diagnosed with cervical epithelial abnormalities and cervical cancer. PCR or PCR-RFLP was used to identify Single Nucleotide Polymorphism (SNP) in the TNFα -308 promoter.

The search started with 1669 studies. We then obtained 44 papers discussing TNFα polymorphisms and cervical cancer incidence. We rescreened these papers and obtained 28 papers reporting the -308 TNFα polymorphism as associated with cervical cancer. A further selection was made to obtain studies using samples from Asian women, resulting in 13 papers. The Asian population was selected due to the high incidence and mortality rate of cervical cancer in this region, as well as the socio-cultural variations that affect the lives of its population. After this, several papers were not analyzed further because they had deviations from the Hardy-Weinberg equilibrium, so the final number of papers analyzed was 5 papers. Deviations from the equilibrium may indicate the presence of evolutionary forces, such as mutation, selection, migration, or non-random mating. The paper selection process is shown in Figure 1.

Authors (HS and MN) extracted data to obtain the following: (a) author's name, (b) year of publication, (c) genotype frequency for cases and controls, (d) genotyping method, (e) country of origin and (f) ethnicity. Data extraction is necessary for the identification of the baseline characteristics of the selected publications.

Quality Assessment of Methodology

The Newcastle-Ottawa scale was used by the authors (HS and MN) to rate the

quality of publications. The factors used in this scale are study selection (4 points), comparison between groups (3 points), and determination of exposure (3 points). Scores were given from 0 to 9, defined as good (score ≥ 7), fair (score 5-6) and poor (score ≤ 4). If there were discrepancies in the scores for a publication, the authors discussed how to reach a consensus. Based on the five reference sources used, the NOS scale obtained was approximately 7.

Outcome Measure

Outcome analysis was evaluated on all allele models and genotypes to assess the relationship between the TNFα -308G/A polymorphism and cervical cancer. The models were G vs A; GG vs AA+RG; AA vs GG+AG and AG vs GG+AA. We did not perform subgroup analysis for this population.

Statistical Analysis

The Z-test was used to calculate the p value of the correlation between cervical cancer incidence and the TNFα -308G/A polymorphism. If the p-value is <0.05, the correlation is significant. The heterogeneity of the data is measured by Q test and I^2 value. The fixed effect model was used when the p-value of heterogeneity was ≥ 0.10, and the random effect model was used when it was < 0.10. Funnel plots were used to assess the possibility of publication bias. The software used was Review Manager ver. 5.4 (Revman Cochrane, London, UK) for statistical analysis, which was performed by both authors (HS and MN). The software can be used to perform a meta-analysis of the provided data and present the results in a graphical format. If there was a discrepancy in the statistical results, this was discussed with the third reviewer in order to reach a consensus.

All studies included in this meta-analysis research received ethical approval from the ethics committees in their country.

RESULT AND DISCUSSION

Paper Selection

Articles were retrieved from Pubmed, Cochrane, Web of Science, and Google Scholar. We started the search with 1,669 articles. Of these, there were 44 articles that discussed the association between TNFα polymorphisms and cervical cancer. From these articles, we made a preliminary selection and excluded 17 articles because they were review articles, meta-analytic studies, or did not address the -308G/A polymorphism. The selection of articles was then carried out again based on the sample sources used. Fifteen articles were excluded because the sample source was not from Asian women. Further selections were made and 7 articles had to be excluded due to deviations from Hardy-Weinberg equilibrium. Therefore, the final number of articles in this study is five (Figure 1).

There are 5 papers that discuss the TNFα -308G/A polymorphism associated with the incidence of cervical cancer in Asian women. There were a total of 1,673 control samples and 1,592 patient samples. We found that the A allele (OR 95%CI = 1.20 [0.70-2.03], p = 0.51) and the AA genotype (OR 95%CI = 0.85 [0.37-1.91], p = 0.69) were not associated with the incidence of cervical cancer in Asian women. The A allele and AA genotype have been shown to increase T lymphocyte cell proliferation and TNFa cytokine production, potentially contributing to the body's defense against cancer growth (Traore et al. 2020; Yang et al. 2022). The same result was observed for the G allele (OR 95%CI = 0.84 [0.49-1.42], p = 0.51) and the GG genotype (OR 95%CI = 0.80 [0.44-1.48], p = 0.48). The results of the correlation between the TNFα -308G/A polymorphism and the incidence of cervical cancer in Asian women are shown in Table 2. The Odd Ratio value indicates the potential relationship between two variables. In this study, there was no significant association between TNFα polymorphism and the incidence of cervical cancer.

