RESEARCH ARTICLE

Lack of Association of Three Common Polymorphisms in Toll-like receptors (TLRs), TLR2+597T>C, +1350C>T and Arg753Gln with Cancer Risk: a Meta-analysis

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Abstract

Background: Single nucleotide polymorphisms (SNPs) occurring in Toll-like receptors (TLRs) may contribute to cancer risk. Many polymorphisms of TLR2 have been studied for associations, but the findings are conflicting. Methodology/Principal Findings: We performed a meta-analysis of 14 studies to confirm the association between TLR2+597T>C (rs3804099), +1350C>T (rs3804100) and Arg753Gln (rs5743708) polymorphisms and cancer risk. Odds ratio (OR) and 95% confidence intervals (95% CI) were used to assess the strength of associations. There was no significant association between TLR2+597T>C and cancer risk in the codominant models (CC vs. TT: OR = 1.01, 95%CI = 0.86-1.17, $P_{heterogeneity}$ = 0.148; CT vs. TT: OR = 0.92, 95%CI = 0.69-1.23, $P_{heterogeneity}$ < 0.001), the recessive model (CC vs. CT+TT: OR = 0.86, 95%CI = 0.67-1.10, $P_{heterogeneity}$ = 0.007) , the dominant model (CC+CT vs. TT: OR = 0.93, 95%CI = 0.76-1.15, $P_{heterogeneity}$ = 0.001) and the allele model (C vs. T: OR = 0.93, 95%CI = 0.81-1.08, $P_{heterogeneity}$ = 0.019). Similarly, no significant associations between TLR2+1350C>T, Arg753Gln polymorphisms and cancer risk were found. However, in the sub-group analysis of ethnicities, the trend of pooled ORs in Asians was opposite to Caucasians. Conclusions: The present meta-analysis suggests that TLR2+597T>C (rs3804099), +1350C>T (rs3804100) and Arg753Gln (rs5743708) polymorphisms are not associated with cancer risk.

Keywords: Toll-like receptor 2 - polymorphism - cancer - meta-analysis

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Introduction

Toll-like receptors (TLRs) belong to a family of transmembrane receptors which play a key role in pathogen recognition and activation of innate immunity (Akira et al., 2001). TLRs are in serving as detectors of infectious diseases and cancer by activating dendritic cells (DCs) and other antigen-presenting cells to secrete proinflammatory cytokines and promoting DCs maturation to induct adaptive immune responses (Wang et al., 2008; Kumar et al., 2009). Ionizing radiation triggers production of generic "danger" signals may also activate effectors of innate immunity through TLR dependent mechanisms, and evoke the immune response to cancer (McBride et al., 2004; Roses et al., 2008). More than ten members (TLR1-10) of the TLR family have been reported (Rock et al., 1998; Takeuchi et al., 1999; Du X et al., 2000; ChuangandUlevitch,2001). TLR2, one of the well characterized TLRs, initially implicated in the recognition of lipopolysaccharide (LPS), is located on chromosome 4q32 protein coding gene (Takeuchi et al., 1999). Many single-nucleotide polymorphisms (SNPs) of TLR2 have been reported that they may be correlated with cancer risk and progression in some genetic studies (El-Omar et al., 2008; Kutikhin,2011). TLR2+597T>C (rs3804099), +1350C>T (rs3804100), Arg753Gln (rs5743708) are three most widely studied sites.

Recently, polymorphisms of TLR2 gene have been studied for the association of cancer risk, but the findings are conflicting. For example, Gast found that no individual polymorphism of TLR2 was associated with malignant melanoma susceptibility except for the observed tendency for TLR2+597T>C, but Zeng and Junjie suggested that TLR2+597T>C was closely associated with susceptibility to gastric and hepatocellular carcinoma (Zeng et al., 2011; Junjie et al., 2012). Furthermore, Junjie and colleagues also found an obvious association between TLR2+1350C>T and hepatocellular carcinoma, while other studies yielded different or even controversial results.

To determine the correlation between TLR2+597T>C

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(rs3804099), +1350C>T (rs3804100) and Arg753Gln (rs5743708) polymorphisms and cancer risk, we performed this meta-analysis by calculating the estimate of overall cancer risk to get a robust conclusion to increase the power of association between these polymorphisms and cancer susceptibility.

