Original Article

Association between single nucleotide polymorphisms of IL-6 and susceptibility to skin cancer: a meta-analysis and systematic review

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Background: As one of the most common body malignant cancers, skin cancers contain a group of highly heterogeneous tumors with different malignant potential, prognosis and treatment methods. Despite the progress in the treatment of skin cancers worldwide, the overall prognosis is still poor. Recent studies indicated single nucleotide polymorphisms (SNPs) of interleukin-6 (IL-6), including 174G/C and 597G/A, might be associated with susceptibility to skin cancer. This meta-analysis aims to clarify the relationship between *IL-6* gene polymorphisms and skin cancers.

Methods: Eligible studies were identified from searching PubMed, Embase, Web of Science and Cochrane. Pooled odds ratio (OR) and corresponding 95% confidence interval (CI) were obtained for the relationships between IL-6 174G/C and 597G/A polymorphisms and skin cancer using random-effects models. For the included studies, the Newcastle-Ottawa scale (NOS) score was calculated to assess study quality. Heterogeneity tests, sensitivity analysis, and publication bias assessments were also performed. Trim-and-fill method was used when publication bias existed aiming to adjusting OR. All data were analyzed in R (version 4.0.2).

Results: This meta-analysis included 1,705 cases and 1,987 controls for 174G/C polymorphism (10 publications), and 968 cases and 998 controls for 597G/A polymorphism (3 publications). No elevated risk of skin cancer was found in all comparisons for 174G/C polymorphism: CC *vs.* GC + GG, OR =1.03 (95% CI: 0.81–1.31); GC + CC *vs.* GG, OR =1.16 (95% CI: 0.96–1.39); CC *vs.* GG, OR =1.14 (95% CI: 0.86–1.53); GC *vs.* GG, OR =1.16 (95% CI: 0.99–1.37); C *vs.* G, OR =1.07 (95% CI: 0.92–1.24). Then we performed subgroup analysis based on publication year, the cancer type, sample size, NOS score. Significant differences were observed in the subgroup of publication year before 2010 (GC + CC *vs.* GG, OR =1.255, P=0.012; GC *vs.* GG, OR =1.277, P=0.01), while there is no statistical significance in the subgroup of publication year after 2010 (P>0.05 for all comparisons). After publication bias adjustment, the results further suggested that 174G/C polymorphism is not associated with the risk of skin cancer. No elevated risk of skin cancer was found in the comparisons for 597G/A polymorphism.

Discussion: Current evidence showed that *IL-6* gene polymorphisms might not be associated with the susceptibility to skin cancer.

Keywords: Skin cancer; interleukin-6 (IL-6); single nucleotide polymorphisms (SNPs); susceptibility

Submitted Aug 03, 2021. Accepted for publication Nov 04, 2021.

doi: 10.21037/tcr-21-1508

View this article at: https://dx.doi.org/10.21037/tcr-21-1508

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Introduction

Skin cancer is one of the most common malignant cancers in the world, which is often caused by ultraviolet radiation, immunosuppressive therapy or radiotherapy (1). Skin cancer can be classified according to the origin of malignant cells, which are usually located in the epidermis, dermis or skin appendages. Malignant cancers derived from the epidermis include cutaneous melanoma (CM) and non-melanoma skin cancers (NMSCs), such as basal cell carcinoma (BCC), squamous cell carcinoma (SCC) and Merkel cell carcinoma (MCC) (2). BCC and SCC are the most common types of skin cancer, which account for about 80% and 16% of all NMSCs, respectively (3). Melanoma accounts for only 10% of skin cancer, but melanoma is the leading cause of death due to skin cancer (4). At present, although there is considerable treatment progress worldwide, skin cancers are heterogenic and present with diverse malignant potential, prognosis and treatment methods.

Several cytokines, such as interleukin-6 (IL-6), are known to inhibit the proliferation of melanoma cell lines and regulate the invasive features of melanoma cells (5). Abnormal IL-6 levels might be associated with the occurrence of skin cancer (6), and has been found to exert an important inhibition effect on melanoma cell growth (7). IL-6 overexpression was confirmed in primary cutaneous lymphoma (8). The levels of STAT3 and IL-6 are also higher in patients with autoimmune diseases (9), in which, IL-6 not only maintains inflammation, but also regulates immune response. It can be considered that IL-6 can regulate the shift of immune response by changing the quality of peptide presentation, so as to activate or tolerate (10). Thus, the gene polymorphisms of cytokines might be associated with the susceptibility to skin cancer.

A number of studies have investigated the relationship of IL-6 single nucleotide polymorphisms (SNPs), including rs1800795-174G/C and rs1800797-597G/A, with disease susceptibility and prognosis. A few literatures found out that polymorphisms of IL-6 might affect the occurrence of skin cancer (11), while several studies suggested the opposite (12). For instance, Sławińska *et al.* found that the C allele in rs1800795-174 was correlated with significantly increased risk of BCC (C *vs.* G: OR =1.86, P=0.004) (13). On the contrary, Wang *et al.* discovered that the G allele in rs1800795-174 might enhance the susceptibility to BCC (G *vs.* C: OR =1.38, P=0.012) (14). Five years earlier, a meta-analysis by Wu *et al.* summarized and analyzed the association between IL-6 polymorphism and skin cancer, and found that rs1800795-174G/C was associated with the risk of skin cancer (for GC *vs.* GG: OR =1.28, P=0.816; for CC/GC *vs.* GG: OR =1.26, P=0.618) (15). However, the data in the meta-analysis by Wang *et al.* could not draw a definite conclusion, and the included literatures were 10 years ago. In the recent decade, several new reports that investigate the association between *IL-6* gene SNP and skin cancer risk have been published. A new meta-analysis is needed to further verify this question. In addition, another SNP (597G/A) of IL-6 has not been fully studied due to the lack of previous literatures. Therefore, this meta-analysis also aims to explore the relationship between two IL-6 SNPs and the risk of skin cancer.

We present the following article in accordance with the PRISMA reporting checklist (available at https://dx.doi.org/10.21037/tcr-21-1508).

