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Original Article

Association between *MC1R* polymorphisms and skin cancer susceptibility

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Abstract: Aims: The purpose of the present study was to discuss the association between *MC1R* R151C, R160W, R163Q, V60L and V92M polymorphisms and skin cancer susceptibility. Methods: We designed a meta-analysis of 5 published case-control studies on the association between *MC1R* polymorphisms and skin cancer risk. Odds ratio (OR) and 95% confidence interval (95% CI) were adopted to express the association between *MC1R* polymorphisms and the relative risk of skin cancer. Sensitivity analysis was performed to test the stability of the results. Results: No significant association of the susceptibility to skin cancer was detected with *MC1R* R151C, R160W, R163Q, V60L or V92M polymorphism in total analysis under all genetic comparisons. However, after stratified analysis by ethnicity, *MC1R* R151C polymorphism expressed a risk increasing effect in Ashkenazi group under TT+CT versus CC contrast (OR=2.55, 95% CI=1.28-5.06); additionally, it also exerted a similar function in hospital-based group under all genetic comparisons after subgroup analysis by source of control. Moreover, *MC1R* R160W and V92M polymorphisms demonstrated a positive relationship with skin cancer susceptibility both in hospital-based group after stratification analysis by source of control. Conclusion: *MC1R* R151C, R160W and V92M polymorphisms may have an increasing effect on the susceptibility to skin cancer in specific populations, which need to be verified in the future.

Keywords: *MC1R*, skin cancer, meta-analysis, polymorphisms

Introduction

Skin cancer, one of the most common cancers in humans (especially in white populations), have severely damaged human health owing to the development of abnormal cells invading into other parts of the body [1, 2]. Over 90% of skin cancer cases are caused by exposure to ultraviolet (UV) radiation from the sun which increases the onset risk of skin cancer [3]. Recent years have seen a rising trend in the morbidity rate of skin cancer all over the world despite the improvement of medical conditions. Skin cancer can be subdivided into basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and malignant melanoma (MM) in accordance with histological types [4]. BCC and SCC are the predominant types of non-melanoma skin cancer, occurring in at least 2-3 million people annually. MM accounts for more than 5% of total cases, but it is the leading cause of death related to skin cancer [5].

Melanocortin 1 receptor (*MC1R*), a small highly polymorphic gene containing one exon with 951 coding nucleotides [6], is a major determinant of human pigmentation located on chromosome 16q24.3, and encodes for a seven-pass transmembrane, G-protein coupled-receptor of 317 amino acids [7]. *MC1R* gene is highly polymorphic, and its encoding protein is a key part involved in regulating mammalian skin and hair color [8]. MC1R protein lying within the cell membrane is signaled by melanocyte-stimulating hormone (MSH), which is released by the pituitary gland, and the MC1R expression is regulated by the microphthalmia-associated transcription factor (MITF) [9]. *MC1R* has been manifested to be a susceptibility gene to skin cancer, especially melanoma, through modulating the response of melanocytes to UV radiation [10].

Additionally, *MC1R* polymorphisms have been reported to greatly affect individual sensitivity to sunlight and tanning ability in response to UV radiation independently of the skin color [11], to be independent risk factors for the onset risks of MM and non-melanoma skin cancer, even after the adjustment for phenotypic pig-

