REVIEW PAPER

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Association of the interleukin-10 (IL-10) gene polymorphisms with ovarian cancer risk: a systematic review and meta-analysis

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ABSTRACT

Background. Ovarian cancer is a cancer with high fatality due to its symptomless nature, which leads to a late diagnosis. Therefore, there is an urgent need to discover genetic markers related to predisposition to the disease. With anti-inflammatory cytokines playing a major role in cancer predisposition, the present systematic review and meta-analysis were undertaken to evaluate the association of the interleukin-10 (IL-10) gene polymorphisms with ovarian cancer risk.

Material and methods. Online databases were searched for articles dating from June 2023 until inception for studies assessing the frequencies of IL-10 polymorphisms in ovarian cancer patients and controls. The odds ratios of the genotypes, alongside their respective 95% confidence intervals, were calculated under three different genetic models.

Results. A total of 5 records studying the IL-10-819 C>T and IL-10-1082 G>A polymorphisms were included in the quantitative analysis. The meta-analysis suggested that the IL-10-819 C>T polymorphism was significantly associated with the risk of ovarian cancer under a dominant (CT + TT vs CC) inheritance model (OR = 2.67; 95% CI = [1.17,6.12]; p = 0.02).

Conclusions. The meta-analysis suggested that the T allele of the IL-10-819 C>T is associated with an increased risk of ovarian cancer. However, no statistically significant association exists between the IL-10-1082 G>A polymorphism and ovarian cancer. Future studies are required to verify these results further.

Introduction

Ovarian cancer is the fatal type of gynaecological cancer globally and accounts for about 2.5% of all malignant neoplastic diseases among females [1]. Approximately only 50% of ovarian cancer patients survive for more than five years after diagnosis [1,2]. The reason underlying this low survival rate is the fact that ovarian cancer is often symptomless in the initial stages, lead-

ing to late diagnosis at stages where classical therapeutic strategies may fail to be successful [3]. Therefore, discovering methods that may help an earlier diagnosis of malignancy in women can improve survival rates [4] Over the recent years, the discovery of genetic polymorphisms related to cancer has significantly assisted clinicians in identifying patients who are at high risk of developing malignancies and, therefore, achieving earlier diagnosis through means of continuous screening [5].

The interleukin genes, encoding for a group of cytokines, have been shown to be associated with carcinogenesis, and studies have indicated that some polymorphisms of these genes are associated with an increased risk of carcinogenesis, including ovarian cancer [6,7]. Specifically, polymorphisms of the interleukin-10 (IL-10) gene are correlated with different types of malignant neoplasms [8,9]. Nevertheless, there is no concrete evidence that these polymorphisms increase the risk of developing ovarian cancer. Hence, in the present study, a systematic review and meta-analysis of the existing literature was performed to assess whether a relationship between the IL-10 polymorphisms and ovarian cancer risk exists and whether the IL-10 gene can be used as a genetic marker of ovarian cancer.

Material and methods

The research protocol of the present systematic review and meta-analysis was not registered in any database.

Search strategy

The online databases PubMed, EMBASE and SCOPUS were searched systematically for articles from June 2023 till inception using the keywords "IL-10", "Interleukin-10", "IL10", "Ovarian cancer", "Ovarian tumour", "Polymorphisms", "Polymorphic", "SNP" and a combination of Boolean operators, excluding review articles, letters and commentaries.

Using the citation manager EndNote, duplicates were removed, and citations were subsequently screened based on their titles and abstracts. Inclusion criteria were case-control studies studying the frequencies of IL-10 gene polymorphisms in healthy individuals and patients with ovarian cancer. All articles reporting polymorphisms of other genes in ovarian cancer and articles reporting polymorphisms of IL1–0 in other diseases other than malignant ovarian cancer were excluded. The final selection was made after the two reviewers assessed the remaining studies based on their full text. Two independent reviewers (Stavri Totou and Datis Kalali) performed the selection process.