Source of Heterogeneity

The variability in studies was evaluated using Q- Test and I^2. Q is distributed as a chi-square statistic with k (numer of studies) minus 1 degrees of freedom. The P value obtained from the Chi-squared test reflects the probability of the null hypothesis, which posits no heterogeneity across studies. If the P value falls below 0.10, we reject the null hypothesis, signifying the existence

of heterogeneity among the studies.The inconsistency index (I^2-statistic) gives an idea of the heterogeneity of the studies. The I^2 index can be interpreted as the percentage of the total variability in a set of effect sizes due to true heterogeneity, that is, to between-studies variability.The I^2 statistic, ranging from 0 to 100%, signifies the extent of heterogeneity, with higher values indicating greater heterogeneity. An I^2 below 40% may imply insignificant heterogeneity, whereas an I2 exceeding 75% may suggest substantial heterogeneity.

In the samples used in this study, heterogeneity was found in the A allele and the AA, AG and GG genotypes. Therefore, the correlation between the polymorphism and cervical cancer incidence was evaluated using a random effect model. The correlation of the G allele was evaluated with the fixed effect model. The heterogeneous data can be seen in Table 1.

Table 1. Baseline characteristic of studies concerning TNFα polymorphism as a risk factor for cervical cancer

Author and Year	Case				Control				X^2 HWE	df	p
	AA	AG	GG	N	AA	AG	GG	N			
Chinchai et al, 2015	2	11	108	121	2	15	113	130	2.86		
Li et al 2018a	4	24	114	142	3	22	125	150	2.67		
Li et al 2018b	0	135	317	452	0	70	424	494	2.87	1	0.05
Yang et al 2022	4	101	875	980	5	167	1001	1173	0.49		
Zuo et al 2011	0	81	158	239	2	25	83	110	0.01		

AA = genotype AA; AG = genotype AG; GG = genotype GG; N = total number of samples; X^2 HWE = Chi-square of Hardy-Weinberg Equilibrium

Table 2. Summary of the correlation between TNFα -308 polymorphism and cervical cancer

Allele and Genotype	NS	Model*	OR	95% CI	pH	p
A vs G	5	Random	1.2	[0.70 -2.03]	< 0.00001	0.51
G vs A	5	Random	0.84	[0.49 - 1.42]	< 0.00001	0.51
AA vs AG + GG	4	Fixed	0.85	[0.37 - 1.91]	0.46	0.69
AG vs AA + GG	5	Random	0.04	[-0.05 - 0.14]	< 0.00001	0.36
GG vs AA + AG	5	Random	0.8	[0.44 - 1.48]	< 0.00001	0.48

NS = number of study; OR = Odd Ratio; 95% CI = 95% Confidence Interval; pH = p-value of heterogeneity; p = p-value

* statistical analysis of variance of samples

Potential Publication Bias

To assess the possibility of publication bias, we used funnel plot. We found a possible publication bias in the AA genotype. However, no publication bias was found for the A allele or the AG and GG genotypes.

Discussion

TNFα is a cytokine that stimulates inflammation and plays a crucial role in the immune response against infections. Additionally, TNFα is involved in the growth of cancer cells through angiogenesis (Duarte et al. 2005; Akkiz et al. 2009; Yang et al. 2022). Studies have found higher TNFα production in patients with cervical cancer compared to healthy individuals.

Tumor Necrosis Factor-α (TNFα) is a pro-inflammatory cytokine that plays a role in the innate immune response to eliminate pathogens from the body. Additionally, TNFα is involved in cancer cell proliferation through anti-apoptotic mechanisms and induction of Reactive Oxygen Species (ROS) and nitric oxide. This can cause DNA damage in cells, leading to tumorigenesis (Amin et al. 2020; Duvlis et al. 2020). In a study conducted in Africa, it was observed that pro-inflammatory genes play a role in the occurrence of cervical cancer (63%) (Kuguyo et al. 2018). Polymorphism in the TNFα -308 G/A promoter is responsible for the change in cytokine production. The A allele in this gene increases the transcription rate, leading to an increase in TNFα production (Duvlis et al. 2020). Therefore, there is a hypothesis that the G/A polymorphism in

the TNFα -308 promoter can result in the formation of cancer cells.