Table 1. Principal characteristics of all studies included in this meta-analysis

First author	Year	Region	Ethnicity	Control source	Genotyping method	SNP	Case			Control			HWE
						R151C	CC	CT	TT	CC	CT	TT	
Cordoba-Lanus	2014	Canary Islands	Caucasian	Population-based	SNaPshot-Sequenom iPLEX		459	21	0	452	54	2	0.776
Guan	2013	USA	Caucasian	Hospital-based	PCR		826	249	31	928	171	7	0.773
Mossner	2007	Germany	Caucasian	Population-based	PCR		256	61	5	301	42	4	0.077
Nan	2011	USA	Caucasian	Population-based	Illumina HumanHap-Affymetrix-OpenArray		616	154	5	1676	289	13	0.888
Galore-Haskel	2009	Israel	Ashkenazi	Hospital-based	PCR		86	24		146	16		/
						R160W	CC	CT	TT	CC	CT	TT	
Cordoba-Lanus	2014	Canary Islands	Caucasian	Population-based	SNaPshot-Sequenom iPLEX		466	7	0	486	23	0	0.602
Guan	2013	USA	Caucasian	Hospital-based	PCR		891	202	13	934	161	11	0.174
Mossner	2007	Germany	Caucasian	Population-based	PCR		255	65	2	293	50	4	0.269
Galore-Haskel	2009	Israel	Ashkenazi	Hospital-based	PCR		97	13		148	14		/
						R163Q	GG	GA	AA	GG	GA	AA	
Cordoba-Lanus	2014	Canary Islands	Caucasian	Population-based	SNaPshot-Sequenom iPLEX		471	9	0	466	43	0	0.320
Mossner	2007	Germany	Caucasian	Population-based	PCR		289	31	2	308	39	0	0.267
Galore-Haskel	2009	Israel	Ashkenazi	Hospital-based	PCR		102	8		147	15		/
						V60L	GG	GT	TT	GG	GT	TT	
Cordoba-Lanus	2014	Canary Islands	Caucasian	Population-based	SNaPshot-Sequenom iPLEX		370	105	8	373	130	5	0.083
Mossner	2007	Germany	Caucasian	Population-based	PCR		254	66	2	267	77	3	0.317
Galore-Haskel	2009	Israel	Ashkenazi	Hospital-based	PCR		50	60		84	78		/
						V92M	GG	GA	AA	GG	GA	AA	
Guan	2013	USA	Caucasian	Hospital-based	PCR		886	210	10	921	173	12	0.232
Mossner	2007	Germany	Caucasian	Population-based	PCR		266	54	2	285	61	1	0.226
Galore-Haskel	2009	Israel	Ashkenazi	Hospital-based	PCR		95	15		143	19		/

Notes: PCR, polymerase chain reaction; HWE: Hardy-Weinberg equilibrium.

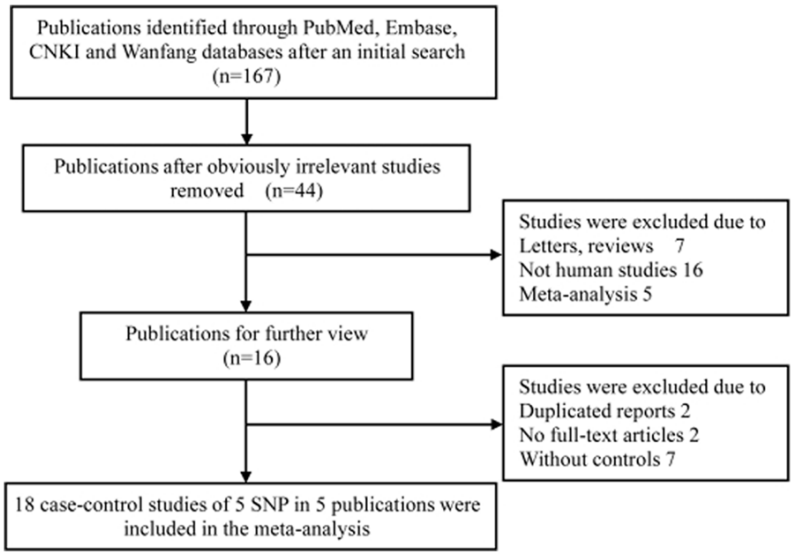

Figure 1. The flow diagram of selecting studies.

mentation features [12, 13], and to decrease eumelanin synthesis as well as the impaired protection against carcinogenic UV radiation [14]. Focusing on the association between *MC1R* polymorphisms and the susceptibility to skin cancer, these studies still got inconsistent results. Consequently, this meta-analysis was performed to comprehensively explore the association of *MC1R* R151C, R160W, R163Q, V60L and V92M polymorphisms with skin cancer susceptibility.

