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Review

Association of the CYP17 (T-34C) Polymorphism and the Risk of Acne Vulgaris: A Meta-Analysis

Mazaher Ramezani[1], Elisa Zavattaro[2], Masoud Sadeghi[3,4*]

[1] Molecular Pathology Research Center, Imam Reza Hospital, Kermanshah University of Medical Sciences, 6714415153 Kermanshah, Iran
[2] Dermatology Unit, Department of Translational Medicine, University of Eastern Piedmont "Amedeo Avogadro", 28100 Novara, Italy
[3] Medical Biology Research Center, Kermanshah University of Medical Sciences, 6714415185 Kermanshah, Iran
[4] Students Research Committee, Kermanshah University of Medical Sciences, 6715847141 Kermanshah, Iran
* Correspondence: sadeghi_mbrc@yahoo.com; Tel.: +xx-xxx-xxx-xxxx

Abstract: Acne vulgaris is one of the most common skin diseases and genetic relationships have been documented. The aim was to evaluate the association of CYP17 (T-34C) polymorphism related to the risk of acne in a meta-analysis study. The databases (Scopus, Web of Science, PubMed, and Cochrane Library) were searched until September 2018 to check the relationship between acne risk and CYP17 (T-34C) polymorphism and impact of this polymorphism on severity of acne. We used Review Manager 5.3 software to analyze the data using OR and 95% CI to check this relationship. Four studies were included and analyzed in the meta-analysis. The OR in analysis of C *versus* T in acne patients compared to the healthy controls was 1.42 (P=0.02), in CC *vs.* TT was 1.54 (P=0.04), in TC *vs.* TT was 1.46 (P=0.12), in TC + CC *vs.* TT was 1.55 (P=0.04), and in CC *vs.* TT + TC was 1.39 (P=0.06). There was no acne risk related to CYP17 (T-34C) in none of genetic models in Caucasian ethnicity, whereas in Asian ethnicity, there was higher acne risk related to CYP17 (T-34C) without heterogeneity. The results of the present meta-analysis showed the presence of C allele and CC genotype of CYP17 polymorphism can be risk factors for acne, mainly in the Asian ethnicity.

Keywords: acne; polymorphism; genetics; CYP17; ethnicity

1. Introduction

Acne vulgaris is one of the most common skin diseases affecting about 85% of adolescents in Western countries [1,2]. The pathogenesis of this disease is multiple and complex, and is still not well defined, but genetic relationships have been documented [3]. The share of genetic factors in the development of this disease has been postulated for a long time, which was supported by genealogical research and the study of twins [4,5]; however, to date, only a few data are reported in the literature [6]. The key role of the disease is attributed to hormonal disorders that cause sebaceous hypertrophy, abnormal keratosis and to the *Propionibacterium acnes* presence [7]. Cytochrome P450 (CYP) is a multiple family of iron-containing hemoproteins that catalyzes the metabolism of endo- and exogenous products such as fatty acids, steroids; and a number of hormones and vitamins [8,9]. The CYP17 gene is located on the chromosome 10q24.3, coding for P450c17, which is one of the key enzymes in the androgen biosynthesis and a mediator of the 17alpha-hydroxylase and 17, 20-lyase activity [10]. The existence of a T> C (T-34C) small nucleotide polymorphism (SNP) in nucleotide 27 has been reported in the promoter of the CYP17 gene and related to breast cancer risk [11,12]. In addition to the investigation of this gene in acne [6,8,13,14], its association between CYP17 with Down syndrome and Alzheimer's disease [15], and prostate cancer [16], has also been studied. Herein, the

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association of CYP17 (T-34C) polymorphism (rs743572) related to the risk of acne was evaluated in a meta-analysis study.

2. Materials and Methods

The study was designed according to the instructions of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [17].

2.1. Literature search strategy

Four databases including Scopus, Web of Science, PubMed, and Cochrane Library were investigated for studies published until September 2018 with no language restriction using the terms ("CYP17", "Cytochrome P450 17A1", "CYP17A1", or "CYP") and ("Acne").