Methods

Database search

We searched all papers focusing on the relationship between IL-6 174G/C and 597G/A polymorphisms and skin cancer through July 2021 in the PubMed, Embase, Web of Science and Cochrane. The keywords were used as following:

- For IL-6 polymorphism: IL-6, interleukin-6, rs1800795, 174G/C, rs1800797 and 597G/A;
- For polymorphism: polymorphism, variant and SNP;
- For skin cancer: skin cancer, basal cell carcinoma, cutaneous squamous cell carcinoma, BCC, SCC and melanoma.

The electronic search was supplemented by examining the reference lists of other articles identified and reviewing original report. Endnotes (version X7) was used to manage search records for literature screening. The protocol of this meta-analysis has been registered in the International Prospective Register of Systematic Reviews (PROSPERO, registration ID: CRD42021271467). The eligibility of identified literatures was independently determined by two authors, and the divergences in the results were resolved through discussion with the other author. All human-related studies were included if the following criteria were met: (I) case-control study; (II) the outcome was skin cancer; (III) relevant genotype data were available to calculate the odds ratios (ORs) with 95% confidence intervals (CIs). The major exclusion criteria were: (I) duplicate data; (II) review, meta-analysis or guideline; (III) case report, letter,

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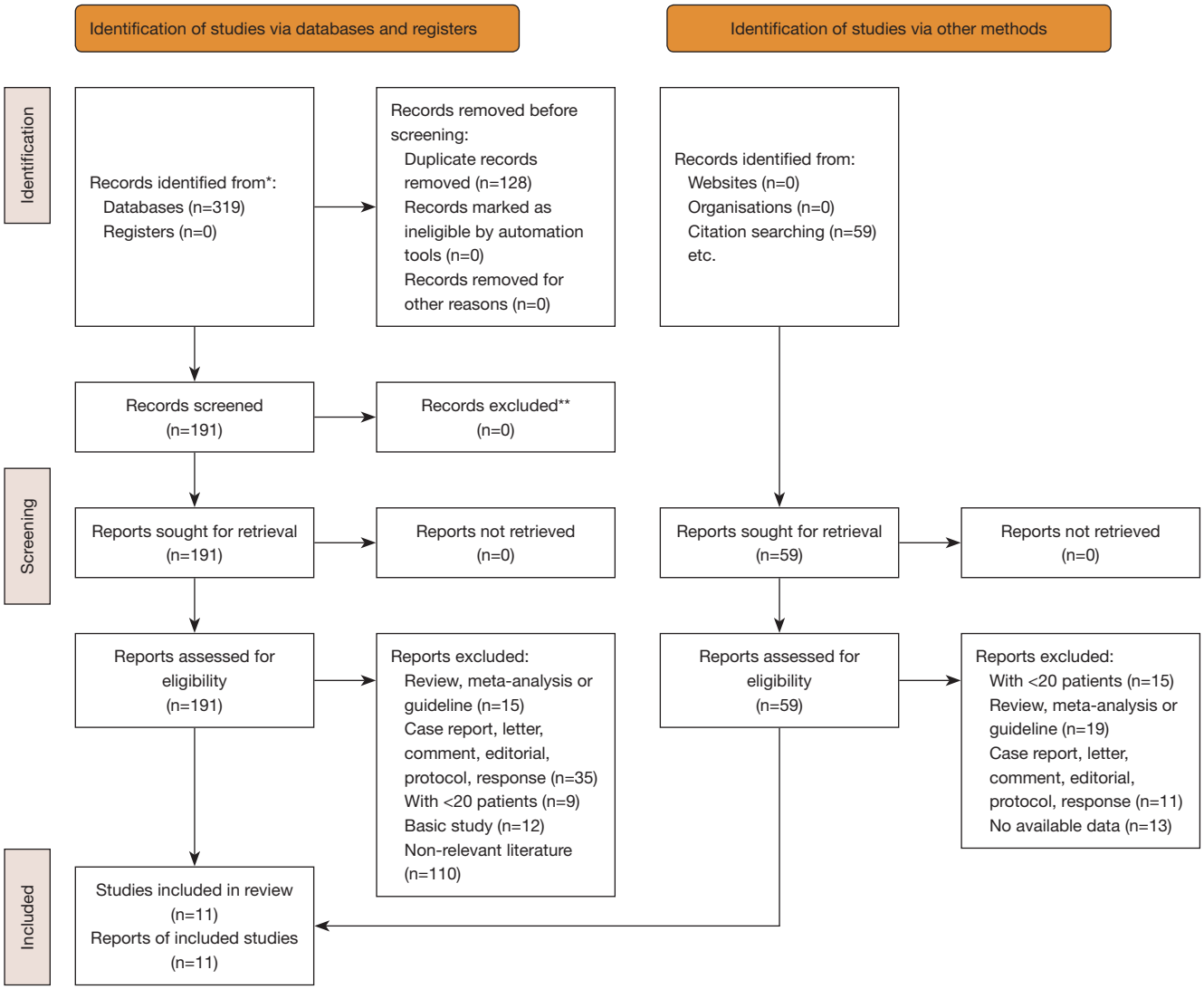

*, consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

**, if automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

From: Page MJ, McKenzie JE, Bossuyt PM, *et al.* The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

Figure 1 Flow chart of selection of studies.

comment, editorial, protocol, reply, etc.; (IV) with less than 20 patients; (V) basic research; (VI) non-relevant topic; (VII) article not in English; (VIII) no available data were reported (*Figure 1*).

Data extraction

According to the inclusion and exclusion criteria listed above, eligible data was extracted by two authors independently from every study. The authors discussed to settle the different result in data extraction. If the authors fails to reach an agreement, the third author will attend the negotiation to resolve the dispute and make the final decision through a majority vote. The following data were extracted: name of the first author, year of publication, genotyping method, region of study, cancer type, the numbers of patients and controls, and the distribution of genotypes in case and control groups.