Materials and methods

Search strategies and literature selection

The electronic databases of PubMed, Embase, China National Knowledge Infrastructure (CNKI) and Wanfang were searched with terms "skin cancer" or "malignant melanoma" or "non-melanoma", "melanocortin 1 receptor" or "*MC1R*" or "*MSHR*" and "polymorphism" or "mutation" or "variant". All selected studies conformed to the following criteria: ① case-control studies on the association between *MC1R* polymorphisms and skin cancer risk; ② with original information; ③ sufficient data for calculating odds ratio (OR) with 95% confidence interval (95% CI); and ④ limited to Chinese and English languages.

Data extraction

The essential information were extracted from each selected study by two independent reviewers, including first author's name, year of publication, country of origin, ethnicity of study population (Caucasian or Ashkenazi), genotyping method, source of controls (hospital-based or population-based), investigated polymorphisms, total numbers of cases and controls and genotype frequencies of *MC1R* polymorphisms in cases and controls.

Statistical analysis

The strength of association between *MC1R* R151C, R160W, R163Q, V60L and V92M polymorphisms and the susceptibility to skin cancer was assessed by calculating pooled OR with 95% CI. Chi-square based Q-test was employed to examine heterogeneity across studies included in this meta-analysis, with $P<0.05$ considered to be statistically significant. Random-effects model was adopted to calculate pooled OR if $P<0.05$, or else, fixed-effects model was used for the evaluation. Sensitivity analysis was carried out through sequentially deleting each included study to observe alteration in whole results so as to detect the stability of the final results. Potential publication bias was examined by Begg's funnel plot and Egger's test in which $P<0.05$ represented significant publication bias [15, 16]. All the above analyses were conducted with STATA 12.0.

Results

Study characteristics

A total of 167 publications were identified after the initial search in the databases. 44 potentially relevant references were left after eliminating obviously irrelevant studies. Then 39 papers were removed (letters or reviews, not about human, meta-analyses, duplicated reports, without full text, and without controls) after further screening. Eventually, 18 case-control studies in 5 publications were involved into the meta-analysis [17-21]. The genotype distributions in the control group of all selected studies were in accordance with Hardy-Weinberg equilibrium (HWE) and polymerase chain reaction (PCR) was the most common

Table 2. The association between *MC1R* polymorphisms and skin cancer susceptibility