Materials and Methods

Search Strategy

A systematic literature searching was performed on PubMed, EMBASE and CNKI (Chinese National Knowledge Infrastructure) up to the end of February, 2013. The search strategy was based on combinations of ''Toll-like receptor 2'' or ''TLR2''; "polymorphism", "variant" or "genotype"; "cancer", "tumor", "malignance" or "neoplasm". The results were supplemented with manual searches of references of the final published articles. Review articles, editorials and conference abstracts were excluded.

Inclusion and exclusion criteria

The major inclusion criteria were (a) case–control studies; (b) tested for TLR2+597T>C (rs3804099), +1350C>T (rs3804100) and Arg753Gln (rs5743708) polymorphisms and cancer risk; (c) genotype frequency was available in cases and controls. The major reasons for exclusion of studies were (a) overlapping data; (b) case-only studies. Two reviewers (Yang and Wang) extracted eligible studies independently according to the inclusion criteria. Disagreement between two reviewers was discussed with another reviewer (Qiu) till consensus was achieved.

Data Extraction

For each study, two reviewers (Yang and Wang) independently extracted the following data: name of first author, year of publication, ethnicity, cancer type, control source, genotyping method and numbers of cases and controls with the various genotypes in TLR2 gene, calculated and summarized in the Table 1. Eligible studies were defined as hospital-based (HB) and population-based (PB) according to the control source. Every eligible study was performed on Hardy-Weinberg equilibrium (HWE) test in the controls through an online program (http://ihg.gsf.de/cgi-bin/hw/hwa1.p) (Qiu et al., 2012).

Statistical Analysis

Odds ratio (OR) with 95% confidence intervals (CIs) was used to assess the strength of association between the TLR2 gene polymorphisms and cancer risk. A 95% CI was used for statistical significance test and it without 1 for OR indicating a significantly increased or reduced cancer risk. We evaluated the risk of the codominant models, the dominant models, the recessive models and the allele models of TLR2 gene polymorphisms respectively. Hardy–Weinberg equilibrium (HWE) among controls subjects was tested by the Chi-square test and a $P<0.05$ was considered as significant disequilibrium. Sensitivity analyses were performed to identify individual study' effect on pooled results and test the reliability of results.

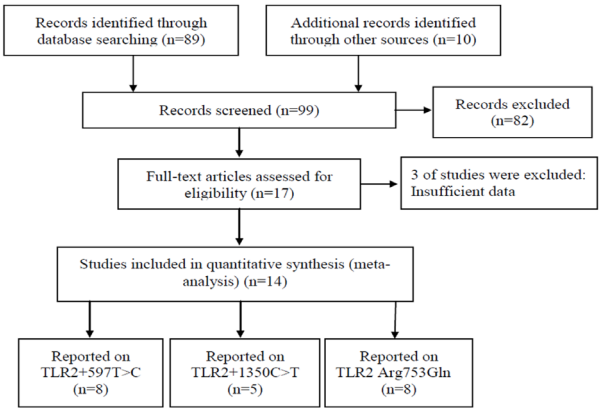

Figure 1. The Flow Chart of the Included Studies for a Meta-analysis of TLR2 Polymorphisms and Cancer Risk

The heterogeneity between these studies was checked using Chi-square based Q test and it was considered statistically significant when P-value was less than 0.10. The quantity I^2 presented variation in OR attributable to heterogeneity. Fixed-effects models were adopted when $P_{heterogeneity}$ was more than 0.10, while random-effects models were more appropriate when $P_{heterogeneity}$ was less than 0.10 (Tian et al., 2012). Publication bias was assessed using Egger's test and Begg's funnel plots, and the statistical significance was defined as $P<0.05$ (BeggandMazumdar,1994; Egger et al., 1997). All P values are two-sided. Statistical analyses were done with Stata (version 12.1; Stata Corp, College Station, Texas USA).