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Table 1 Characteristics of studies included

Author	Year	Region	Cancer type	No. of patients	No. of controls	Genotype method	NOS score
Martínez-Escribano	2002	Spain	Melanoma	42	48	PCR-SSP	7
Howell	2003	UK	Melanoma	161	224	ARMS-PCR	8
Zhang	2004	Sweden	BCC	241	260	Pyrosequencing	8
Vasku	2004	Czech Republic	CTCL	63	105	PCR-RFLP	6
Nikolova	2007	Bulgaria	Melanoma	120	120	PCR-SSP	6
Wilkening	2006	Germany	BCC	529	533	TaqMan	7
Vogel	2007	Denmark	BCC	304	315	TaqMan	9
Gu	2008	USA	Melanoma	207	204	TaqMan	7
Sławińska	2019	Poland	BCC	243	198	PCR-SSP	8
Vlaykova	2020	Bulgaria	Melanoma	59	173	PCR-RFLP	8
Wang	2020	China	BCC	265	340	PCR-SSP	9

NOS, Newcastle-Ottawa scale; BCC, basal cell carcinoma; CTCL, cutaneous T-cell lymphoma; PCR-SSP, polymerase chain reaction with sequence-specific primers; ARMS-PCR, amplification refractory mutation system-polymerase chain reaction; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism.

Assessment of study quality

For the included studies, the Newcastle-Ottawa scale (NOS) was calculated for quality assessment. If the research score is 8 or 9, the research quality is considered to be high; If the study score is 6 or 7, the study is considered to be of medium quality; If the study score is <6, the study is considered to be of poor quality.

Statistical analysis

Deviation of frequencies of *IL-6* gene -174G/C and 597G/A polymorphisms from Hardy-Weinberg equilibrium (HWE) was tested by Chi-square test in cases and controls, and P<0.05 was considered as significant. ORs and 95% CI were used to measure the related strength of IL-6 174G/C and 597G/A polymorphisms and the skin cancer. The Z test determined the significance of OR, and P<0.05 was considered statistically significant. Subgroup analysis was carried out according to publication year, cancer type, sample size, and NOS score. I^2 statistic test was performed to examine the heterogeneity of the studies, and P<0.05 was considered significant. Due to the substantial heterogeneity found in the included studies, we used the random effects model to analyze the cumulative incidence rate via the package of *meta* in R version 4.0.2 (https://www.r-project.org/).

Publication bias was estimated by using funnel-plot and Egger's test. Trim-and-fill method aiming to adjust OR value was performed when publication bias was found. By using the meta package in R, sensitivity analysis was carried out through omitting each study successively.

Results

Characteristics of included studies

The flow chart of study selection is depicted in *Figure 1*. A total of 378 articles regarding *IL-6* gene 174G/C and 597G/A polymorphisms and skin cancer were recognized. One hundred and twenty-eight articles were excluded because due to duplicates, and 187 articles were excluded due to the type of publication, sample size and non-relevant topic. In addition, 5 publications were excluded due to the language other than English. Another 47 publications were excluded due to no available data. Finally, 11 studies were included in the meta-analysis (5,11-14,16-21). For each included study, we evaluated the NOS score to estimate the literature quality.

As shown in *Table 1*, 11 publications included 1,705 cases and 1,987 controls for IL-6 174G/C polymorphism (10 publications), and 968 cases and 998 controls *IL-6* gene 597G/A polymorphism (3 publications). For IL-6 174G/C polymorphism, there were 5 melanoma studies, 4 BCC

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Table 2 Main outcomes of studies included

Author	174G/C-case			P_{HWE}	174G/C-control			P_{HWE}	597G/A-case			P_{HWE}	597G/A-control			P_{HWE}
	GG	GC	CC		GG	GC	CC		GG	GA	AA		GG	GA	AA	
Martínez-Escribano	14	26	2	0.078	20	26	2	0.2	NA	NA	NA	NA	NA	NA	NA	NA
Howell	48	79	34	0.99	79	101	44	0.53	NA	NA	NA	NA	NA	NA	NA	NA
Zhang	57	126	58	0.778	62	130	68	1	59	112	70	0.567	68	123	69	0.686
Vasku	19	35	9	0.54	36	46	23	0.53	NA	NA	NA	NA	NA	NA	NA	NA
Nikolova	35	56	29	0.78	51	55	14	0.99	NA	NA	NA	NA	NA	NA	NA	NA
Wilkening	NA	NA	NA	NA	NA	NA	NA	NA	207	226	96	0.051	171	270	92	0.709
Vogel	65	176	63	0.023	89	157	69	1	NA	NA	NA	NA	NA	NA	NA	NA
Gu	69	106	32	0.706	69	102	33	0.9	28	102	68	0.58	34	100	71	0.993
Sławińska	96	91	56	0.002	93	74	31	0.052	NA	NA	NA	NA	NA	NA	NA	NA
Vlaykova	30	22	7	0.651	74	83	16	0.57	NA	NA	NA	NA	NA	NA	NA	NA
Wang	28	117	120	0.998	23	131	186	1	NA	NA	NA	NA	NA	NA	NA	NA

HWE, Hardy-Weinberg equilibrium; NA, not available.

studies, and 1 cutaneous T-cell lymphoma (CTCL) study. Meanwhile there were 1 melanoma studies and 2 BCC studies for IL-6 597G/A polymorphism. The detailed genotype distribution is listed in *Table 2*. The distributions of genotypes in the case group and control group were in accordance with the Hardy-Weinberg balance except for 2 studies (*Table 2*).

Quantitative synthesis

The assessments of the relationship of 174G/C and 597G/A polymorphisms and skin cancer risk are shown in *Figures 2*,*3*, respectively. When all eligible studies were included in analysis, no elevated risk of skin cancer was found in all genotypes for 174G/C (*Figure 2*):

CC *vs.* GC + GG, OR =1.03 (95% CI: 0.81–1.31);
GC + CC *vs.* GG, OR =1.16 (95% CI: 0.96–1.39);
CC *vs.* GG, OR =1.14 (95% CI: 0.86–1.53);
GC *vs.* GG, OR =1.16 (95% CI: 0.99–1.37);
C *vs.* G, OR =1.07 (95% CI: 0.92–1.24).