2.2. Eligibility criteria

M.S as the first reviewer searched the articles among the databases and checked their titles and abstracts and if they were not relevant, they would be deleted. After that, the full-texts of the relevant studies were checked based on the eligibility criteria**.** The second reviewer (M.R) re-assessed the full-texts. The inclusion criteria were the case-control studies evaluating genotype distributions of CYP17 (T-34C) polymorphism in acne patients using the odds ratio (OR) and 95% confidence intervals (CIs). The exclusion criteria were animal studies, review articles, meeting abstracts, letter to editors, studies without a control group, and family-based studies.

2.3. Data extraction

Three reviewers (M.M.I, E.Z, & M.S) extracted independently the data. The data extracted from each study are shown in **Table 1**.

2.4. Quality assessment

M.R assessed the quality of each case-control study using questionnaire of the Newcastle-Ottawa Quality Assessment Scale (NOS) [18].

2.5. Statistical analysis

We used Review Manager 5.3 software to analyze the data using OR and 95% CI for to check the relationship between acne risk and CYP17 (T-34C) polymorphism and impact of this polymorphism on severity of acne. Five genetic models were used to show this correlation [19]. P-value <0.05 showed a significant relationship. The Cochrane Q test and I^2 statistic was used to estimate heterogeneity across the studies that if P-value <0.1 or I^2>50%, there was statistically significant heterogeneity. If it was no significant heterogeneity, fixed-effect model, otherwise, the random-effect model was applied to estimate the pooled ORs and CI values. In addition, the chi-square test was used for calculation of HWE in the control groups of each study. A subgroup analysis was done according to ethnicity. Also, the CMA Software version 2.0 was used for a funnel plot analysis using both Egger's and Begg's tests that P-value<0.05 was showed a significant existence of publication bias.

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79 **Table 1**. Characteristics of the studies included in the meta-analysis (n=4).

Study	Study population	Source of controls	Sample size (NSCL/P : Control)	Acne			Control			Genotyping method	P-value for HWE in controls	Score*
				TT	TC	CC	TT	TC	CC			
He, 2006 [8]	China	HB	206 : 200	45	103	58	59	99	42	PCR	0.968	7
Tian, 2010 [13]	China	PB	79 : 39	20	30	29	11	18	10	PCR	0.633	8
Sobjanek, 2015 [6]	Poland	-	115 : 94	40	53	22	34	43	17	PCR-RFLP	0.599	6
Chamaie-Nejad, 2018 [14]	Iran	HP	198 : 195	132	66	0	164	31	0	PCR-RFLP	0.227	8

80 **Abbreviations**: HB, hospital-based; PB, population-based; HWE, Hardy-Weinberg equilibrium; PCR: polymerase chain reaction; RFLP: restriction fragment length
81 polymorphism. * Quality score according to Newcastle-Ottawa Quality Assessment Scale (NOS)

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3. Results

Among 61 studies identified in the databases, 4 studies were included and analyzed in quantitative analysis (meta-analysis) (**Figure 1**).