Results

Characteristics of Studies

As shown in Figure 1, a total of 14 studies were finally identified (Nieters et al., 2006; Etokebe et al., 2009; Purdue et al., 2009; Ashton et al., 2010; Balistreri et al., 2010; Gast et al., 2011; Zeng et al., 2011; Junjie et al., 2012; Kim et al., 2012; Nischalke et al., 2012; Slattery et al., 2012; Yang et al., 2012; Pimentel-Nunes et al., 2013). For the +597T>C polymorphism (rs3804099), 8 studies were available, including a total of 3987 cases and 5079 controls. For the +1350C>T polymorphism (rs3804100), 5 studies were available, including a total of 3179 cases and 3188 controls. For the Arg753Gln polymorphism (rs5743708), 8 studies involved a total of 4416 cases and 5370 controls. The detailed characteristics of the studies included in this meta-analysis such as first author, publication year, ethnicity, cancer type, control source, genotyping method and numbers of various genotypes in both cases and controls were shown in Table 1. All studies were consistent with Hardy–Weinberg equilibrium ($P > 0.05$).

Meta-analysis results

The meta-analysis results of the association between TLR2+597T>C (rs3804099), +1350C>T (rs3804100) and Arg753Gln (rs5743708) polymorphisms and cancer risk were shown in Table 2. There was no significant association between TLR2+597T>C and cancer risk in

Table 1. Characteristics of Eligible Studies

Study	Year	Ethnicity	Cancer type	Control source	Genotyping method	No. of case/control	TLR2 polymorphism
Nieters	2006	Caucasian	Lymphoma	HB	PCR-RFLP	678/669	Arg753Gln
Etokebe	2009	Caucasian	Breast cancer	PB	TaqMan	130/101	+597T>C +1350C>T
Purdue	2009	Caucasian	Non-Hodgkin lymphoma	PB	GoldenGate chemistry	1942/1798	+1350C>T
Balistreri	2010	Caucasian	Prostate cancer	PB	PCR-RFLP	50/125	Arg753Gln
Ashton	2010	Caucasian	Endometrial cancer	PB	PCR-RFLP	191/291	Arg753Gln
Gast	2011	Caucasian	Malignant melanoma	PB	Sequencing	763/736	+597T>C +1350C>T Arg753Gln
Zeng	2011	Asian	Gastric cancer	HB	PCR-RFLP	248/496	+597T>C
Yang	2012	Asian	Nasopharyngeal carcinoma	PB	PCR-RFLP	236/287	Arg753Gln
Nischalke	2012	Caucasian	Hepatocellular cancer	PB	PCR-RFLP	189/347	Arg753Gln
Kim	2012	Asian	Thyroid cancer	PB	Sequencing	133/321	+597T>C +1350C>T
Junjie	2012	Asian	Hepatocellular carcinoma	HB	SNaPshot	211/232	+597T>C +1350C>T
Slattery	2012	Caucasian	Colon cancer	PB	GoldenGate chemistry	1555/1956	+597T>C Arg753Gln
Slattery	2012	Caucasian	Rectal cancer	PB	GoldenGate chemistry	754/959	+597T>C Arg753Gln
Pedro*	2013	Caucasian	Colorectal cancer	HB	TaqMan	193/278	+597T>C

PB, population-based; HB: hospital-based; *The Pedro's paper only provided the data of recessive model (CC vs. CT+TT)

Table 2. Meta-analysis Results

Statistical models	Genotype/Allele	OR	95%CI	I^2%	$P_{heterogeneity}$	$P_{Egger's}$	Analysis model
TLR2+597T>C							
Allele Model	C vs. T	0.93	0.81-1.08	63.00%	0.019	0.324	R
Codominant model	CC vs. TT	1.01	0.86-1.17	38.70%	0.148	0.396	F
	CT vs. TT	0.92	0.69-1.23	80.00%	<0.001	0.199	R
Recessive model	CC vs. CT+TT	0.86	0.67-1.10	63.70%	0.007	0.411	R
Dominant model	CC+CT vs. TT	0.93	0.76-1.15	73.10%	0.001	0.17	R
TLR2+1350C>T							
Allele Model	T vs. C	1	0.88-1.13	28.40%	0.233	0.757	F
Codominant model	TT vs. CC	0.89	0.57-1.41	0.00%	0.619	0.755	F
	TC vs. CC	0.97	0.72-1.32	69.70%	0.01	0.89	R
Recessive model	TT vs. TC+CC	0.92	0.59-1.43	12.90%	0.328	0.79	F
Dominant model	TT+TC vs. CC	0.96	0.74-1.25	60.80%	0.037	0.781	R
TLR2 Arg753Gln							
Allele Model	G vs. A	1.07	0.86-1.35	0.00%	0.721	0.957	F
Dominant model	GG+GA vs. AA	1	0.84-1.19	0.00%	0.469	0.163	F