Similarly, no significant risk of skin cancer was found in all genotypes for 597G/A (*Figure 3*):

GG *vs.* GA + AA, OR =1.07 (95% CI: 0.77–1.49);
GA + GG *vs.* AA, OR =0.94 (95% CI: 0.76–1.16);
GG *vs.* AA, OR =1.01 (95% CI: 0.78–1.30);
GA *vs.* AA, OR =0.89 (95% CI: 0.71–1.12);
G *vs.* A, OR =1.03 (95% CI: 0.90–1.18).

Due to the limited number of studies for 597G/A (n=3), the following subgroup analysis, sensitivity analysis and publication bias were only evaluated for 174G/C.

Subgroup analysis

We performed subgroup analysis based on publication year, the cancer type, the subtypes of non-melanoma (BCC and CTCL), sample size and NOS score. As shown in *Table 3*, the analysis results of the subtypes of non-melanoma group were non-significant. BCC is the most common NMSC, and our result indicated there was no association between *IL-6* gene -174GC polymorphism and BCC. However, due to the limited research included in our study, this conclusion still needs to be confirmed by future research. In conclusion, none of the subgroups showed meaningful results except the subgroup of publication year before 2010 (GC + CC *vs.* GG: OR =1.255, P=0.012; GC *vs.* GG: OR =1.277, P=0.01), which is consistent with the previous meta-analysis by Wu *et al.* (15). On the contrary, there is no statistical significance in the other subgroup of publication year after 2010 (P>0.05 for all genotypes). Thus, publication date might also be one of the sources of heterogeneity.

Sensitivity analysis

As shown in *Figure 4*, for all comparisons of 174G/C

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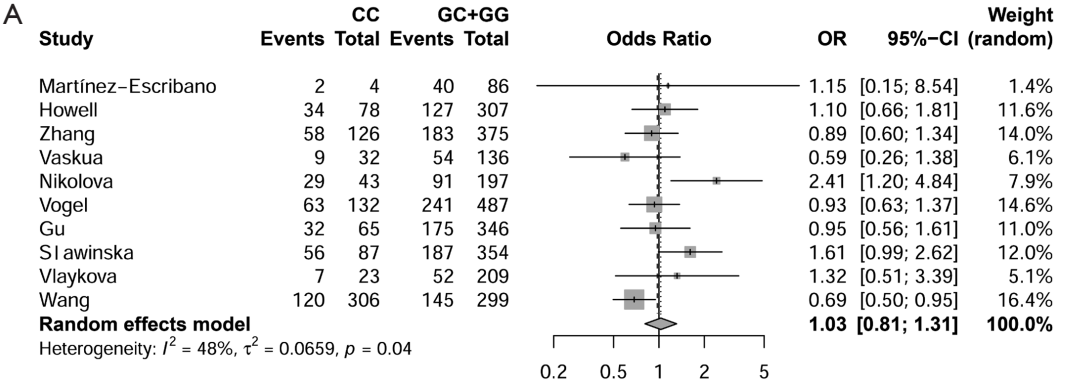
A



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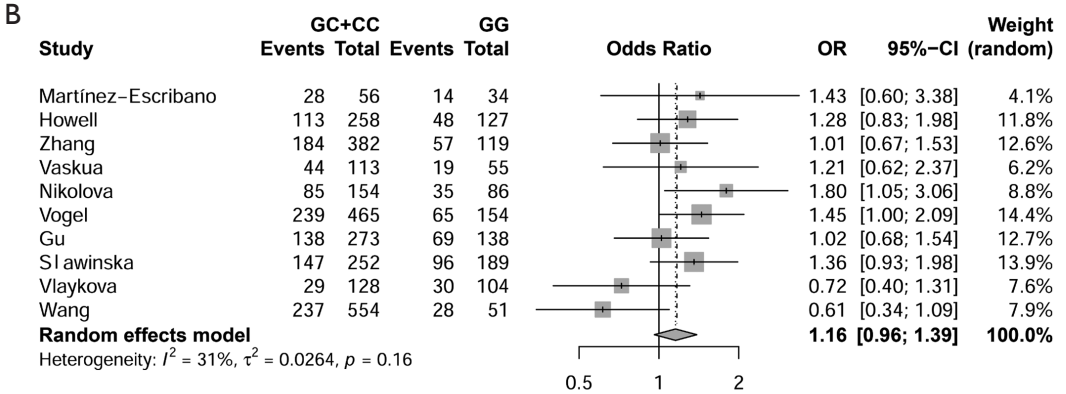

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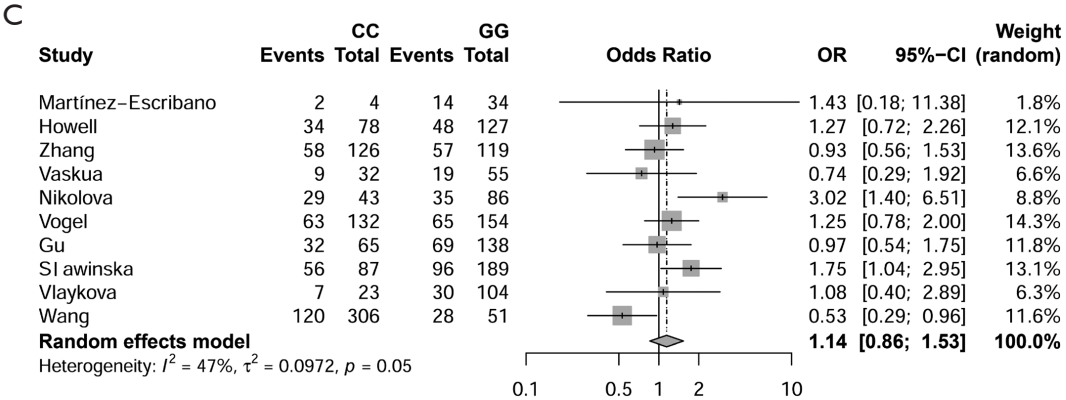

