# -196 to -174del, rs4696480, rs3804099 polymorphisms of Toll-like receptor 2 gene impact the susceptibility of cancers: evidence from 37053 subjects 

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#### Abstract

Relationship between Toll-like receptor-2 (TLR2) and cancer risk has been illustrated in some studies, but their conclusions are inconsistent. Therefore, we designed this meta-analysis to explore a more accurate conclusion of whether TLR2 affects cancer risks. Articles were retrieved from various literature databases according to the criteria. We used STATA to calculate the odds ratio $(\mathrm{OR})$ and $95 \%$ confidence interval $(95 \% \mathrm{Cl})$ to evaluate the relationship between certain polymorphism of TLR2 and cancer risk. Finally, 47 case-control studies met the criteria, comprising 15851 cases and 21182 controls. In the overall analysis, people are more likely to get cancer because of -196 to -174 del in $T L R 2$ in all five genetic models, $B$ vs. $\mathrm{A}(\mathrm{OR}=1.468,95 \% \mathrm{Cl}=1.129-1.91, \mathrm{P}=0.005)$; BB vs. $\mathrm{AA}(\mathrm{OR}=1.716,95 \% \mathrm{Cl}=$ $1.178-2.5, P=0.005)$; $B A$ vs. $A A(O R=1.408,95 \% \mathrm{Cl}=1.092-1.816, P=0.008) ; B B+B A$ vs. $\mathrm{AA}(\mathrm{OR}=1.449,95 \% \mathrm{Cl}=1.107-1.897, P=0.007)$; BB vs. $\mathrm{BA}+\mathrm{AA}(\mathrm{OR}=1.517,95 \%$ $\mathrm{Cl}=1.092-2.107, P=0.013$ ). Meanwhile, rs4696480 could significantly increase the risk of cancer in Caucasians, furthermore, rs3804099 significantly decreased cancer risk in overall analysis, but more subjects are necessary to confirm the results. All in all, this meta-analysis revealed that not only -196 to -174 del increased the risk of among overall cancers, Caucasians are more likely to get cancer because of rs4696480, while rs3804099 polymorphism could reduce the risk of cancer in some genetic models. There is no direct evidence showing that rs5743708, rs3804100 and rs1898830 are related to cancer. culate the odds ratio (OR) and 95\% confidence interval ( $95 \% \mathrm{Cl}$ ) to evaluate the relationship between certain polymorphism of $T L R 2$ and cancer risk. Finally, 47 case-control studies


## Introduction

Cancer prevalence increases rapidly and becomes a major threat to human health in today's world. As we all know, genes are inextricably linked to the development of cancer. In many cancer studies, such as gastric cancer [1], colorectal cancer, breast cancer [2], cervical cancer [3], Toll-like receptor (TLR)-2 (TLR2) has been determined as a pathogenic factor involved in tumorigenesis. The TLR2 gene located on human chromosome 4 q 32 , includes one coding exon and two non-coding exons [4]. TLRs are mainly expressed in immune-related cells and immune-related epithelial cells, their role in tissue resistance to microbes is achieved by identifying conserved bacterial molecules [5]. Therefore some researchers believe that TLR2 play a significant role in the innate immune response through releasing pro-inflammatory cytokines [6].

- 196 to -174 del is a 22 -bp deletion in TLR2 gene, which has been shown to cause a decrease in the transcriptional activity of the TLR2 gene [7]. However, in the past few years, there are inconsistent conclusions about the relationship between -196 to -174 del and cancer risk. One paper noted that -196 to -174 del in



Figure 1. Flowchart of enrolled studies selection procedure
association with Helicobacter pylori significantly increased the risk of gastric cancer in patients [1]. But Hishida et al. [8] suggested that -196 to -174 del had no relationship with gastric cancer. About reproductive tumors, some literatures suggested that -196 to -174 del is not associated with breast cancer [9] and cervical cancer [3], but on the contrary, Theodoropoulos et al. [10] think that -196 to -174del may produce a significant increase in the risk of breast cancer. Mandal et al. [11] revealed that -196 to - 174del polymorphism in TLR2 gene seems to be associated with the upgraded prostate cancer risk, while Singh et al. [12] drew out that - 196 to -174del showed a three- to five-folds risk of bladder cancer comparison with people without this mutation.