R, Random-effect models; F, Fixed-effect models

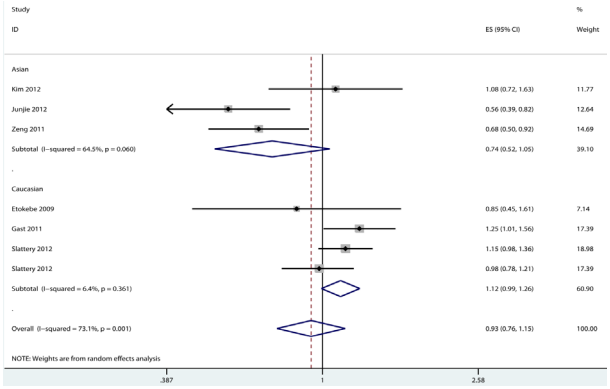

Figure 2. Forest Plots for the Association Between TLR2+597T>C Polymorphism and Cancer Risk for Dominant Models

the codominant models (CC vs. TT: OR = 1.01, 95%CI = 0.86-1.17, $P_{heterogeneity}$ = 0.148; CT vs. TT: OR = 0.92, 95%CI = 0.69-1.23, $P_{heterogeneity}$ <0.001), the recessive model (CC vs. CT+TT: OR = 0.86, 95%CI = 0.67-1.10, $P_{heterogeneity}$ = 0.007) , the dominant model (CC+CT vs. TT: OR = 0.93, 95%CI = 0.76-1.15, $P_{heterogeneity}$ = 0.001, Figure 2) and the allele model (C vs. T: OR = 0.93, 95%CI = 0.81-1.08, $P_{heterogeneity}$ = 0.019). We still did not found any significant association between TLR2+1350C>T and cancer risk in the codominant models (TT vs. CC: OR = 0.89, 95%CI =0.57-1.41 , $P_{heterogeneity}$ = 0.619; TC vs. CC: OR = 0.97, 95%CI = 0.72-1.32, $P_{heterogeneity}$ = 0.01), the recessive model (TT vs. TC+CC: OR = 0.92, 95%CI = 0.59-1.43, $P_{heterogeneity}$ = 0.328) , the dominant model (TT+TC vs. CC: OR = 0.96, 95%CI = 0.74-1.25, $P_{heterogeneity}$ = 0.037, Figure 3) and the allele model (T vs. C: OR = 1.00, 95%CI = 0.88-1.13, $P_{heterogeneity}$ = 0.233). As for the association of TLR2 Arg753Gln polymorphism and cancer risk, the number of homozygote mutant alleles GG was too small. Therefore we only studied the dominant model and the allele model of TLR2 Arg753Gln polymorphism. No significant association between TLR2 Arg753Gln

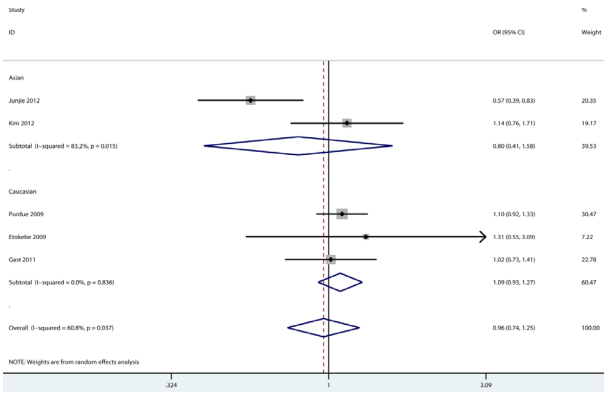

Figure 3. Forest Plots for the Association Between TLR2+1350C>T Polymorphism and Cancer Risk for Dominant Models