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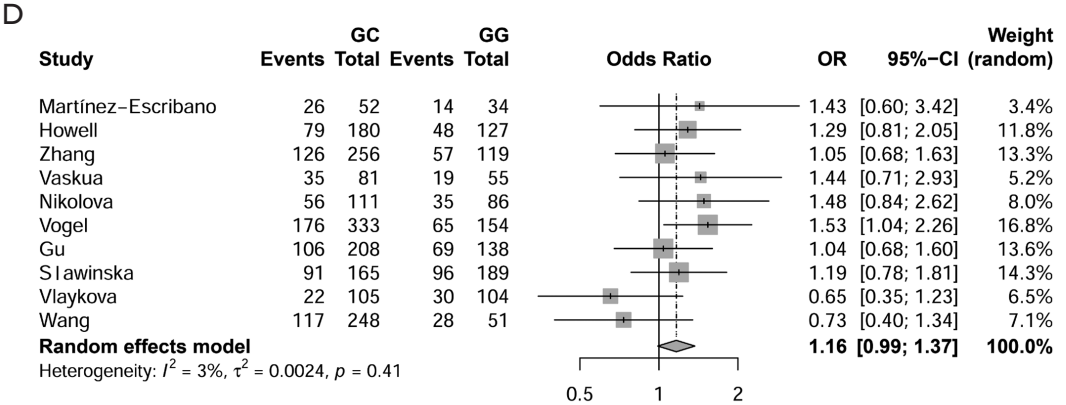

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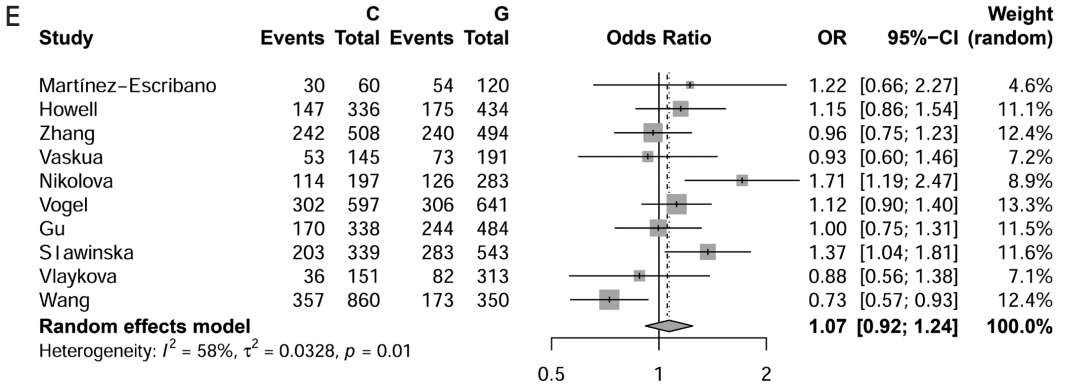
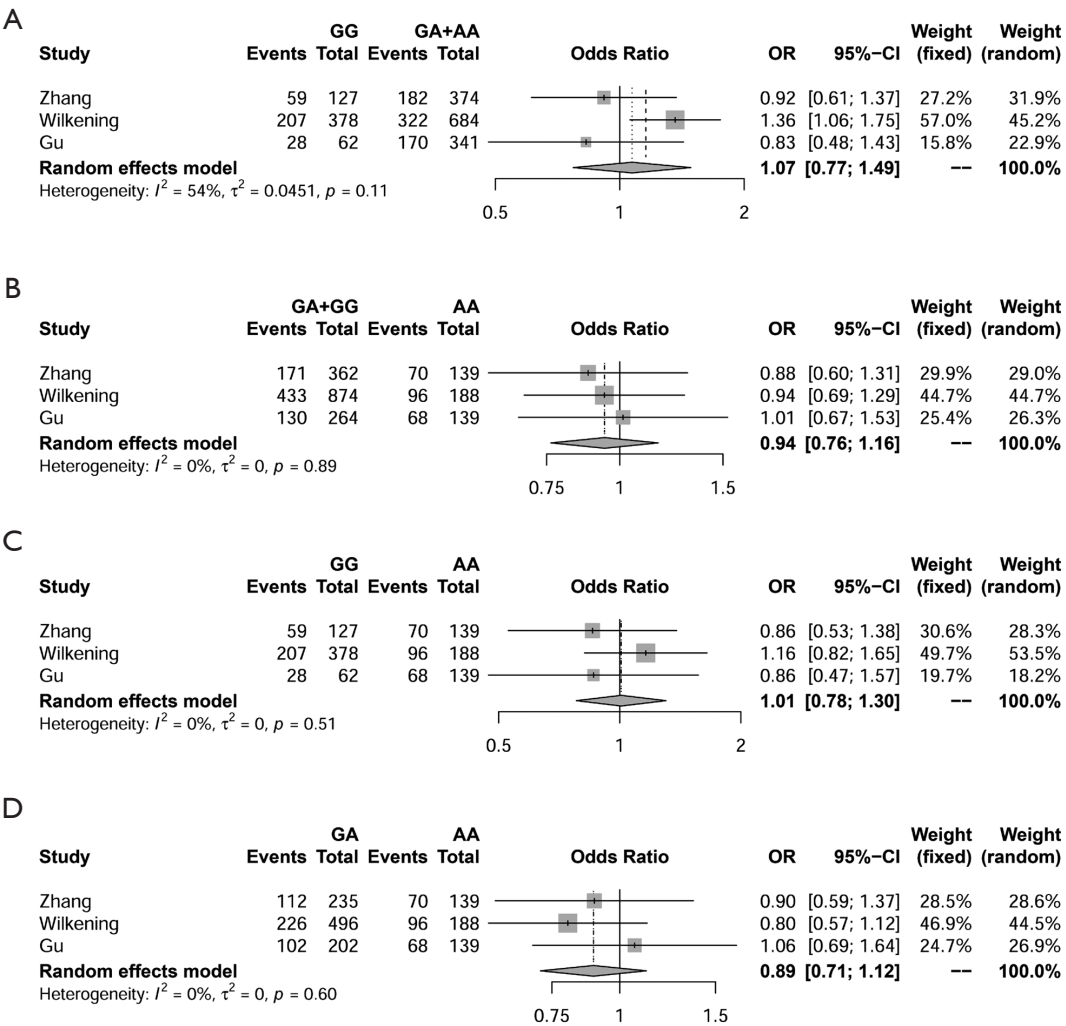


Figure 2 OR and 95% CI for the association of *IL-6* gene 174G/C polymorphism and skin cancer. (A) CC *vs.* GC + GG; (B) GC + CC *vs.* GG; (C) CC *vs.* GG; (D) GC *vs.* GG; (E) C *vs.* G. OR, odds ratio; CI, confidence interval; IL-6, interleukin-6.