For rs3804099 (c.597T>C) and rs3804100 (c.1350T>C), Etokebe et al. [13] and Semlali et al. [14] found no association between these two SNPs and breast cancer; Tongtawee et al. [15] demonstrated that rs3804099 and rs3804100 had no relationship with gastric cancer. However, the study of Xie et al. [16] found that the risk of hepatocellular carcinoma in TLR2 rs3804099 and rs3804100 carriers was reduced. For rs4696480 (g.6686T>A), de Barros Gallo et al. [17] thought that rs4696480 was associated with oral cancer in Caucasians, but Semlali et al. [18] found no difference in rs4696480 expression between the breast cancer patients and the controls in Asians.

Therefore, considering the limitations of individual study sample sizes and the contradictions of their conclusions, we designed this meta-analysis to study the relationship between TLR2 polymorphisms. (rs3804099, rs3804100, rs4696480, rs5743708 (c.2258G>A), rs1898830 (g. $8013 \mathrm{~A}>\mathrm{G}$ ) and -196 to -174del) and cancer risk.

## Materials and methods <br> Database searching

Up to October 2019, PubMed, Embase, Google Scholar, Web of Science, Wanfang database and CNKI database were used by two investigators for article identification. We used the following strategy for the searching of relevant citations: (TLR2 OR (Toll-like receptors-2) OR CD282) AND (cancer OR tumor OR carcinoma OR neoplasms OR malignancy) AND (polymorphism OR mutation OR variant OR SNP OR genotype). Since the present study is a meta-analysis, no institutional review board approval and patient consent were required.


Figure 2. Meta-analysis of the association between TLR2-196 to -174 del polymorphism and cancer risk

## Inclusion and exclusion criteria

Articles included in our research must meet the following conditions: (1) study the relationship between cancer risk and TLR2 polymorphism; (2) provide sufficient data for extraction and calculation; (3) subjects are human patients; (4) the case-control study included control group and cancer patients case group. When duplicate data appeared in different publications, only the latest publication data were used. If the study did not meet the above criteria, it was excluded.

## Data extraction and quality assessment

We extracted data from these articles, such as cancer type, first author, ethnicity, source of control, publication year, number of cases and controls, etc. Any differences were resolved through group discussions until all consensus was reached. We used Newcastle-Ottawa Scale (NOS) to evaluate the quality of the article (http://www.ohri.ca/programs/ clinical_epidemiology/oxford.asp). We carefully recorded seven aspects including 'adequacy of case definition', 'representativeness of the cases', 'selection of controls', 'definition of controls', 'comparability cases/controls', 'ascertainment of exposure' and 'ascertainment of exposure' to evaluate.

## Statistical analysis

The STATA software was used for meta-statistical analysis. The relationship between the TLR2 rs3804099, rs3804100, rs4696480, rs5743708, rs1898830, -196 to -174del and cancer risk was assessed using pooled odds ratios (ORs) with $95 \%$ confidence intervals ( $95 \%$ CIs) under dominant, recessive, homozygous codominance, heterozygous codominance, and allelic control genetic models. Heterogeneity was estimated using Q test and $I^{2}$ statistics [19]. When heterogeneity existed $(P<0.1)$, random-effects model was applied, otherwise, fixed-effect model was used [20]. The Hardy-Weinberg equilibrium (HWE) of the control group was calculated using the chi-square test. In addition, we performed a stratified analysis based on cancer type, race, source of control and quality score. The sensitivity analysis was used to evaluate the stability of the overall analysis and the publication bias was evaluated by Egger's test and Begg's funnel plot [21].