Data extraction and qualitative analysis

The following data was extracted from each study and included in the qualitative analysis by two reviewers (Stavri Totou and Datis Kalali):

- Number of ovarian cancer patients and controls enrolled in the study,
- The genetic polymorphisms studied and their respective genotypes,
- The frequency of genotypes in cases and controls,
- The odds ratios of the polymorphisms (cases vs controls) and their respective p-values.

The qualities of the included studies were assessed by two independent reviewers (Stavri Totou and Datis Kalali) using the Newcastle-Ottawa scale for case-control studies [10]. No disagreements arose between the reviewers during the quality assessment.

Quantitative analysis

Initially, the odds ratios of the polymorphisms were extracted or calculated separately (in case the study did not report the ratio) alongside their respective 95% confidence intervals under four different inheritance models: dominant, recessive, co-dominant and allele. An alpha value of 0.05 was used. Thus, the ratios are considered statistically significant if their 95% confidence intervals do not contain the number 1, or their respective p-value is less than 0.05 [11]. The Higgins and Thompson I^2 statistic was used to assess the heterogeneity between the studies, where an I^2 value than 50% indicates the presence of statistical heterogeneity [12]. If heterogeneity is present, a random effects model is preferred for performing a meta-analysis, or a fixed effects model is used. Subsequently, a meta-analysis of all included studies was undertaken to create forest plots and calculate a pooled odds ratio for all studies under the four different inheritance models. A funnel plot was constructed, and Egger's

test was performed to assess whether significant publication bias existed within the meta-analysis. All statistical analyses were performed using STATA release version 17.0 (StataCorp LL, College Station, Texas, USA) and Review Manager release version 5.4.1 (RevMan, Cochrane, London).

Results

Included studies

The database search on the internet retrieved a total of 55 citations (12 citations from PubMed, 20 citations from SCOPUS and 23 citations from EMBASE) and an addition of another two citations were retrieved manually through other sources. After removing duplicates, a total of 32 citations remained, amongst which 21 were excluded after screening since irrelevance to the research question was evident from their titles or abstracts. Among the remaining 11 studies, which were assessed based on their full texts, a total of two studies were reviewed, and four did not contain relevant data for the research. Thus, a total of 5 studies were included in the present meta-analysis. **Figure 1** provides a graphical overview of the literature identification, screening and inclusion process. **Table 1** contains a summary of the characteristics of all the studies that were included.

Quality analysis

The Newcastle-Ottawa scale was used to assess the qualities of all included studies, and **Table 2** contains the recorded results of this assessment. Generally, the studies were of adequate quality, so they did not carry a high risk of biased results.

Meta-analysis

Two polymorphisms were identified in the studies: IL-10–1082 G>A (rs1800896) and IL-10–819 C>T (rs1800871). The meta-analysis did not indicate any statistically significant result relating the IL-10–1082 G>A polymorphism to the risk of ovarian cancer. However, regarding the IL-10–819 C>T polymorphism, it was found that the CT and TT genotypes were significantly related to the risk