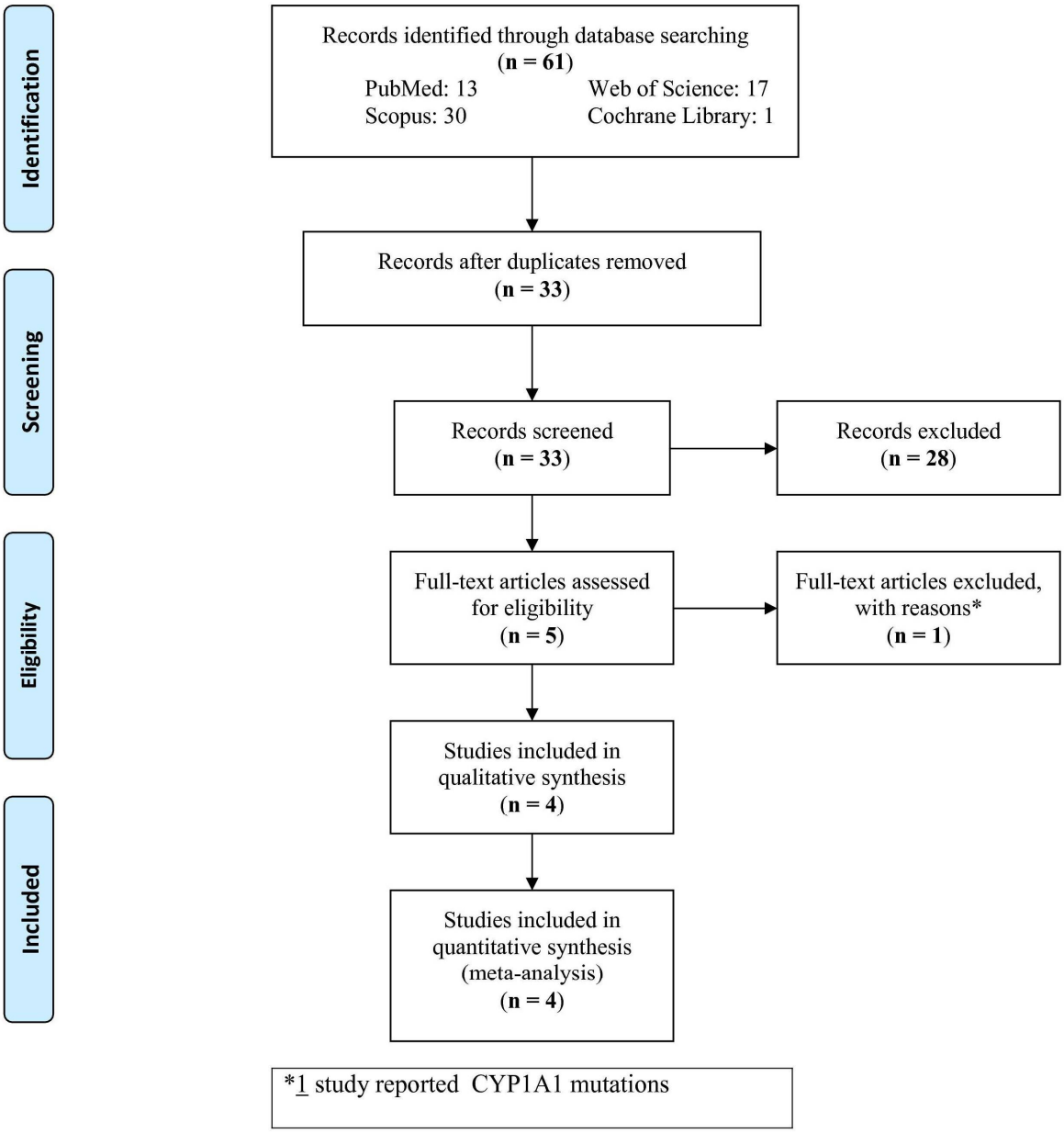

Figure 1. Flow chart of the study.

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Some of characteristics of four studies included in the meta-analysis are shown in **Table 1**. Two studies [8,13] were reported from Chinese, one [6] from Iranian, and one [14] from Polish populations. In all studies [6,8,13,14], the genotype distribution of the polymorphism in controls corresponded with Hardy-Weinberg equilibrium (HWE). The meta-analysis included 598 acne patients and 528 controls.

The pooled OR of acne risk related to CYP17 (T-34C) polymorphism based on the allele, the homozygote, the heterozygote, the dominant, and the recessive models are shown in **Table 1**. The OR in analysis of C *versus* T in acne patients compared to the healthy controls was 1.42 [95%CI=1.05, 1.93; P=0.02], in CC *vs.* TT was 1.54 [95%CI=1.02, 2.33; P=0.04], in TC *vs.* TT was 1.46 [95%CI= 0.90, 2.34; P=0.12], in TC + CC *vs.* TT was 1.55 [95%CI=1.02, 2.37; P=0.04], and in CC *vs.* TT + TC was 1.39 [95%CI=0.98, 1.98; P=0.06].