## False-positive report probability analysis and trial sequential analysis

We also used the false-positive report probability (FPRP) to evaluate the results; 0.2 was set as thePRP threshold and assigned a prior probability of 0.25 to detect the OR of $0.67 / 1.50$ (protective/risk effects). The significant result


Figure 3. Meta-analysis of the association between TLR2 rs3804009 del polymorphism and cancer risk


Figure 4. Begg's funnel plot for TLR2 polymorphisms and overall cancer publication bias (B vs. A)
For Begg's funnel plot, the $x$-axis is $\log (O R)$, and the $y$-axis is natural logarithm of OR. The horizontal line in the figure represents the overall estimated $\log (O R)$. The two diagonal lines indicate the pseudo $95 \%$ confidence limits of the effect estimate.
with the FPRP values less than 0.2 were considered a worthy finding [22,23]. Trial sequential analysis (TSA) was conducted with the guideline of a former publication [24,25]. We set a significance of $5 \%$ for type I error, as well as a $30 \%$ significance of type II error, to calculate the required sample size, and built the TSA monitoring boundaries.

## In silico analysis

For evaluating the linkage disequilibrium (LD) between different polymorphisms, we downloaded the dataset including the polymorphisms information of TLR2 gene from the 1000 Genomes Project, which contained the distribution of gene polymorphisms among CHB (Han Chinese in Beijing, China), CHS (southern Han Chinese, China), CEU (Utah residents with Northern and Western European ancestry from the CEPH collection), JPT (Japanese in Tokyo, Japan) and YRI (Yoruba in Ibadan, Nigeria), ESN (Esan in Nigeria) patients, and we used Haplpoview software to visualize the association between different polymorphisms, the relationship between them were assessed by $r^{2}$ statistics. We also performed the expression quantitative trait loci (eQTL) analysis using GTEx portal website (http://www.gtexportal.org/home/) to predict potential associations between the SNPs and gene expression levels [26,27].

## Results

## Search results

We used online databases to find 242 articles, and found another 36 articles by reviewing the references. After removing the duplicates, we found a total of 268 records in the database. We first screened the duplicate articles and then screened 43 of the high-quality articles on the NOS (Supplementary Table S1). Of the 43 articles selected, 13 were rejected for insufficient data. At last, 30 articles met the criteria, including 47 case-control studies. The flowchart of our study selection is shown in Figure 1. This meta-analysis collected individuals with different genetic backgrounds (e.g. Asians, Africans and Caucasians). The detailed characteristics of these publications are provided in Table 1.