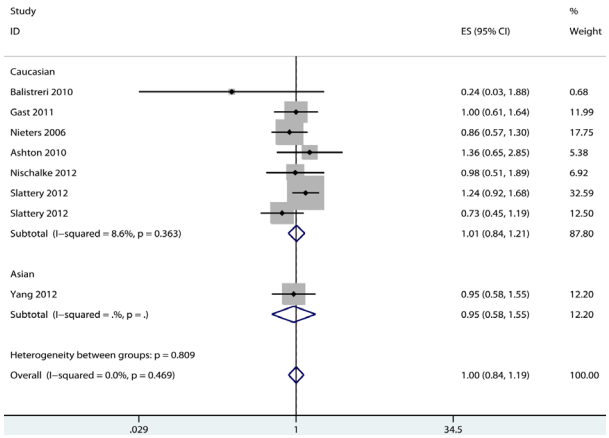

Figure 4. Forest Plots for the Association Between TLR2 Arg753Gln Polymorphism and Cancer Risk for Dominant Models

polymorphism and cancer risk was found in the dominant model (GG+GA vs. AA: OR = 1.00, 95%CI = 0.84-1.19, $P_{heterogeneity}$ = 0.469, Figure 4) and the allele model (G vs. A: OR = 1.07, 95%CI = 0.86-1.35, $P_{heterogeneity}$ = 0.721). When stratified by ethnicity, we still found no significant association of cancer risk in four models of these three polymorphisms among Asians and Caucasians.

Evaluation of Heterogeneity, Sensitivity Analyses and Publication Bias

As shown in Table 2, the results of heterogeneity evaluation and statistical models were performed on each genetic model. We adopted random-effects model when existed significant heterogeneity, or we adopted fixed-effects models. Sensitivity analysis was performed to assess the influence of each individual study on the pooled OR by deleting one single study each time. Begg's funnel plot and Egger's test were performed to assess publication bias. Begg's funnel plot was roughly symmetrical in all genetic models (The results of the dominant model were shown in Figure 5). The results still did not show significant publication bias by Egger's test (Table 2).

Discussion

TLRs play a key role in the realization of innate and adaptive immune response though directly recognizing antigen determinants of viruses, bacteria, protozoa,

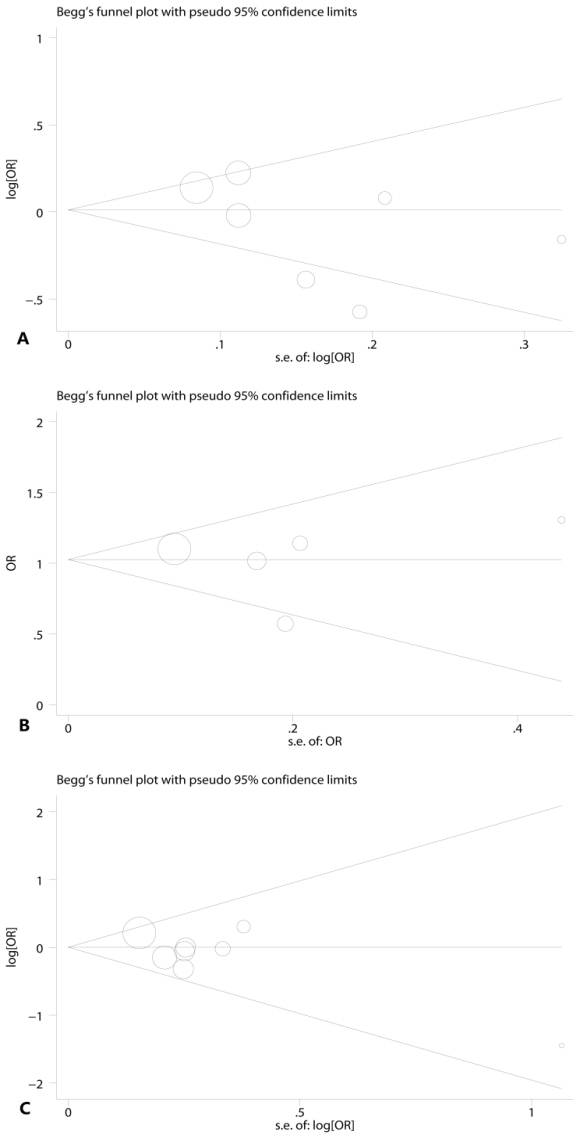

Figure 5. A: Funnel plots for the association between TLR2+597T>C polymorphism and cancer risk for dominant models. B: Funnel plots for the association between TLR2+1350C>T polymorphism and cancer risk for dominant models. C: Funnel plots for the association between TLR2 Arg753Gln polymorphism and cancer risk for dominant models