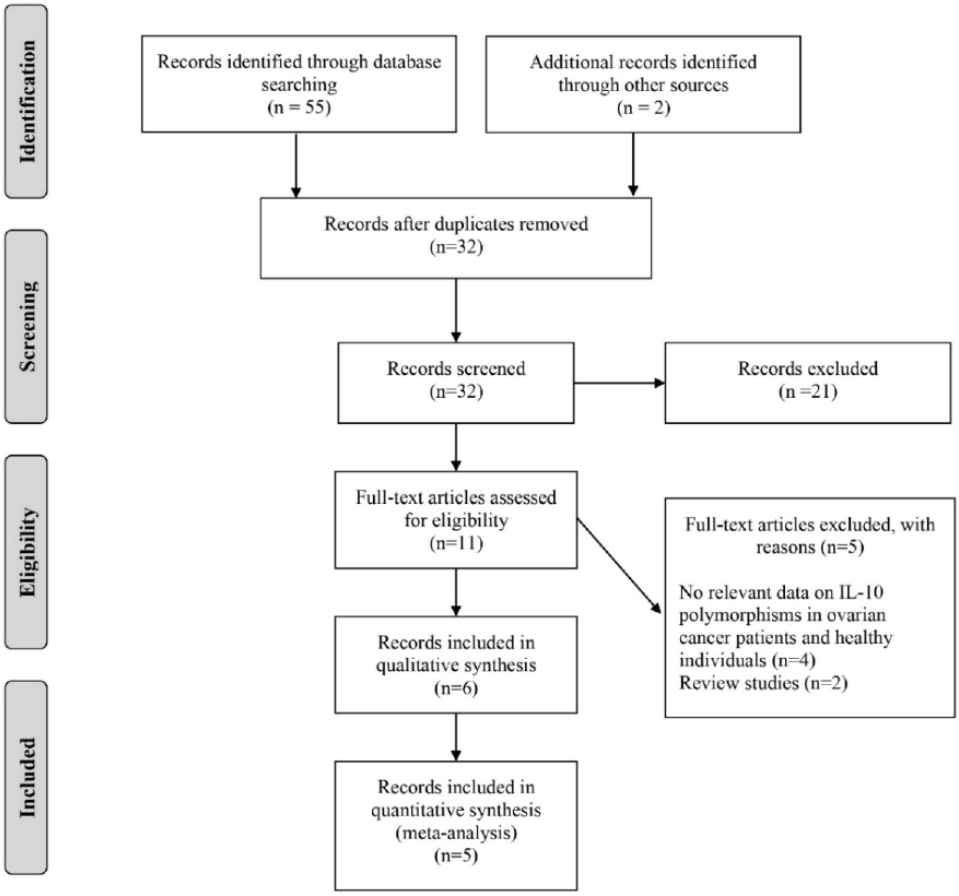

Figure 1. PRISMA diagram of the search strategy and inclusion process.

of ovarian cancer (OR=2.67; p=0.02), indicating that the T-allele of the polymorphism is related to ovarian cancer under a dominant inheritance model. **Tables 3** and **4** summarize the pooled odds ratios and other statistical measures retrieved in the meta-analysis. **Figure 2** shows a forest plot that explores the association between ovarian cancer risk and the IL-10–819 C>T polymorphism under a dominant inheritance model. Forest plots of the meta-analysis of all other genetic models for both polymorphisms have been provided in the Supplementary material.

Publication bias

The symmetrical shape of the funnel plot (see **Figure 3**) indicated no evident bias under the dominant model, confirming the reliability of the retrieved results. A P-value of 0.36 (greater than

Table 1. Characteristics of included studies.

Study (Author, year)	Country	Participants (cases/ controls)	Age of participants (cases/ controls)	Sample type	Genotyping method	Polymorphisms studied
Almolakab et al., 2022 [13]	Egypt	48/48	45.3/50.6 (Mean)	Blood	SSP-PCR	IL-10-819 C>T and IL-10-1082 G>A
Briacu et al., 2007 [14]	Germany	147/129	45.5/55 (Median)	Blood	Pyrosequencing™	IL-10-819 C>T and IL-10-1082 G>A
Bushley et al., 2004 [15]	USA	180/218	54.7/54.7 (Mean)	Blood	SSP-PCR	IL-10-819 C>T and IL-10-1082 G>A
He et al., 2008 [16]	China	33/90	Unknown	Blood	SSP-PCR	IL-10-819 C>T
Kutikhin et al., 2014 [17]	Russia	74/168	55.3/58.3 (Mean)	Blood	SSP-PCR	IL-10-1082 G>A

Table 2. Quality assessment of studies in the meta-analysis.