## Meta-analysis results

The results of pooled analysis for TLR2 polymorphism and cancer susceptibility are provided in Table 2. For - 196 to -174 del , we collected 18 articles containing 3943 cases and 4574 controls [1-3,6,8-12,28-36]. In the overall analysis, -196 to -174 del significantly increased the risk of cancer [ B vs. $\mathrm{A}(\mathrm{OR}=1.468,95 \% \mathrm{Cl}=1.129-1.91, P=0.005)$; BB vs. AA ( $\mathrm{OR}=1.716,95 \% \mathrm{Cl}=1.178-2.5, P=0.005$ ); BA vs. $\mathrm{AA}(\mathrm{OR}=1.408,95 \% \mathrm{Cl}=1.092-1.816, P=0.008)$; $\mathrm{BB}+\mathrm{BA}$ vs. $\mathrm{AA}(\mathrm{OR}=1.449,95 \% \mathrm{Cl}=1.107-1.897, P=0.007)$; BB vs. $\mathrm{BA}+\mathrm{AA}(\mathrm{OR}=1.517,95 \% \mathrm{Cl}=1.092-2.107, P=0.013)$ ] (Figure 2). Among the subgroup of Caucasians, -196 to -174del produces a significant increase in the risk of cancer, too [B vs. A ( $\mathrm{OR}=3.291,95 \% \mathrm{Cl}=1.139-9.51, P=0.028$ ); BB vs. $\mathrm{AA}(\mathrm{OR}=9.878,95 \% \mathrm{Cl}=1.83-53.322, \mathrm{P}=0.008)$; BA vs. $\mathrm{AA}(\mathrm{OR}=3.156,95 \% \mathrm{Cl}=1.034-9.634, P=0.044)$; $\mathrm{BB}+\mathrm{BA}$ vs. $\mathrm{AA}(\mathrm{OR}=3.555,95 \% \mathrm{Cl}=1.098-11.51$, $P=0.034$ ); BB vs. $\mathrm{BA}+\mathrm{AA}(\mathrm{OR}=7.294,95 \% \mathrm{Cl}=1.752-30.369, P=0.006)]$. During the subgroup analysis of HB , -196 to -174del was found to be associated with cancer [ B vs. $\mathrm{A}(\mathrm{OR}=1.576,95 \% \mathrm{Cl}=1.193-2.08, \mathrm{P}<0.001$ ); BB vs. $\mathrm{AA}(\mathrm{OR}=2.274,95 \% \mathrm{Cl}=1.43-3.616, \mathrm{P}<0.001)$; BA vs. $\mathrm{AA}(\mathrm{OR}=1.543,95 \% \mathrm{Cl}=1.143-2.081, \mathrm{P}<0.001)$; $\mathrm{BB}+\mathrm{BA}$ vs. $\mathrm{AA}(\mathrm{OR}=1.624,95 \% \mathrm{Cl}=1.186-2.223, \mathrm{P}<0.001)$; BB vs. $\mathrm{BA}+\mathrm{AA}(\mathrm{OR}=2.011,95 \% \mathrm{Cl}=1.317-3.07$, $P=0.001)]$. In addition, in the subgroup analysis of Asians, the models of $\mathrm{BB}+\mathrm{BA}$ vs. $\mathrm{AA}(\mathrm{OR}=1.203,95 \% \mathrm{Cl}=$ $1.015-1.427, P=0.033$ ) and B vs. A ( $\mathrm{OR}=1.169,95 \% \mathrm{Cl}=1.005-1.361, P=0.043$ ) suggested that -196 to -174 del increased the risk of cancer. Meanwhile, when - 196 to -174 del conformed to HWE in the control group, analysis of all models showed that the deletion of these 22 genes increased the risk of cancer (Supplementary Table S2). By the way, the BA vs. AA model in the N subgroup suggested that -196 to- 174 del was related to the cancer risk $(\mathrm{OR}=1.335$, $95 \% \mathrm{Cl}=1.015-1.757, P=0.039$ ).

There are nine studies on rs3804099 polymorphism including a total of 3456 cases and 4574 controls [13-16,18,37-40]. According to overall analysis, rs3804099 significantly decreased cancer risk [BA vs. AA (OR $=$ $0.827,95 \% \mathrm{Cl}=0.717-0.952, P=0.008), \mathrm{BB}+\mathrm{BA}$ vs. $\mathrm{AA}(\mathrm{OR}=0.85,95 \% \mathrm{Cl}=0.744-0.97, P=0.016)]$ (Figure 3). About Asians, rs3804099 polymorphism reduced the risk of cancer in the model of BA vs. AA (OR $=0.69,95 \% \mathrm{Cl}$ $=0.55-0.867, P=0.001)$ and BB vs. $\mathrm{AA}(\mathrm{OR}=0.65,95 \% \mathrm{Cl}=0.482-0.877, P=0.005)$. In the subgroup of gastric cancer patients, we found that rs3804099 polymorphism reduced the risk of cancer [B vs. A ( $\mathrm{OR}=0.728,95 \% \mathrm{Cl}$ $=0.594-0.893, P=0.002), \mathrm{BB}$ vs. $\mathrm{AA}(\mathrm{OR}=0.605,95 \% \mathrm{Cl}=0.389-0.942, P=0.026), \mathrm{BA}$ vs. $\mathrm{AA}(\mathrm{OR}=0.706,95 \%$ $\mathrm{Cl}=0.529-0.942, P=0.018), \mathrm{BB}+\mathrm{BA}$ vs. $\mathrm{AA}(\mathrm{OR}=0.681,95 \% \mathrm{Cl}=0.524-0.886, P=0.004)]$ and the model of BB vs. BA + AA is not associated with reduced risk of gastric cancer. Part of the model in the hospital-based analysis was associated with reduced cancer risk [BA vs. AA ( $\mathrm{OR}=0.713,95 \% \mathrm{Cl}=0.564-0.902, P=0.005$ ), $\mathrm{BB}+\mathrm{BA}$ vs. AA (OR $=0.734,95 \% \mathrm{Cl}=0.591-0.912, P=0.005)]$.