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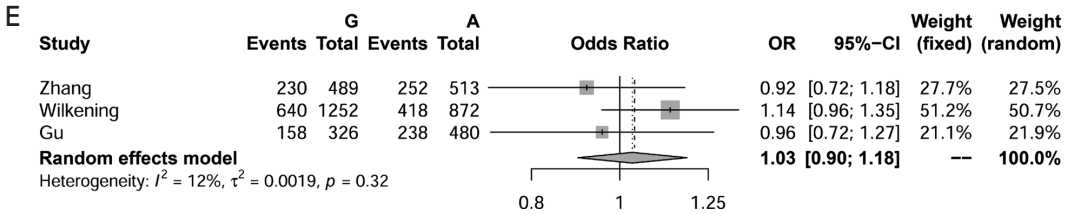

Figure 3 OR and 95% CI for the association of *IL-6* gene 597G/A polymorphism and skin cancer. (A) GG *vs.* GA + AA; (B) GA + GG *vs.* AA; (C) GG *vs.* AA; (D) GA *vs.* AA; (E) G *vs.* A. OR, odds ratio; CI, confidence interval; IL-6, interleukin-6.

Table 3 Subgroup analysis for the association of *IL-6* gene -174GC polymorphism and skin cancer

Subgroup	No. of studies	CC *vs.* GC + GG		GC + CC *vs.* GG		CC *vs.* GG		GC *vs.* GG		C *vs.* G	
		OR	P value	OR	P value	OR	P value	OR	P value	OR	P value
Total	10	1.03	0.818	1.16	0.126	1.14	0.363	1.16	0.066	1.07	0.4
Publication year											
Before 2010	7	1.02	0.875	1.255	0.012	1.198	0.221	1.277	0.01	1.109	0.135
After 2010	3	1.086	0.801	0.878	0.629	1.003	0.994	0.882	0.531	0.96	0.855
Type of cancer											
Melanoma	5	1.257	0.19	1.178	0.258	1.381	0.134	1.125	0.373	1.157	0.189
Non-melanoma	5	0.906	0.522	1.127	0.391	0.997	0.989	1.189	0.143	1.003	0.973
BCC	4	0.949	0.755	1.106	0.548	1.036	0.88	1.153	0.305	1.016	0.904
CTCL	1	0.594	0.227	1.208	0.581	0.741	0.537	1.442	0.312	0.931	0.754
Sample size											
<300	4	1.262	0.52	1.218	0.361	1.416	0.35	1.168	0.461	1.159	0.395
≥300	6	0.958	0.718	1.132	0.252	1.065	0.688	1.166	0.095	1.031	0.724
NOS score											
≤7	4	1.131	0.708	1.266	0.094	1.321	0.433	1.249	0.134	1.175	0.284
>7	6	0.982	0.893	1.082	0.539	1.082	0.635	1.1	0.435	1.021	0.826

IL-6, interleukin-6; OR, odds ratio; BCC, basal cell carcinoma; CTCL, cutaneous T-cell lymphoma; NOS, Newcastle-Ottawa scale.

genotypes, OR estimates (ranging from 1.03 to 1.16) showed well stability within the 95% confidence interval of the combined OR. The OR estimates of CC *vs.* GC + GG, GC + CC *vs.* GG, CC *vs.* GG, GC *vs.* GG, and C *vs.* G, remained stable when omitting one study at each analysis. Most estimates showed no statistically significance (P>0.05).

Publication bias

In the five comparisons of 174G/C genotypes, Egger's test did not reveal significant publication bias (P>0.05 for all). Funnel plots are shown in *Figure 5*. Slight asymmetry was found in the funnel of CC *vs.* GC + GG (*Figure 5A*). Therefore, we carried out the trim-and-fill method to evaluate the missing literatures, so as to make the OR value more reliable. After the trim-and-fill adjustment, three miss literatures were added (*Figure 5F*), and the OR value was further decreased (OR =0.855; 95% CI: 0.647–1.128; P=0.268). This further supports the conclusion that *IL-6* gene 174G/C polymorphism might not be associated with the risk of skin cancer.