A study by Li et al. 2018a found that A allele frequency plays a role in the degree of cancer malignancy. However, it is not directly related to an individual's susceptibility to cervical cancer. This study has limitations due to subject bias resulting from varying socio-economic conditions, which may affect the analysis of the role of TNFα polymorphisms in cervical cancer. Additionally, the researchers did not mention the HPV subtype that infected the study subjects, which may play a role in disease severity (Song et al. 2013).

Li et al. 2018b, in their study, indeed showed that the frequency of the A allele was higher in patients with squamous cell carcinoma of Han ethnicity. This study did not include patients with adenocarcinoma and CIN. Additionally, the authors hypothesize that mutations in the TNFα promoter may lead to alterations in TNFα production. However, TNFα levels were not measured in either group of subjects. However, this study can show the possible role of TNF α polymorphisms in individual susceptibility to cervical cancer.

A study by Yang et al. 2022 shows that the A allele is a protective factor against the incidence of cervical cancer. It should also be noted that the AA genotype may increase T cell proliferation, thereby activating these cells and reducing an individual's susceptibility to cancer. This study is limited by the lack of analysis on the socioeconomic similarities among the subjects. In addition, the role of TNFα polymorphisms in the progression of cervical cancer cannot be illustrated due to the small number of subjects with cervical cancer grades III and IV. However, this paper presents an important analysis of the inheritance model for each SNP on the incidence of cervical cancer and the course of the disease.

A study by Zuo et al. 2011 showed that the frequency of AG in cervical cancer patients was higher than in controls. However, this research has not been able to prove a relationship between the TNFα -308 polymorphism and the level of the TNF α cytokine in patients or controls. The sample size for each group is relatively small, which may affect the validity of the presented data. Small sample sizes can impact the statistical power of a study. Additionally, the various ethnicities of the subjects used should be considered in future research. Apart from that, this study also used patients who had varying degrees of disease, from CIN to cervical cancer.

A Study from Thailand (Chinchai et al. 2016) is also limited by the small number of subjects and the lack of information on their characteristics, such as age and socioeconomic status.

The association between the TNFα -308G/A polymorphism and cervical cancer incidence has been a topic of controversy. While some studies including subjects from various ethnicities have found a positive correlation between the TNFα -308 G/A polymorphism and women's susceptibility to cervical cancer (Gupta et al. 2016; Chagas et al. 2019; Du et al. 2019; Thakre et al. 2019; Behboodi et al. 2021), other studies have reported the opposite result (Zidi et al. 2015; Duvlis et al. 2020; Traore et al. 2020), which is consistent with the findings of our meta-analysis.

Several studies have investigated the role of TNFα polymorphism in cervical cancer incidence, but the results have been inconclusive. Studies conducted in Portugal and Brazil have shown that TNFα polymorphisms may play a role in women's susceptibility to cervical cancer or in the progression of cancer from non-malignant to invasive cells (Duarte et al. 2005; Sousa et al. 2014; Tavares et al. 2016; Chagas et al. 2019).

Other studies conducted in America, Mexico, Tunisia, Argentina, Africa, and Macedonia have reported contradictory findings (Calhoun et al. 2002; Nieves-Ramirez et al. 2011; Barbisan et al. 2012; Zidi et al. 2015; Duvlis et al. 2020; Traore et al. 2020).

The varying results may be attributed to differences in sample size, ethnicity among samples, and publication bias. Other factors that could impact the analysis of TNF gene polymorphism include socioeconomic differences among subjects, contraceptive use, pregnancy history, and daily habits. To limit the influence of ethnicity on the results, our study solely included Asian women.

To obtain results that demonstrate the mechanism of the role of TNFα

polymorphism in cervical cancer patients, studies should consider the above characteristics. Furthermore, future research should thoroughly investigate the mechanism by which TNFα cytokines support the development of cancer cells.

Chagas et al. (2019) found that the IL10-1082 and TNFα-308G/A haplotypes may contribute to the incidence of cervical cancer. The study hypothesizes that these haplotypes increase a person's susceptibility to cervical cancer compared to a single allele of TNFα-308G/A.