Five genetic models for analysis of acne risk related to CYP17 (T-34C) according to patients ethnicity are showed in **Table 2**. In overall analysis, there was heterogeneity in the allele, the heterozygote, and the dominant, models. There was no acne risk related to CYP17 (T-34C) in none of genetic models in Caucasian ethnicity [6,14], whereas in Asian ethnicity [8,13], there was acne risk related to CYP17 (T-34C) without heterogeneity in analyses of C *versus*. T, CC *vs.* TT, CC + TC *vs.* TT, and CC *vs.* TT + TC in acne patients compared to the healthy controls that OR was 1.34 (95%CI=1.05, 1.72), 1.76 (95%CI=1.08, 2.87), 1.42 (95%CI=0.95, 2.11), and 1.52 (95%CI=1.02, 2.27), respectively.

Two studies analyzed acne risk related to CYP17 (T-34C) in the patients with severe acne compared to mild and moderate acne (**Table 3**). There was a significant risk without heterogeneity in analyzes of C *versus* T, CC *vs.* TT, and CC *vs.* TT + TC, that OR was 1.47 (95%CI=1.07, 2.02), 2.79 (95%CI=1.24, 6.25), and 1.92 (95%CI=1.04, 3.55), respectively.

Publication bias

The funnel plots of overall analysis based on the genetic models are shown in **Figure 3**. Egger's and Begg's tests didn't identify any publication bias among the analyses.

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115 **Table 2.** Analysis of acne risk related to CYP17 (T-34C) according to ethnicity.

		No. of study	C vs. T			CC vs. TT			TC vs. TT			CC + TC vs. TT			CC vs. TT + TC		
			OR (95%CI)	I^2 (%)	P_h	OR (95%CI)	I^2 (%)	P_h	OR (95%CI)	I^2 (%)	P_h	OR (95%CI)	I^2 (%)	P_h	OR (95%CI)	I^2 (%)	P_h
Overall		4	**1.42 (1.05, 1.93)**	57	0.07	**1.54 (1.02, 2.33)**	0	0.59	1.46 (0.90, 2.34)	61	0.05	**1.55 (1.02, 2.37)**	56	0.08	1.39 (0.98, 1.98)	0	0.68
Ethnicity	Asian	2	**1.34 (1.05, 1.72)**	0	0.96	**1.76 (1.08, 2.87)**	0	0.83	1.26 (0.82, 1.92)	0	0.46	**1.42 (0.95, 2.11)**	0	0.61	**1.52 (1.02, 2.27)**	0	0.79
	Caucasian	2	1.55 (0.71, 3.36)	85	0.01	1.10 (0.50, 2.40)	-	-	1.70 (0.69, 4.20)	82	0.02	1.70 (0.69, 4.15)	83	0.02	1.07 (0.53, 2.16)	-	-

116 **Table 3.** Analysis of acne risk related to CYP17 (T-34C) in the patients with severe acne compared to mild + moderate acne.

References	C vs. T			CC vs. TT			TC vs. TT			CC + TC vs. TT			CC vs. TT + TC		
	OR (95%CI)	I^2 (%)	P_h	OR (95%CI)	I^2 (%)	P_h	OR (95%CI)	I^2 (%)	P_h	OR (95%CI)	I^2 (%)	P_h	OR (95%CI)	I^2 (%)	P_h
[8,14]	**1.47 (1.07, 2.02)**	16	0.28	**2.79 (1.24, 6.25)**	-	-	1.37 (0.84, 2.22)	0	0.45	1.51 (0.95, 2.42)	25	0.25	**1.92 (1.04, 3.55)**	-	-