There are four studies on rs4696480 polymorphism including a total of 492 cases and 500 controls [14,17,18,38]. In some models of the overall analysis, rs4696480 significantly increased cancer risk [ B vs. $\mathrm{A}(\mathrm{OR}=1.216,95 \% \mathrm{Cl}$ $=1.019-1.452, P=0.03)$; BB vs. $\mathrm{AA}(\mathrm{OR}=1.463,95 \% \mathrm{Cl}=1.034-2.069, P=0.032)]$. It is worth mentioning that rs4696480 makes Caucasians more susceptible to cancer [B vs. A ( $\mathrm{OR}=1.393,95 \% \mathrm{Cl}=1.094-1.775, P=0.007$ ), BB

Table 1 Characteristics of the enrolled studies on TLR2 polymorphism and cancer

| First author | Year | Ethnicity | Genotyping method | Source of control | Cancer type | Cases |  |  |  |  |  | Control |  |  |  |  |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  |  |  |  |  |  | AA | BA | BB | Total | A\% | B\% | AA | BA | BB | Total | A\% | B\% | HWE |
| (-196 to -174del) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Tahara et al. | 2007 | Asian | AS-PCR | PB | Gastric cancer | 126 | 112 | 51 | 289 | 63.0\% | 37.0\% | 73 | 65 | 8 | 146 | 72.3\% | 27.7\% | Y |
| Pandey et al. | 2009 | Asian | PCR | PB | Cervical cancer | 102 | 43 | 5 | 150 | 82.3\% | 17.7\% | 114 | 35 | 1 | 150 | 87.7\% | 12.3\% | Y |
| Hishida et al. | 2010 | Asian | PCR | HB | Gastric cancer | 243 | 267 | 73 | 583 | 64.6\% | 35.4\% | 722 | 730 | 184 | 1636 | 66.4\% | 33.6\% | Y |
| Srivastava et al. | 2010 | Asian | PCR-RFLP | PB | Gallbladder cancer | 132 | 94 | 6 | 232 | 77.2\% | 22.8\% | 163 | 87 | 4 | 254 | 81.3\% | 18.7\% | N |
| Zeng et al. | 2011a | Asian | DHPLC | HB | Gastric cancer | 119 | 110 | 19 | 248 | 70.2\% | 29.8\% | 187 | 246 | 63 | 496 | 62.5\% | 37.5\% | Y |
| Nischalk et al. | 2011 | Caucasian | PCR | PB | Hepatocellular carcinoma | 115 | 63 | 11 | 189 | 77.5\% | 22.5\% | 248 | 92 | 7 | 347 | 84.7\% | 15.3\% | Y |
| Oliveira et al. | 2012 | Caucasian | PCR-RFLP | PB | Gastric cancer | 116 | 50 | 8 | 174 | 81.0\% | 19.0\% | 189 | 34 | 2 | 225 | 91.6\% | 8.4\% | Y |
| Mandal et al. | 2012 | Asian | PCR | PB | Prostate cancer | 135 | 54 | 6 | 195 | 83.1\% | 16.9\% | 193 | 52 | 5 | 250 | 87.6\% | 12.4\% | Y |
| Theodoropoulos et al. | 2012 | Caucasian | PCR | PB | Breast cancer | 120 | 113 | 28 | 261 | 67.6\% | 32.4\% | 432 | 46 | 2 | 480 | 94.8\% | 5.2\% | Y |
| Singh et al. | 2013 | Asian | PCR | PB | Bladder cancer | 110 | 79 | 11 | 200 | 74.8\% | 25.3\% | 119 | 73 | 8 | 200 | 77.8\% | 22.3\% | Y |
| Bi et al. | 2014 | Asian | PCR | PB | Cervical cancer | 40 | 47 | 15 | 102 | 62.3\% | 37.7\% | 36 | 50 | 14 | 100 | 61.0\% | 39.0\% | Y |
| Castano-Rodriguez et al. | 2014 | Asian | MassARRAY | HB | Gastric cancer | 7 | 44 | 35 | 86 | 33.7\% | 66.3\% | 19 | 95 | 106 | 220 | 30.2\% | 69.8\% | Y |
| Zidi et al. | 2014 | African | PCR | HB | Cervical cancer | 89 | 20 | 13 | 122 | 81.1\% | 18.9\% | 196 | 37 | 27 | 260 | 82.5\% | 17.5\% | N |
| Devi et al. | 2015 | Asian | PCR | PB | Breast cancer | 251 | 191 | 20 | 462 | 75.0\% | 25.0\% | 491 | 246 | 33 | 770 | 79.7\% | 20.3\% | Y |
| Proenca et al. | 2015 | African | PCR | PB | Colorectal cancer | 144 | 39 | 5 | 188 | 87.0\% | 13.0\% | 200 | 36 | 4 | 240 | 90.8\% | 9.2\% | Y |
| Zidi et al. | 2015 | African | PCR | PB | Cervical cancer | 93 | 26 | 11 | 130 | 81.5\% | 18.5\% | 196 | 37 | 27 | 260 | 82.5\% | 17.5\% | N |
| AL-Harras et al. | 2016 | African | PCR-RFLP | PB | Breast cancer | 44 | 22 | 6 | 72 | 76.4\% | 23.6\% | 61 | 33 | 6 | 100 | 77.5\% | 22.5\% | Y |
| Huang et al. | 2018 | Asian | PCR | PB | Gastric cancer | 105 | 124 | 31 | 260 | 64.2\% | 35.8\% | 132 | 113 | 15 | 260 | 72.5\% | 27.5\% | Y |
| Etokebe et al. | 2009 | Caucasian | TaqMan | PB | Breast cancer | 29 | 44 | 16 | 89 | 57.3\% | 42.7\% | 26 | 48 | 15 | 89 | 56.2\% | 43.8\% | Y |
| Slattery et al. | 2012 | Caucasian | GoldenGate | PB | Colon cancer |  |  | 300 | 1555 | - | - | 1531 |  |  | 1956 | - | - | - |
| Xie et al. | 2012 | Asian | SNaPshot | HB | Hepatocellular carcinoma | 19 | 71 | 121 | 211 | 25.8\% | 74.2\% | 15 | 117 | 100 | 232 | 31.7\% | 68.3\% | N |

Table 1 Characteristics of the enrolled studies on TLR2 polymorphism and cancer (Continued)