and fungi (Kutikhin, 2011). Recently, many studies have investigated the association between TLRs polymorphisms and cancer risk (Zhou et al., 2006; He et al., 2007; Purdue et al., 2009; Ng et al., 2010; Monroy et al., 2011), but the results were inconclusive. Different from the similar meta-analysis in Neoplasma (Wang et al., 2013), the Delta22 polymorphism (-196 to 174 del) was not analyzed in our manuscript. There were many studies reported the association between Delta22 polymorphism and cancer risk and we also performed a meta-analysis on Delta22 inspired by the meta-analysis in Neoplasma. However, we found a significant publication bias by Begg's funnel plots and sensitivity analysis suggested that the study by Theodoropoulos et al. (2012) significantly affect the pooled results (data not shown). In addition, for the +1350C>T polymorphism (rs3804100), we excluded a study of acute lymphoblastic leukemia (ALL), and added another one of thyroid cancer (Kim et

al., 2012). The reason was that ALL did not belong to solid tumors. Furthermore, for the +597T>C polymorphism (rs3804099), we updated two new studies (Kim et al., 2012; Slattery et al., 2012), and no significant association was found in Asians or Caucasians.

TLRs activation may act as a double-edge sword. There is a hypothesis that many immunoadjuvants can stimulate antitumor immunity by reinforcing TLRs activation, so enhanced TLRs activation can inhibit carcinogenesis (OkamotoandSato, 2003; Killeen et al., 2006). The antitumor immune system is able to recognize and eliminate tumor cells. However, another hypothesis suggests that TLRs activation may also result in immunosuppression caused by chronic inflammation which may contribute to cancer susceptibility and progression (Tsan, 2006; Chen et al., 2007). Therefore, a critical value may mediate the balance between low and high TLR activity. SNPs may affect TLRs activity through altering transcription factor binding sites and mRNA stability (TierneyandMedcalf, 2001; Thomas et al., 2006). However, the mechanism between SNPs and TLRs activity is still uncertain. Studies on the associations between TLRs polymorphisms and cancer have provided new insights into the molecular mechanisms of cancer development. Under the consideration of the above theories, the association between TLR2 gene polymorphisms and cancer risk was worthy of further studying.

Finally, 14 studies about TLR2 gene polymorphisms and cancer risk conforming to inclusion criteria were recruited into this meta-analysis. According to the pooled ORs, insignificant associations were found in allele models, codominant, dominant and recessive models between TLR2+597T>C (rs3804099), +1350C>T (rs3804100) and Arg753Gln (rs5743708) polymorphisms and cancer risk. However, in the sub-group analysis of ethnicity, we had an interesting founding that the trend of pooled ORs in Asians was opposite to Caucasians. TLR2+597T>C polymorphism appeared to be related to decreased cancer risk in Asians, while it may contribute to increased cancer risk in Caucasians. Similar results were found in the association between TLR2+1350C>T polymorphism and cancer risk. Although the trend was no statistically significant, it was still merit attention. There are some feasible explanations for lack of the functional association of TLR2 polymorphisms and the contrary trend based on ethnicities. Firstly, the number of publications on TLR2 polymorphisms and cancer risk is small, and most of them are also small sample size (<1000 participants). Studies of small sample size may contribute to a small-study effect, in which effects reported are larger, and lead to between studies variance. Secondly, these contradictory results may derive from different experimental designs and methods, which call for further investigation. Thirdly, the above mentioned critical value which mediated the balance between low and high TLR activity was different in Asians and Caucasians, but results from current researches were insufficient to support this view.

In addition, there are some limitations should be considered in this meta-analysis. Firstly, our meta-analysis only recruited 14 publications, while covered 11 cancers (breast, melanoma, gastric, thyroid, hepatocellular, colon, rectal, prostate, endometrial, nasopharyngeal and lymphoma). Thus, it is difficult to perform a subgroup analysis stratified by cancer types. Stratified analysis according to cancer types will be available till more studies are published. Secondly, individual data was not available and a more precise analysis should be conducted on other covariates such as age, sex, and environmental exposure. Thirdly, there were actually few individuals with the homologous genotypes of minor alleles in Arg753Gln polymorphism. Fourthly, the number of large sample size studies (> 1000 participants) was too small.

In conclusion, we got a comprehensive result from this meta-analysis that TLR2+597T>C (rs3804099), +1350C>T (rs3804100) and Arg753Gln (rs5743708) polymorphisms may not be associated with cancer risk. More well-designed studies with larger sample size should be considered to further clarify the association.

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