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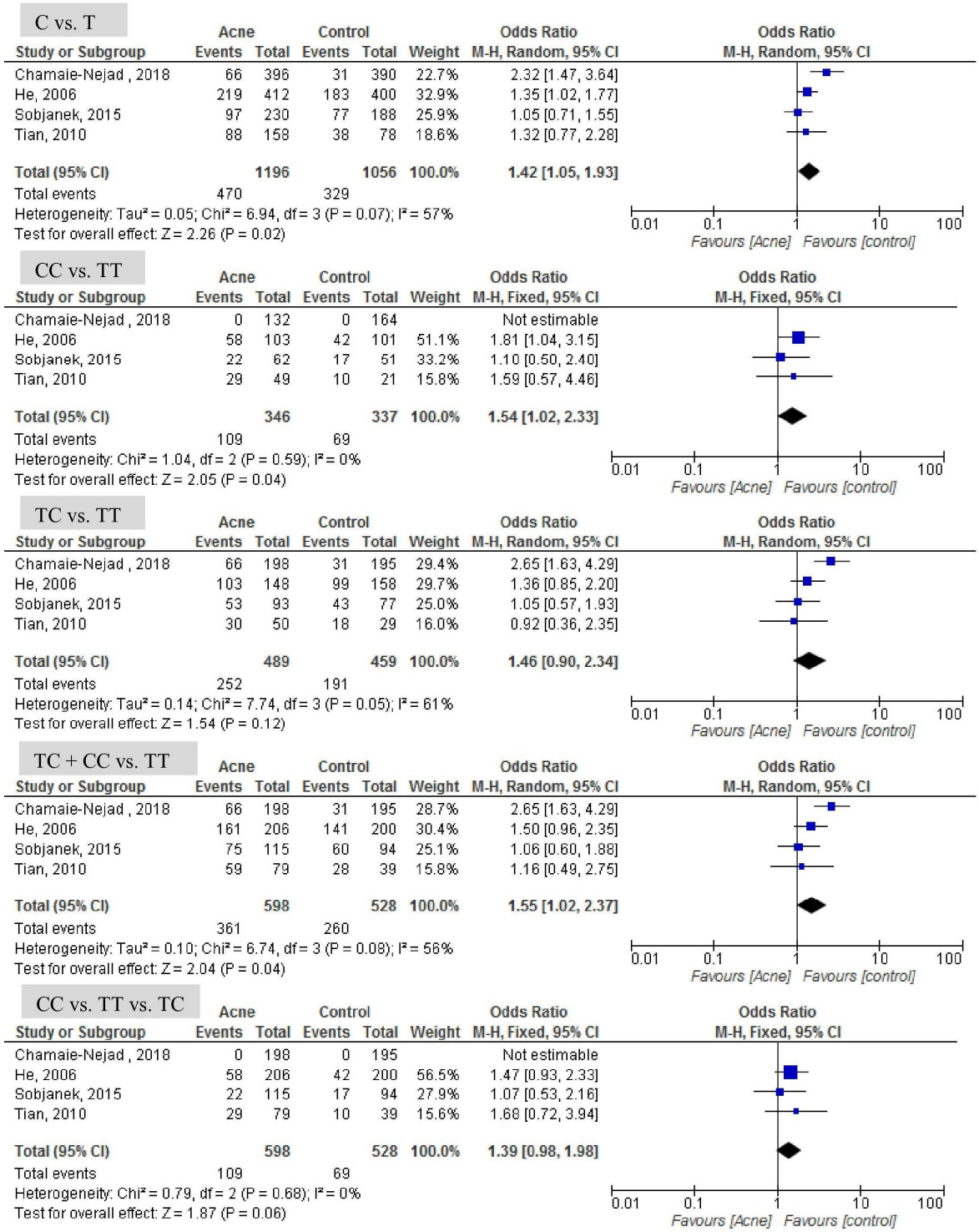

Figure 2. Forest plot of acne risk related to CYP17 (T-34C) polymorphism.