| First author | Year | Ethnicity | Genotyping method | Source of control | Cancer type | Cases |  |  |  |  |  | Control |  |  |  |  |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  |  |  |  |  |  | AA | BA | BB | Total | A\% | B\% | AA | BA | BB | Total | A\% | B\% | HWE |
| Miedema et al. | 2012 | Caucasian | AS-PCR | HB | Lymphoblastic leukemia | 51 | 94 | 37 | 182 | 53.8\% | 46.2\% | 48 | 102 | 28 | 178 | 55.6\% | 44.4\% | N |
| Slattery et al. | 2012 | Caucasian | GoldenGate | PB | Rectal cancer | 238 | 372 | 144 | 754 | 56.2\% | 43.8\% | 299 | 477 | 183 | 959 | 56.0\% | 44.0\% | Y |
| Zeljic et al. | 2013 | Caucasian | TaqMan | PB | Oral cancer | 29 | 39 | 25 | 93 | 52.2\% | 47.8\% | 37 | 67 | 0 | 104 | 67.8\% | 32.2\% | N |
| Semlali et al. | 2017 | Asian | TaqMan | PB | Breast cancer | 35 | 58 | 32 | 125 | 51.2\% | 48.8\% | 33 | 71 | 42 | 146 | 46.9\% | 53.1\% | Y |
| Semlali et al. | 2018 | Asian | TaqMan | PB | Colon cancer | 42 | 50 | 19 | 111 | 60.4\% | 39.6\% | 28 | 47 | 27 | 102 | 50.5\% | 49.5\% | Y |
| Tongtawee et al. | 2018 | Asian | TaqMan | HB | Gastric cancer | 62 | 13 | 13 | 88 | 77.8\% | 22.2\% | 194 | 56 | 62 | 312 | 71.2\% | 28.8\% | N |
| Zeng et al. rs3804100 | 2011b | Asian | PCR-RFLP | HB | Gastric cancer | 132 | 99 | 17 | 248 | 73.2\% | 26.8\% | 216 | 231 | 49 | 496 | 66.8\% | 33.2\% | Y |
| Purdu et al. | 2008 | Caucasian | TaqMan | PB | Non-Hodgkin lymphoma | 1658 | 272 | 12 | 1942 | 92.4\% | 7.6\% | 1556 | 233 | 9 | 1798 | 93.0\% | 7.0\% | Y |
| Etokebe et al. | 2009 | Caucasian | TaqMan | PB | Breast cancer | 76 | 13 | 0 | 89 | 92.7\% | 7.3\% | 84 | 11 | 0 | 95 | 94.2\% | 5.8\% | Y |
| Xie et al. | 2012 | Asian | SNaPshot | HB | Hepatocellular carcinoma | 14 | 67 | 130 | 211 | 22.5\% | 77.5\% | 11 | 110 | 111 | 232 | 28.4\% | 71.6\% | N |
| Miedema et al. | 2012 | Caucasian | AS-PCR | HB | Lymphoblastic leukemia | 170 | 18 | 1 | 189 | 94.7\% | 5.3\% | 165 | 18 | 0 | 183 | 95.1\% | 4.9\% | Y |
| Castano-Rodriguez et al. | 2014 | Asian | MassARRAY | HB | Gastric cancer | 47 | 34 | 4 | 85 | 75.3\% | 24.7\% | 122 | 76 | 14 | 212 | 75.5\% | 24.5\% | Y |