Study (Author, year)	Newcastle-Ottawa scale scores			
	Selection	Comparability	Exposure	Total
Almolakab et al., 2022 [13]	3	1	3	7
Briacu et al., 2007 [14]	3	1	2	7
Bushley et al., 2004 [15]	3	2	3	8
He et al., 2008 [16]	3	1	1	5
Kutikhin et al., 2014 [17]	3	1	3	7

Table 3. Pooled odds ratios for IL-10–819 C>T polymorphism (cases vs. controls).

Genetic model		Odds ratio [95% CI]	Meta-analysis model	I-squared	P-value
Co-dominant model	CC	1			
	CT	1.59 [0.99, 2.55]	Random effects	56%	0.05
	TT	1.18 [0.84, 1.66]	Fixed effects	37%	0.34
Dominant model	CT + TT vs. CC	2.67 [1.17, 6.12]	Random effects	70%	0.02
Recessive model	CC + CT vs. TT	0.81 [0.57, 1.14]	Fixed effects	48%	0.12
Allele model	C vs. T.	1.12 [0.88, 1.42]	Random effects	81%	0.35

Table 4. Pooled odds ratios for IL-10–1082 G>A polymorphism (cases vs. controls).

Genetic model		Odds ratio [95% CI]	Meta-analysis model	I-squared	P-value
Co-dominant model	GG	1			
	GA	1.21 [0.94, 1.57]	Fixed effects	6%	0.14
	AA	0.80 [0.50, 1.29]	Random effects	60%	0.36
Dominant model	GA + AA vs. GG	0.87 [0.48, 1.59]	Random effects	71%	0.66
Recessive model	GG + GA vs. AA	1.30 [0.84, 2.00]	Random effects	52%	0.24
Allele model	G vs. A	1.14 [0.95, 1.36]	Random effects	66%	0.16

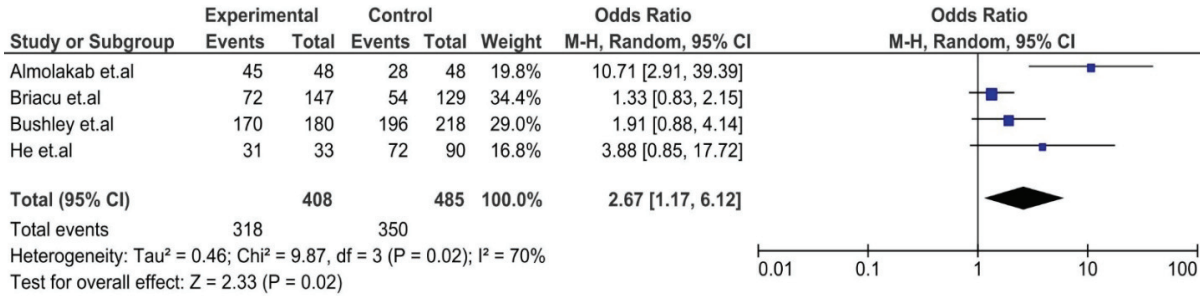

Figure 2. Forest plot of meta-analysis of the IL-10-819 C>T polymorphism (dominant model).