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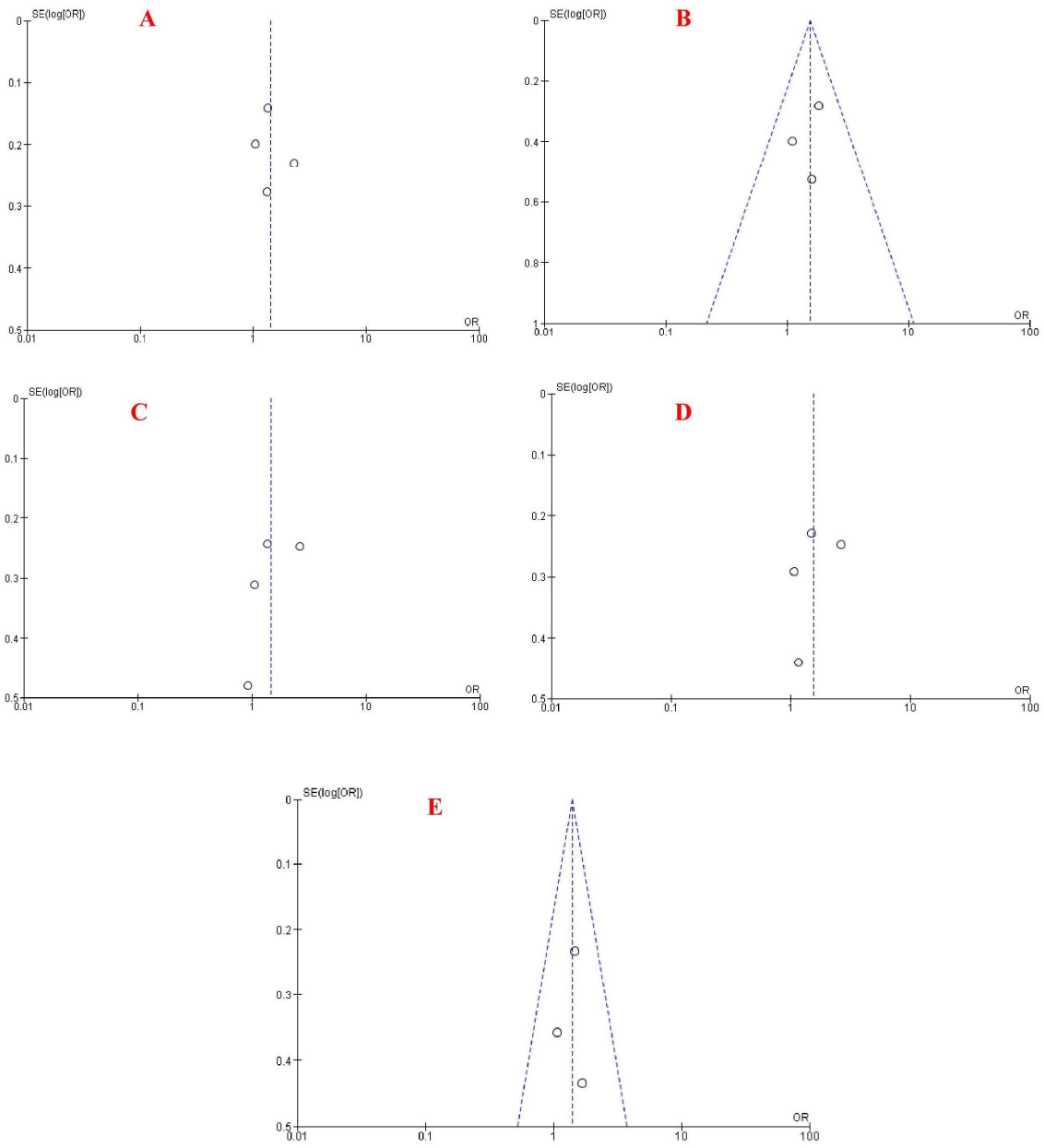

Figure 3. Funnel plot acne risk related to CYP17 (T-34C).