SNP	Odds ratio (95% confidence interval)/*P* value for heterogeneity									
R151C	TT vs. CC		TT+CT vs. CC		TT vs. CC+CT		T vs. C		CT vs. CC	
Caucasian	1.65 (0.56, 4.87)	0.036	1.18 (0.73, 1.90)	0.000	1.56 (0.55, 4.46)	0.045	1.16 (0.73, 1.84)	0.000	1.17 (0.74, 1.85)	0.000
Ashkenazi	/	/	2.55 (1.28, 5.06)	0.000	/	/	/	/	/	/
Population	1.05 (0.48, 2.32)	0.489	0.99 (0.47, 2.11)	0.000	0.99 (0.45, 2.18)	0.543	0.96 (0.47, 1.95)	0.000	1.01 (0.48, 2.14)	0.000
Hospital	4.98 (2.18, 11.36)	/	1.82 (1.49, 2.23)	0.319	4.53 (1.99, 10.33)	/	1.79 (1.48, 2.17)	/	1.64 (1.32, 2.03)	/
Total	1.65 (0.56, 4.87)	0.036	1.33 (0.86, 2.05)	0.000	1.56 (0.55, 4.46)	0.045	1.16 (0.73, 1.84)	0.000	1.17 (0.74, 1.85)	0.000
R160W	TT vs. CC		TT+CT vs. CC		TT vs. CC+CT		T vs. C		CT vs. CC	
Caucasian	1.07 (0.52, 2.20)	0.425	0.99 (0.56, 1.74)	0.005	1.02 (0.49, 2.09)	0.410	0.98 (0.58, 1.63)	0.008	1.00 (0.56, 1.79)	0.004
Ashkenazi	/	/	1.42 (0.64, 3.14)	0.000	/	/	/	/	/	/
Population	0.57 (0.10, 3.16)	/	0.71 (0.16, 3.09)	0.002	0.54 (0.10, 2.95)	/	0.69 (0.17, 2.73)	0.003	0.72 (0.16, 3.30)	0.001
Hospital	1.24 (0.55, 2.78)	/	1.32 (1.07, 1.63)	0.853	1.18 (0.53, 2.65)	/	1.27 (1.04, 1.56)	/	1.32 (1.05, 1.65)	/
Total	1.07 (0.52, 2.20)	0.425	1.08 (0.68, 1.70)	0.014	1.02 (0.49, 2.09)	0.410	0.98 (0.58, 1.63)	0.008	1.00 (0.56, 1.79)	0.004
R163Q	AA vs. GG		AA+GA vs. GG		AA vs. GG+GA		A vs. G		GA vs. GG	
Caucasian	5.33 (0.25, 111.45)	0.000	0.44 (0.10, 1.90)	0.001	5.42 (0.26, 113.35)	0.000	0.47 (0.11, 2.07)	0.001	0.43 (0.11, 1.73)	0.002
Ashkenazi	/	/	0.77 (0.31, 1.88)	/	/	/	/	/	/	/
Population	5.33 (0.25, 111.45)	0.000	0.44 (0.10, 1.90)	0.001	5.42 (0.26, 113.35)	0.000	0.47 (0.11, 2.07)	0.001	0.43 (0.11, 1.73)	0.002
Hospital	/	/	0.77 (0.31, 1.88)	/	/	/	/	/	/	/
Total	5.33 (0.25, 111.45)	0.000	0.53 (0.20, 1.37)	0.004	5.42 (0.26, 113.35)	0.000	0.47 (0.11, 2.07)	0.001	0.43 (0.11, 1.73)	0.002
V60L	TT vs. GG		TT+GT vs. GG		TT vs. GG+GT		T vs. G		GT vs. GG	
Caucasian	1.27 (0.50, 3.25)	0.441	0.86 (0.69, 1.08)	0.810	1.33 (0.52, 3.38)	0.426	0.90 (0.73, 1.10)	0.993	0.85 (0.67, 1.07)	0.675
Ashkenazi	/	/	1.29 (0.80, 2.10)	/	/	/	/	/	/	/
Population	1.27 (0.50, 3.25)	0.441	0.86 (0.69, 1.08)	0.810	1.33 (0.52, 3.38)	0.426	0.90 (0.73, 1.10)	0.993	0.85 (0.67, 1.07)	0.675
Hospital	/	/	1.29 (0.80, 2.10)	/	/	/	/	/	/	/
Total	1.27 (0.50, 3.25)	0.441	0.93 (0.76, 1.14)	0.325	1.33 (0.52, 3.38)	0.426	0.90 (0.73, 1.10)	0.993	0.85 (0.67, 1.07)	0.675
V92M	AA vs. GG		AA+GA vs. GG		AA vs. GG+GA		A vs. G		GA vs. GG	
Caucasian	0.96 (0.44, 2.12)	0.486	1.17 (0.97, 1.41)	0.290	0.93 (0.42, 2.05)	0.462	1.14 (0.96, 1.36)	0.405	1.18 (0.97, 1.43)	0.223
Ashkenazi	/	/	1.19 (0.58, 2.45)	/	/	/	/	/	/	/
Hospital	0.87 (0.37, 2.02)	/	1.23 (1.00, 1.52)	0.919	0.83 (0.36, 1.93)	/	1.19 (0.97, 1.45)	/	1.26 (1.01, 1.57)	/
Population	2.14 (0.19, 23.77)	/	0.97 (0.65, 1.44)	/	2.16 (0.20, 23.96)	/	0.99 (0.68, 1.44)	/	0.95 (0.63, 1.42)	/
Total	0.96 (0.44, 2.12)	0.486	1.17 (0.97, 1.41)	0.570	0.93 (0.42, 2.05)	0.462	1.14 (0.96, 1.36)	0.405	1.18 (0.97, 1.43)	0.223