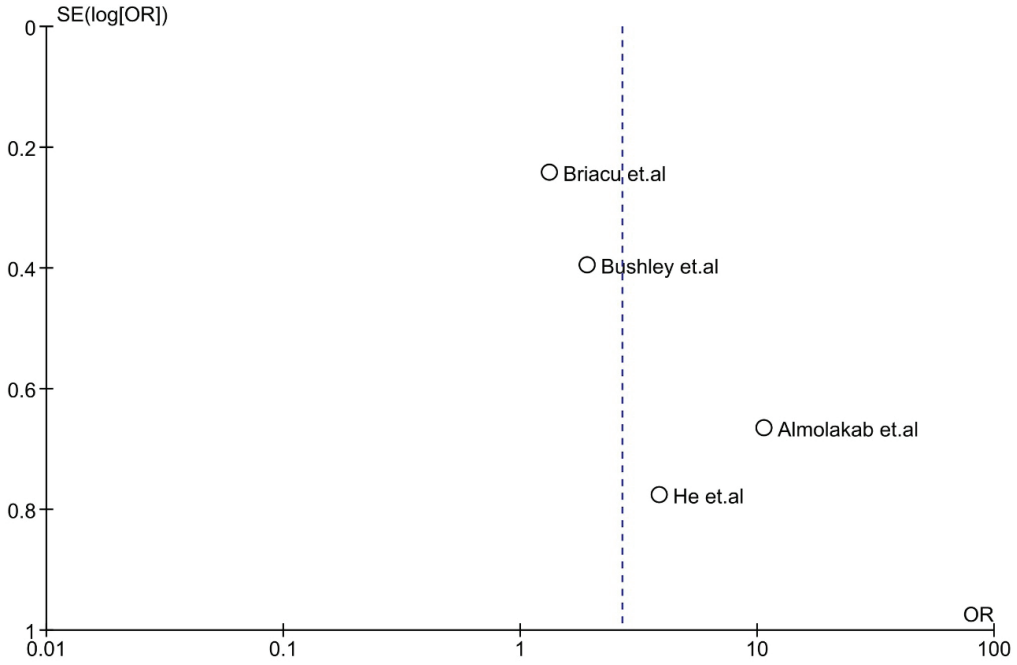

Figure 3. Funnel plot of meta-analysis of the IL-10–819 C>T polymorphism (dominant model).

0.1) in Egger's test further verified these results. Egger's regression test showed an intercept of 3.58 (95% CI:[-4.07,11.23]). Funnel plots of the meta-analysis of all other genetic models for both polymorphisms have been provided in the Supplementary material.

Discussion and conclusions

The results of the present systematic review indicate that the IL-10–819 C>T gene polymorphism is directly related to ovarian cancer. A previous network meta-analysis by Hu et al., screening different genetic markers, did not find IL-10 polymorphisms related to ovarian cancer [18]. Simultaneously, a 2015 meta-analysis investigating the IL-10–1082 G>A polymorphism with cancer did not obtain any significant results for ovarian cancer [19]. Nevertheless, one meta-analysis conducted in 2013, which assessed the relation of the IL-10–819 C>T polymorphism with cancer. However, it contained only three studies relating to ovarian cancer [20]. Thus, the present updated meta-analysis further verifies the latter result. It is worth mentioning that Il-10 is known to be an anti-inflammatory cytokine and thus can contribute to an increased risk of tumourigenesis and tumour aggressiveness [21]. Specifically, an increased expression of IL-10 induces a decreased expression of the pro-inflammatory cytokines IL-1a, IL-1b, IL-6, IL-12 and TNF-alpha and regulates the expression of the BCL-2 protein [21,22]. Interestingly, the IL-10–819 C>T polymor-

phism of the promoter region is known to correlate to higher gene expression, possibly explaining the results of the meta-analysis [13,23]. Overall, more studies must be conducted to verify our obtained results further and assess whether other polymorphisms of the IL-10 gene are related to the development of ovarian cancer.

Limitations

Even though the present meta-analysis was performed according to PRISMA guidelines and all means of assessment indicated a low risk of bias, it contains some substantial limitations. First, only a few studies were eligible for inclusion in the meta-analysis, decreasing the statistical power for calculating a pooled odds ratio [24]. Moreover, a moderate level of statistical heterogeneity was found, possibly due to the differences in the number of participants included in each study and the differences between the characteristics of the included participants [25]. Unfortunately, due to the lack of sufficient data on genotype distribution according to gender, age and environmental factors, a meta-analysis on subgroups based on these factors could not be performed in order to assess the latter assertation. It is also worth mentioning that most studies were performed in countries with Caucasian and Asian populations, indicating that the meta-analyses did not include a broad range of ethnicities. Finally, the literature search was limited to articles written in English; thus, articles in other languages may have been missed in this meta-analysis.

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Conflict of interest statement
The authors declare no conflict of interest.

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