4. Discussion

The present meta-analysis evaluated the CYP17 (T-34C) polymorphisms (rs743572) in acne vulgaris patients compared with controls and showed that subjects carrying C allele or CC genotypes were at higher risk for acne in its severe form. The association between such polymorphism and acne was first presented by He et al. in 2006 [8]. It is well known that the etiology of acne vulgaris is multifactorial and correlated to both genetic and environmental factors [6]. CYP17 is a microsome enzyme and a potent oxidant to catalyze two distinct activities, 17α-hydroxylase and 17, 20-lyase, which are essential for the anabolism of adrenal and gonads steroids [20], especially in androgen production [21,22]. When the androgen level increases, also the production of sebum and follicular keratosis rises and the acne development is promoted [8]. Indeed androgens play a key role in the pathogenesis of acne and anti-androgen therapy, in some patients, allows a very successful treatment [23]. To date, in the literature no conclusive data are reported on the effect of CYP17 polymorphisms on 17alfa-hydroxylase/ 17-20 -lyase activity; unless this SNP has been extensively studied in several hormone-related neoplasms (i.e. prostate, breast, endometrial cancer) with controversial results [11,12,16].

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Interestingly, the allele variant T/C at the -34 bp position (rs743572) is relative to the start codon located in the 5'-UTR promoter region of CYP17, a region strictly associated with gene expression. Other CYP17 SNPs (rs6162 and rs6163) are in strong linkage disequilibrium with rs743572 and they have been detected in patients with high levels of androgens, thus suggesting that such polymorphisms may influence sex hormones gene expression [24].

Out of four studies involved in the present meta-analysis, two studies [8,13] performed in the Asian ethnicity showed the presence of C allele and CC genotype as significant risk factors in acne, whereas two other studies [6,14] involving the Caucasian ethnicity didn't show any risk factor related to the CYP17 polymorphism. In addition, overall results of two studies [8,14] reporting the correlation between SNPs and acne risk showed that there was a positive association between the presence of C allele and CC genotype and acne severity. The first study [8] compared the association between SNP and acne risk in females and males separately. In the male group affected by severe acne, the allele C compared to T allele and CC genotype showed a significantly increased risk of the disease compared with TT and TC genotypes, while no significant difference in genotype and allele distribution was reported in females. Accordingly, Tian et al. [13] reached similar results on female post-adolescent acne [8]. In addition, the study of Chamaie-Nejad et al. [14] including 198 acne patients (85.4% females) and 195 healthy controls (73.3% females), showed that the C allele and TC genotype were the main risk factors in acne. Therefore, further studies considering the role of gender in the association of the CYP17 polymorphism and acne risk are needed.

It has to be taken in account that, with regard to the studies included in the present meta-analysis, one study [8] did not report the age of patients, while the other studies reported different age range (13-43 years, age >20 years, and 26-42 years, respectively) [6,13,14]. Hence, age, in addition to gender, can impact on this association. Worthy of note, in the present meta-analysis two important limitations can be represented by the difference in age range and sex percentage between the studies; unfortunately, only few studies reported that they can be responsible for the heterogeneity in a number of analyzes. On the contrary, no bias in overall analysis and also in subgroup analysis of the Asian ethnicity was reported.

5. Conclusions

The results of the present meta-analysis showed that the presence of C allele and CC genotype of CYP17 SNP can represent risk factors for acne, mainly in the Asian ethnicity. However, age and gender can act as two confounding factors and modify the association between CYP17 polymorphism and acne risk. Further studies need to examine such two factors in acne patients in order to obtain more accurate result.

Author Contributions: Conceptualization, M.R. and M.S.; Methodology, M.S.; Software, M.S.; Validation, E.Z and M.S.; Formal Analysis, M.S.; Investigation, E.Z. and M.S.; Writing-Original Draft Preparation, M.S; Writing-Review & Editing, M.R. and E.Z.; Visualization, M.R and M.S.; Supervision, M.R.; Project Administration, M.R. and M.S.

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