Although our study has shown the effect of TNFα polymorphisms on the incidence of cervical cancer in Asian women, it has several limitations. These include the potential for bias in study selection. Additionally, the results of this study have not been compared to those of other populations, including non-Asian populations. We also have a small size of sample in this study. We only analyzed 5 studies due to limited availability (see figure 1). This may produce inaccurate results when representing a larger population. For future research we will include a more diverse population to understand the role of TNFα polymorphism in different ethnic group.

The results of this meta-analysis study show that the TNFα -308 polymorphism is not a factor that plays a role in the susceptibility of Asian women to cervical cancer. This results may provide a deeper understanding of the pathogenicity mechanisms of HPV causing cervical cancer, particularly regarding individual genetic factors in the course of the disease. However, further research is necessary to examine the complexity of an individual's genetic factors in relation to cancer susceptibility.

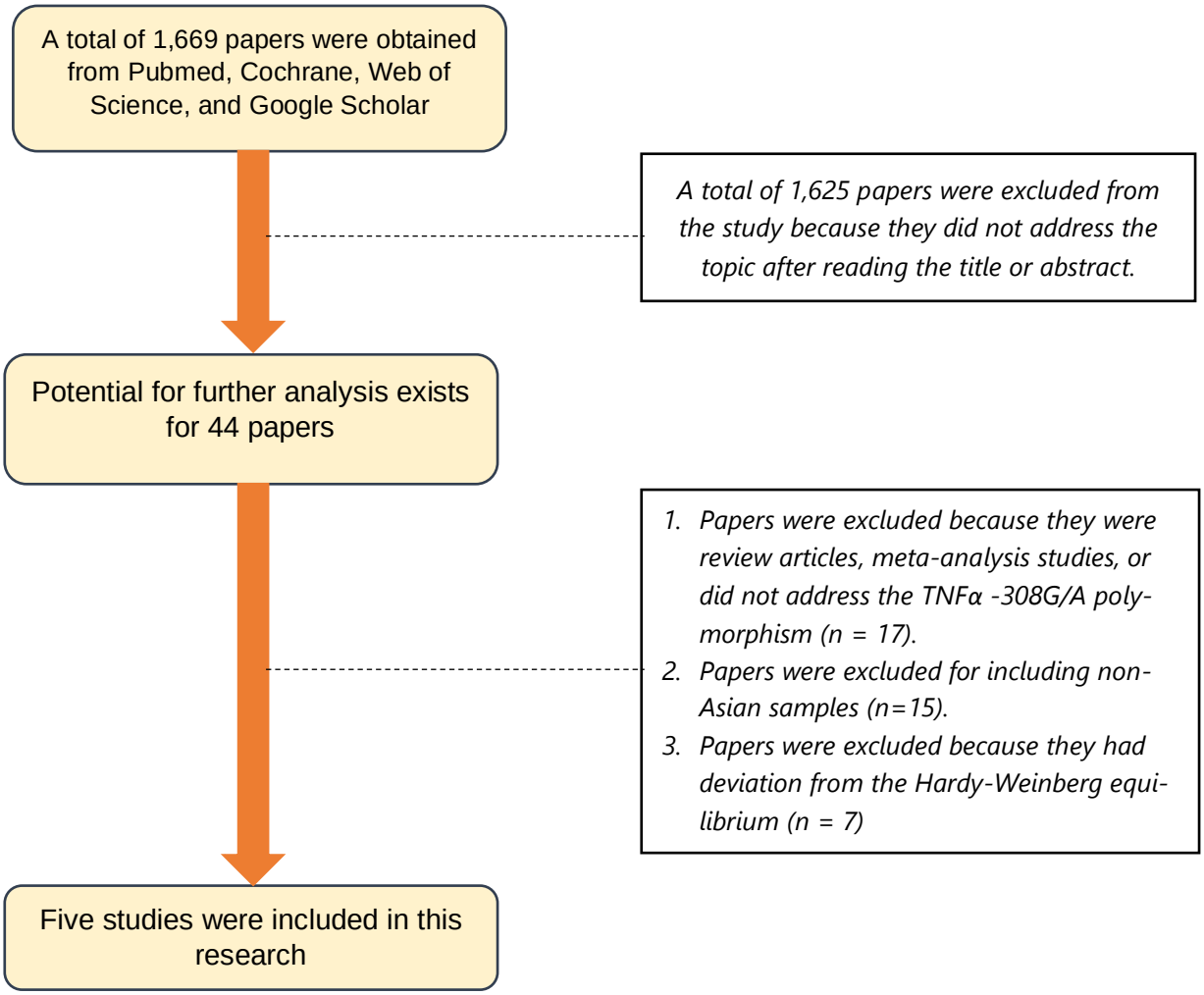

Figure 1. Study Selection Process for Meta-Analysis on TNFα-308 G/A Polymorphism and Susceptibility to Cervical Cancer