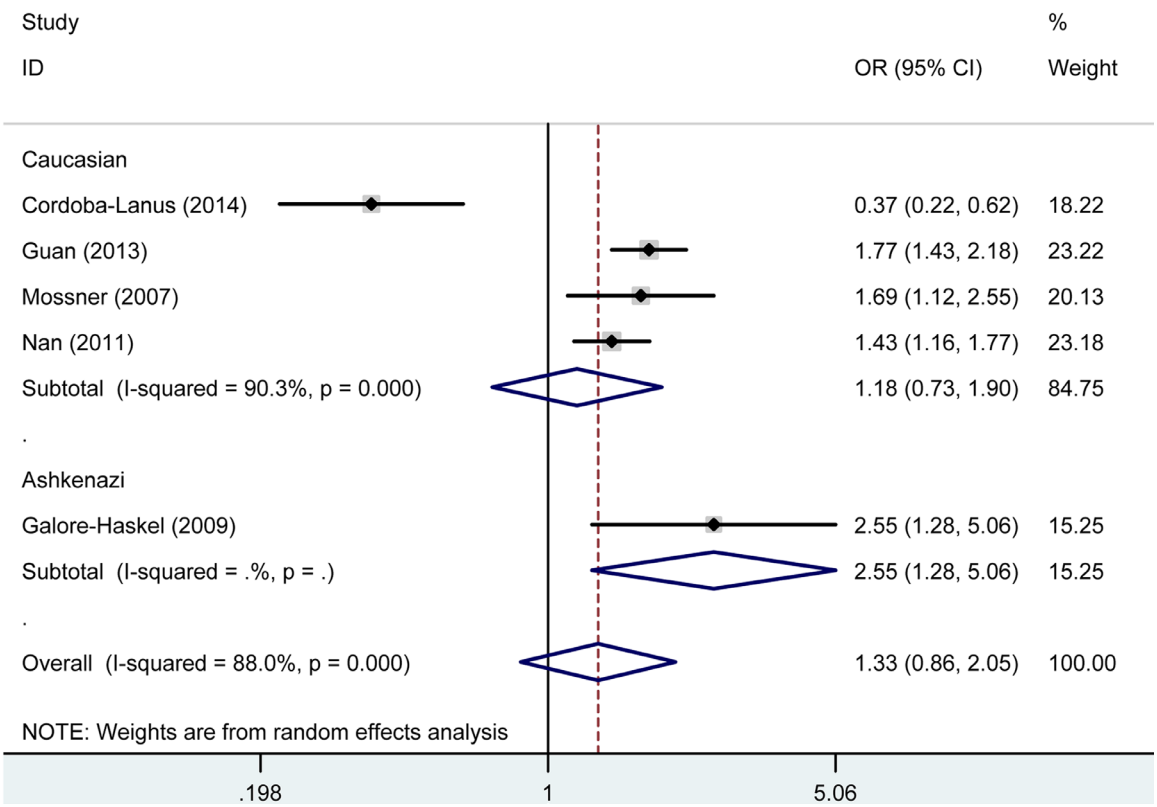

Figure 2. Forest plot of *MC1R* R151C polymorphism and skin cancer risk under TT+CT vs. CC contrast in the stratified analyses by ethnicity.