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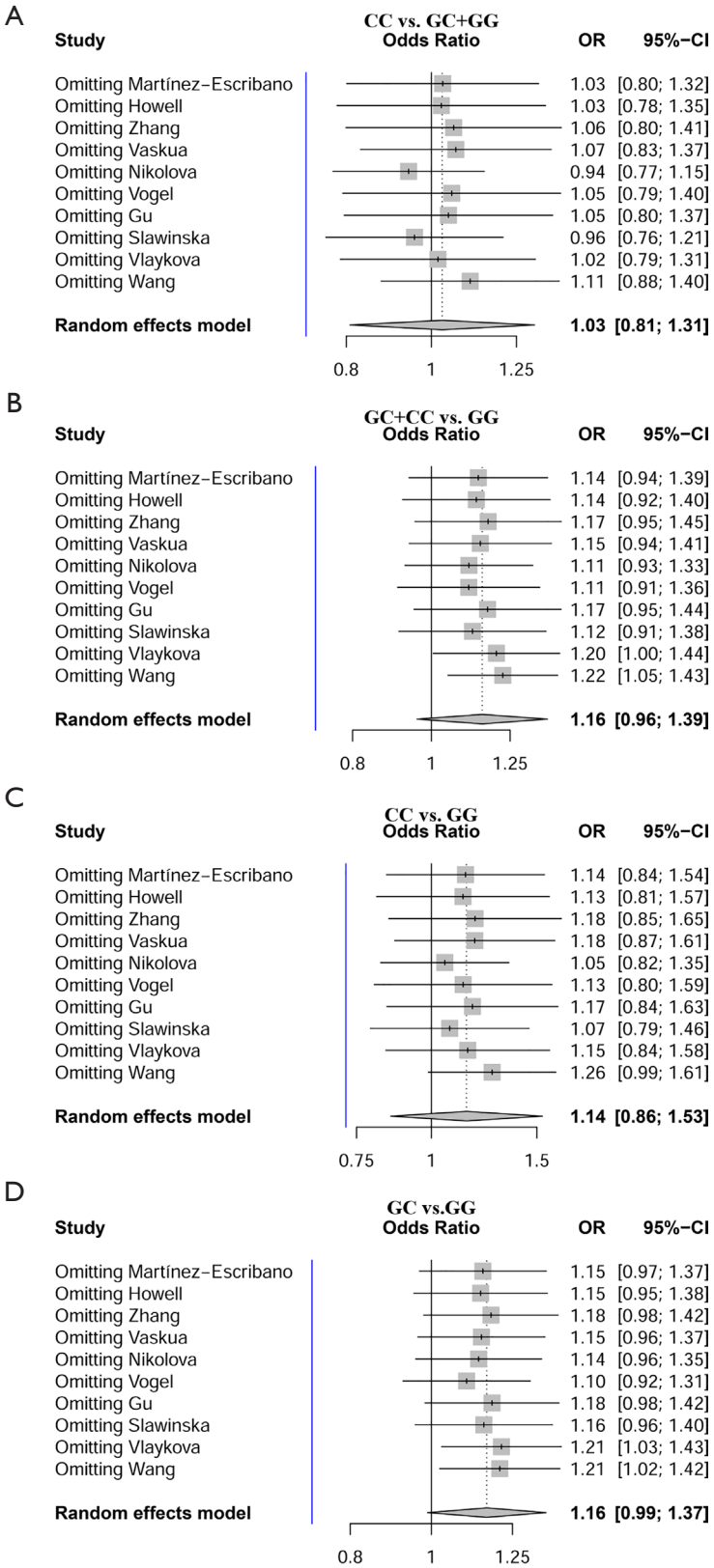

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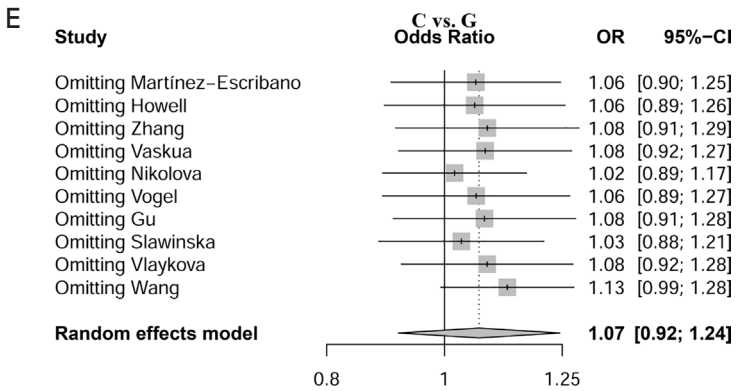

Figure 4 Sensitivity analysis for the association of *IL-6* gene 174G/C polymorphism and skin cancer. (A) CC *vs.* GC + GG; (B) GC + CC *vs.* GG; (C) CC *vs.* GG; (D) GC *vs.* GG; (E) C *vs.* G. IL-6, interleukin-6.