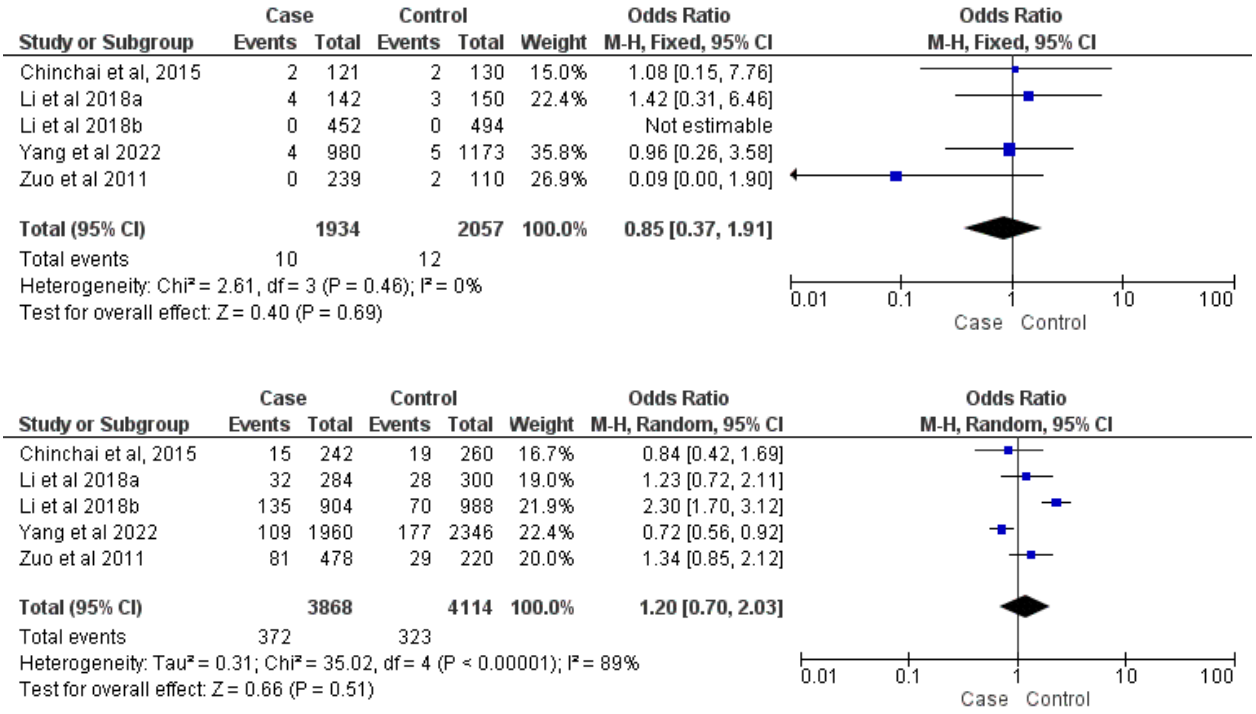

Figure 2. Forest plot of the correlation between TNFα polymorphism and cervical cancer (AA vs AG+GG) (a), and (A vs G) (b).

CONCLUSION

Cervical cancer is a type of cancer with a high incidence in women. The mortality rate is also relatively high. It is caused by human papillomavirus types 16 and 18. However, not all people infected with HPV 16 or 18 will develop cervical cancer. This is because host genetic factors play a role in an individual's susceptibility to cervical cancer. The study aims to prove the association of the TNFα-308 gene polymorphism as a risk factor for cervical cancer. The results of the research show that neither the A allele (OR 95%CI = 1.20 [0.70-2.03], p = 0.51) nor the AA genotype (OR 95%CI = 0.85 [0.37-1.91], p = 0.69) were associated with the susceptibility of cervical cancer in Asian women. Other studies in non-Asian populations have shown conflicting results. Some showed an association of TNFα polymorphisms with cervical cancer incidence, while others did not. Therefore, future research should include studies in diverse populations, taking into account the complexity of individual genetic factors on cancer incidence. In addition, this study has limitations that may have an impact on the interpretation of the results.

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