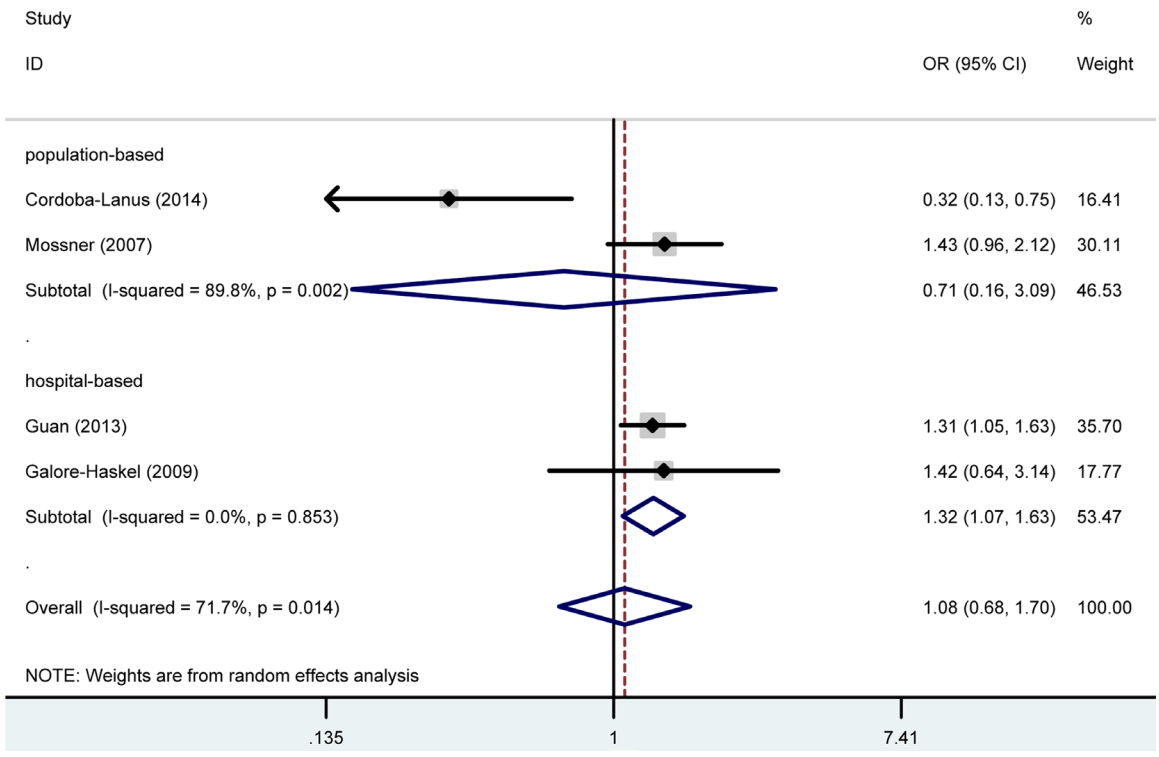

Figure 3. Forest plot of *MC1R* R160W polymorphism and skin cancer risk under TT+CT vs. CC contrast in the stratified analyses by source of control.