| Semlali et al. | 2017 | Asian | TaqMan | PB | Breast cancer | 99 | 24 | 1 | 124 | 89.5\% | 10.5\% | 115 | 27 | 4 | 146 | 88.0\% | 12.0\% | Y |
| Semlali et al. | 2018 | Asian | TaqMan | PB | Colon cancer | 99 | 13 | 2 | 114 | 92.5\% | 7.5\% | 82 | 19 | 2 | 103 | 88.8\% | 11.2\% | Y |
| Tongtawee et al. rs4696480 | 2018 | Asian | TaqMan | HB | Gastric cancer | 66 | 22 | 0 | 88 | 87.5\% | 12.5\% | 230 | 70 | 12 | 312 | 84.9\% | 15.1\% | N |
| Miedema et al. | 2012 | Caucasian | AS-PCR | HB | Hepatocellular carcinoma | 42 | 99 | 44 | 185 | 49.5\% | 50.5\% | 60 | 83 | 38 | 181 | 56.1\% | 43.9\% | Y |
| Gallo et al. | 2017 | Caucasian | TaqMan | PB | Oral cancer | 12 | 39 | 24 | 75 | 42.0\% | 58.0\% | 31 | 34 | 24 | 89 | 53.9\% | 46.1\% | N |
| Semlali et al. | 2017 | Asian | TaqMan | PB | Breast cancer | 46 | 51 | 29 | 126 | 56.7\% | 43.3\% | 50 | 63 | 25 | 138 | 59.1\% | 40.9\% | Y |
| Semlali et al. rs5743708 | 2018 | Asian | TaqMan | PB | Colon cancer | 30 | 49 | 27 | 106 | 51.4\% | 48.6\% | 26 | 41 | 25 | 92 | 50.5\% | 49.5\% | Y |
| Nischalk et al. | 2011 | Caucasian | PCR | PB | Hepatocellular carcinoma | 174 | 15 | 0 | 189 | 96.0\% | 4.0\% | 319 | 28 | 0 | 347 | 96.0\% | 4.0\% | Y |
| Slattery et al. | 2012 | Caucasian | GoldenGate | PB | Rectal cancer | 727 |  |  | 754 | - | - | 913 |  |  | 959 | - | - |  |
| Slattery et al. | 2012 | Caucasian | GoldenGate | PB | Colon cancer | 1467 |  |  | 1555 | - | - | 1864 |  |  | 1956 | - | - |  |
| Kina et al. rs1898830 | 2018 | Caucasian | PCR | PB | Glioma | 32 | 18 | 70 | 120 | 34.2\% | 65.8\% | 184 | 35 | 6 | 225 | 89.6\% | 10.4\% | N |
| Xie et al. | 2012 | Asian | SNPshot | HB | Hepatocellular carcinoma | 47 | 92 | 72 | 211 | 44.1\% | 55.9\% | 34 | 118 | 80 | 232 | 40.1\% | 59.9\% | Y |
| Slattery et al. | 2012 | Caucasian | GoldenGate | PB | Rectal cancer | 305 | 363 | 86 | 754 | 64.5\% | 35.5\% | 410 | 437 | 111 | 958 | 65.6\% | 34.4\% | Y |
| Slattery et al. | 2012 | Caucasian | GoldenGate | PB | Colon cancer | 705 | 674 | 176 | 1555 | 67.0\% | 33.0\% | 896 | 833 | 227 | 1956 | 67.1\% | 32.9\% | Y |