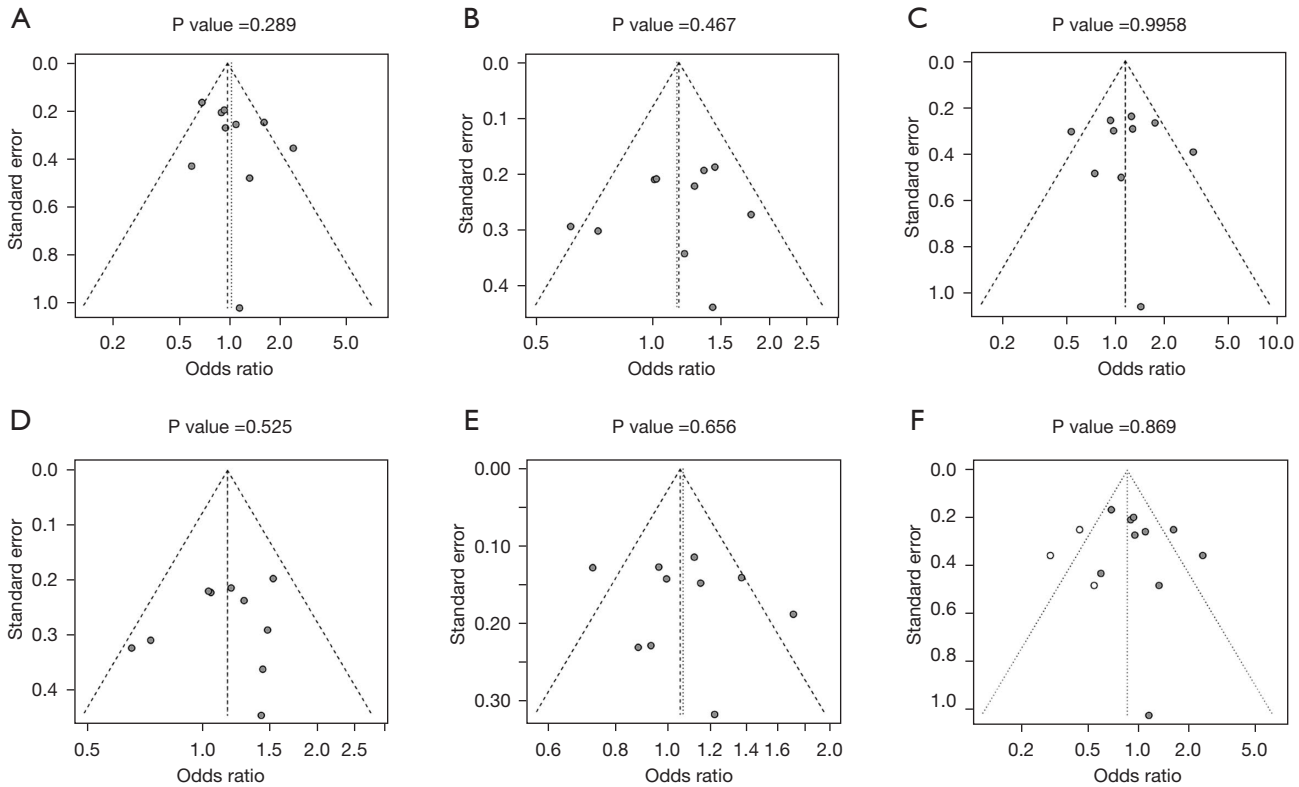

Figure 5 Funnel plots for evaluating publication bias. (A) CC *vs.* GC + GG; (B) GC + CC *vs.* GG; (C) CC *vs.* GG; (D) GC *vs.* GG; (E) C *vs.* G; (F) CC *vs.* GC + GG after adjusting publication bias.

Discussion

The incidence rate of melanoma and NMSCs has increased worldwide in recent decades. Epidemiological and experimental evidence shows that inflammation is one of the signs of skin cancer induced by solar ultraviolet radiation and several other environmental factors (3). Inflammatory cytokines play a considerable role in the initial stage of tumorigenesis, so as to influence the risk of

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cancer. IL-6 is a pleiotropic cytokine produced by multiple cell types in a variety of tissues, which has been proven to regulate the immune defense mechanism by initiating the acute phase of immune response (2,22). In addition to being an effective immunomodulator, it can also affect the growth of transformed cells (10). The polymorphism of cytokine gene regulatory region is related to the amount of cytokine produced *in vitro*, and the synthesis of IL-6 has been proved to be related to the genotype variation at position 174G/C (23-25). Gene polymorphisms can exert a pathophysiological effect role by regulating the host's immune response to skin cells. By regulating the level of gene expression as well as its function, polymorphisms of immune related genes could have direct functional significance.

Recently, increasing studies have investigated the relationship between *IL-6* gene 174G/C and 597G/A polymorphisms and skin cancer risk, yet the results remain controversial. In order to get a comprehensive conclusion, we performed this meta-analysis which include a total of 11 studies. Overall, we found that the risk of skin cancer was not related with both *IL-6* gene polymorphisms. The earlier meta-analysis by Wu *et al.* found the *IL-6* gene 174G/C might be associated with increased skin cancer risk (15), which is contradictory as compared with ours. We considered that the reasons for the different results may be due to the newly published studies. The included literatures in the meta-analysis by Wu *et al.* were before 2010 (15), and the number of literatures and patients included were less. Meanwhile, the newly included literatures in our meta-analysis were published within recent 3 years, which is far from the age of previous literatures. Therefore, the selection criteria of patients and the control of confounding factors in the literatures can be quite different. For instance, the control groups of our newly included literature were all healthy controls, but several literatures in previous years did not mention whether the source of the control was healthy individuals or patients with other diseases. On the other hand, the NOS score of the newly included literature is evaluated as high quality (8 and 9 points), while a proportion of literatures in previous years is relatively lower (<8 points). These factors may lead to the different results between ours and those previously published by Wu *et al.*

The relationship between IL-6 polymorphisms and skin cancer risk has been under debate. Zhang *et al.* supported the conclusion that *IL-6* gene 597G/A polymorphism was not related with an increased risk of skin cancer (16), meanwhile Vogel *et al.* also suggested that *IL-6* gene 174G/C polymorphism did not increase the risk of skin cancer (19). In addition, the most recent two studies by Vlaykova and Wang, respectively, both indicated that the allele G might be associated with a higher risk of skin cancer, which is to the past views the patients with allele C are at hazard of melanoma and BCC (14,21). Furthermore, when evaluating the publication bias, we used the trim-and-fill method to estimate the missing unpublished literatures. Instead, the OR value after adjustment was less than 1, indicating that there might be publication bias of the literatures in previous years. Taken together, the existing evidence suggests that there might not be significant correlation between *IL-6* gene 174G/C polymorphism and skin cancer.

597G/A is another SNP located in the promoter region of IL-6, which can regulate the immune response by regulating the level of IL-6 *in vivo* (16). There are few studies on this SNP in the past, and some studies have found 597G/A was related with an increase risk of skin cancer (16,18), while the other suggested the opposite (20). Our meta-analysis included three articles which had data on the relationship between 597G/A and skin cancer. The raw data were pooled and analyzed, but no significant association was found. The number of literatures included was relatively small, which limited the power of data analysis, thus the relationship between *IL-6* gene 597G/A and skin cancer needs to be verified by more future studies.

Despite the efforts we made to adjust for potential bias and to elucidate the relationship between *IL-6* gene 174G/C and 597G/A polymorphisms and skin cancer, several limitations existed in the study. First, current available data could not further clarify the inter-reaction between SNPs and environment based on the aggregate data. Secondly, although comprehensive literatures were searched in PubMed, Embase, Web of Science and Cochrane, which have no language restrictions, the funnel plots still suggested that there might be publication bias in terms of the association of *IL-6* gene 174G/C polymorphism and skin cancer, and the positive results were more likely to be published as compared with negative results and inconclusive results. Despite all this, we performed trim-and-fill method to reduce this type of bias and obtained more credible results. Third, the sample size is not large enough, which limits the statistical power, especially for the studies of 597G/A polymorphisms. More studies, especially large-scale prospective studies, are still required to further explore the relationship between *IL-6* gene 174G/C and 597G/A polymorphisms and skin cancer.

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Conclusions

Overall, the results in this meta-analysis showed that *IL-6* gene polymorphisms might not be associated with the risk of skin cancer. In the future, large-scale and well-designed studies are needed to further address this issue.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://dx.doi.org/10.21037/tcr-21-1508

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/tcr-21-1508). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Guo K, Lu Z, Wang X, Qiao J. Association between single nucleotide polymorphisms of IL-6 and susceptibility to skin cancer: a meta-analysis and systematic review. Transl Cancer Res 2021;10(12):5110-5122. doi: 10.21037/tcr-21-1508

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