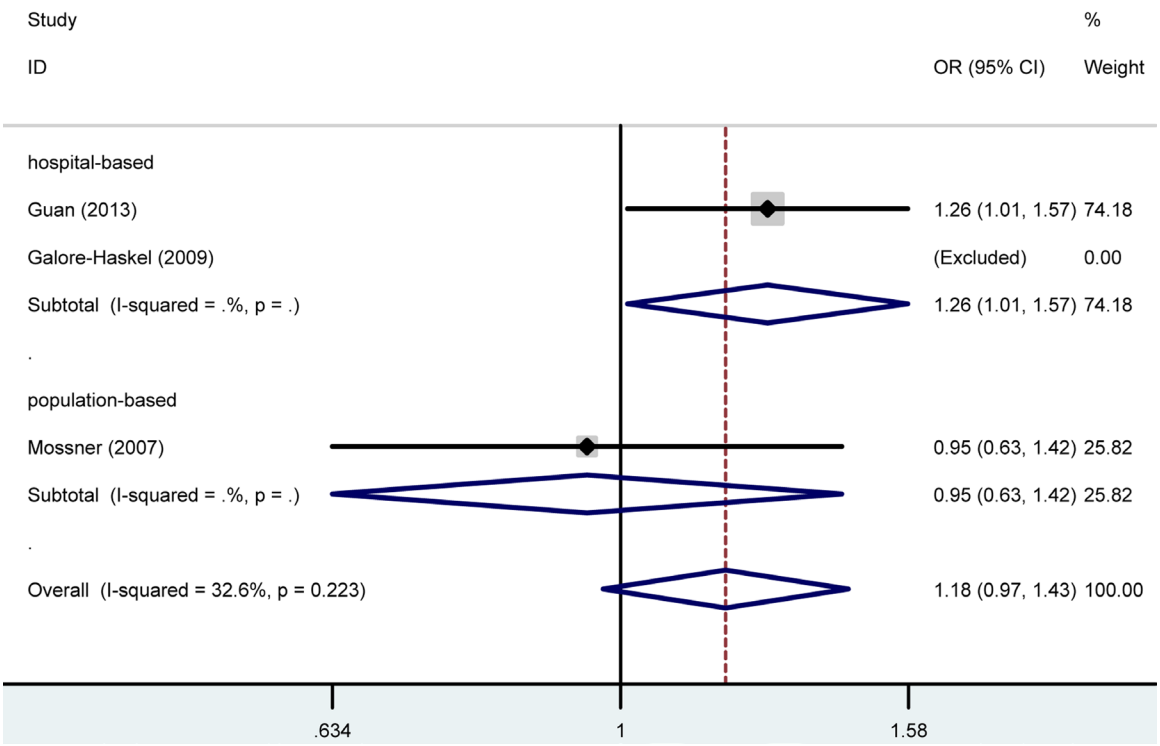

Figure 4. Forest plot of *MC1R* V92M polymorphism and skin cancer risk under GA vs. GG contrast in the stratified analyses by source of control.

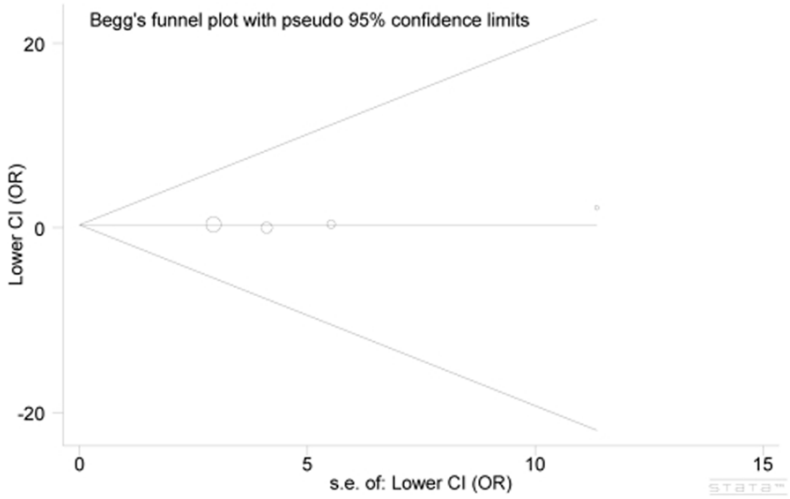

Figure 5. Begg's funnel plot of publication bias for *MC1R* R151C polymorphism under TT vs. CC contrast.

genotyping method used in these included studies. The details of enrolled study characteristics are listed in **Table 1** and the process of study selection is shown in **Figure 1**.

Meta-analysis

The main results of the present study are displayed in **Table 2**. No significant correlation was observed between *MC1R* polymorphisms and skin cancer susceptibility in all genetic models. However, after subgroup analyses by ethnicity and source of control, *MC1R* R151C polymorphism demonstrated an increasing effect on the risk of skin cancer in Ashkenazi group under TT+CT vs. CC (OR=2.55, 95% CI=1.28-5.06) (**Figure 2**) as well as in hospital-based group under TT vs. CC (OR=4.98, 95% CI=2.18-11.36), TT+CT vs. CC (OR=1.82, 95% CI=1.49-2.23), TT vs. CC+CT (OR=4.53, 95% CI=1.99-10.33), T vs. C (OR=1.79, 95% CI=1.48-2.17) and CT vs. CC (OR=1.64, 95% CI=1.32-2.03). In addition, in hospital-based group after stratification analysis by ethnicity, a similar function was also revealed for *MC1R* R160W polymorphism under TT+CT vs. CC (**Figure 3**), T vs. C and CT vs. CC comparisons as well as for *MC1R* V92M polymorphism under GA vs. GG genetic contrast (**Figure 4**).

Heterogeneity evaluation

Table 2 demonstrated significant heterogeneity for *MC1R* R151C polymorphism under all models ($P<0.05$), for the R160W polymorphism under TT+CT vs. CC, allele T vs. allele C and CT vs. CC contrasts ($P<0.05$), and for the R163Q polymorphism under all models ($P<0.05$), so the random-effects model was adopted for calculating ORs in these cases. As for under other genetic contrasts or for other polymorphisms without significant heterogeneity, the fixed-effects model was employed.

Sensitivity analysis

Due to small number of included studies, sensitivity analysis was conducted only for *MC1R* R151C and R160W polymorphisms to discuss the effect of individual study on combined results and to verify the strength of the conclusions. We excluded one single study included in the meta-analysis in turn, and pooled ORs were not substantially altered, proving that the results were relatively stable (data not shown).

Publication bias

Begg's funnel plot and Egger's test were applied to investigate publication bias across recruited studies in all models. The shape of funnel plots seemed symmetrical (**Figure 5**), indicating the absence of significant publication, which were confirmed by statistical evidence from Egger's test ($P=0.292$).

Discussion

Skin cancer, a multifactorial disease, has been considered as an important public health problem with an increasing incidence rate during the last few years, and can be classified into melanoma and non-melanoma according to epidemiology [2]. Its etiology and pathogenesis caused by the interactions of environmental and genetic factors are complex. For instance, the UV and ionizing radiations, environmental pollutants and an increasing list of chemical carcinogens resulting in DNA damage are taken as the primary causes of the development of skin cancer [2, 22]. It has been widely accepted that the exposure to UV radiation that causes multiple DNA damages is extremely important in the occurrence and progress of skin cancer [23]. Besides, genetic polymorphisms greatly influence the susceptibility to skin cancer as well. Furthermore, numerous epidemiological evidence have proved that the initiation of skin cancer may be related to variants in genes involved in DNA transcription, replication, and repair, genome stability and stem-cell differentiation [24].

MCR includes only one single exon and the encoded number of amino acids ranges from 296 (*MC2R*) to 332 (M*C4R*). *MC1R*, the major contributor to pigmentation diversity in humans, binds to a class of pituitary peptide hormone known as melanocortin, which consist of adrenocorticotropic hormone (ACTH) and varying forms of MSH, and is primarily involved in melanogenesis. *MC1R* is a cyclic adenosine monophosphate (cAMP)-stimulating G-protein-coupled receptor, and is conducive to the regulation of melanogenesis through eumelanin synthesis caused by the activation of enzyme tyrosinase [10]. The stimulation of MC1R can activate the mitogen-activated protein kinase (MAPK) pathway and regulate the target genes involved in inflammation through NF-Kb pathway [25, 26]. Mutations of *MC1R* not only can create a receptor that constantly signals but also can lower the receptor's activity when not stimulated. High MC1R activity causes increased synthesis of eumelanin, while low activity results in increased synthesis of phaeomelanin.

It has been reported that some *MC1R* missense mutations (D84E, R151C, R160W, D294H) are in association with fair skin, red hair, freckles and poor tanning ability, and those red hair color (RHC) variants increase the onset risk of MM [27]. Additionally, some *MC1R* variants have been reported to be able to increase MM risk in diverse ethnic groups [28] Guan et al. proved that *MC1R* R151C and R160W polymorphisms were associated with a significant melanoma risk in Texas population [19]. In 2007, Mossner et al. found an association between *MC1R* R151C polymorphism and increased melanoma risk in their study [20]. Similarly, a strongly positive correlation of *MC1R* R151C with BCC risk was discovered by Nan et al. in their case-control study [21]. However, no meta-analysis has been published to discuss the relation between *MC1R* polymorphisms and skin cancer susceptibility. In consequent, we designed the present study so as to provide more evidences for the comprehension of the association between them. According to

our findings, there was no significant association between any one of the five studied polymorphisms and the risk of skin cancer in total analysis, but a positive relationship was found for *MC1R* R151C, R160W and V92M polymorphisms in subgroup analyses under corresponding genetic comparisons.

The powerful method of meta-analysis conferred some strength in our findings, but it is better to be prudent when applying these results due to certain limitations in the present study. First, the most majority of included studies were performed in Caucasians, which might reduce the representativeness of the conclusion in other ethnicities. Second, language limitation in literature selection might miss some potent articles, thus contributing to the relatively small number of included studies. Third, all included case-control studies were retrospective researches, which have methodological deficiencies.

Generally speaking, no significant association existed between *MC1R* R151C, R160W, R163Q, V60L or V92M polymorphism and skin cancer susceptibility, but *MC1R* R151C, R160W and V92M polymorphisms might increase the susceptibility in specific populations. Nevertheless, in view of those limitations in this meta-analysis, better-designed studies with larger size should be carried out to provide more comprehensive perspective on this issue.

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Disclosure of conflict of interest

None.

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