Abbreviations: H-B, hospital based; P-B, population based. $P>0.05$ means conformed to HWE.

Table 2 Results of pooled analysis for TLR2 polymorphism and cancer susceptibility

| Comparison | Subgroup | $n$ | Cases | Controls | $\boldsymbol{P}_{\mathrm{H}}$ | $P_{Z}$ | HR (95\% CI) |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| (-196 to -174del) |  |  |  |  |  |  |  |
| B vs. A | Overall | 18 | 3943 | 6394 | <0.001 | 0.005* | 1.468 (1.129-1.91) |
| BB vs. AA | Overall | 18 | 3943 | 6394 | <0.001 | 0.005* | 1.716 (1.178-2.5) |
| BA vs. AA | Overall | 18 | 3943 | 6394 | <0.001 | 0.008* | 1.408 (1.092-1.816) |
| $B B+B A$ vs. $A A$ | Overall | 18 | 3943 | 6394 | <0.001 | 0.007* | 1.449 (1.107-1.897) |
| $B B$ vs. $B A+A A$ | Overall | 18 | 3943 | 6394 | <0.001 | 0.013* | 1.517 (1.092-2.107) |
| $B$ vs. $A$ | Asian | 11 | 2807 | 4482 | <0.001 | $0.043^{*}$ | 1.169 (1.005-1.361) |
| BB vs. AA | Asian | 11 | 2807 | 4482 | 0.003 | 0.098 | 1.373 (0.943-2) |
| BA vs. AA | Asian | 11 | 2807 | 4482 | 0.039 | 0.054 | 1.168 (0.997-1.367) |
| $B B+B A$ vs. $A A$ | Asian | 11 | 2807 | 4482 | 0.008 | 0.033* | 1.203 (1.015-1.427) |
| $B B$ vs. $B A+A A$ | Asian | 11 | 2807 | 4482 | 0.005 | 0.177 | 1.256 (0.902-1.748) |
| B vs. A | Caucasian | 3 | 624 | 1052 | $<0.001$ | 0.028* | 3.291 (1.139-9.51) |
| BB vs. AA | Caucasian | 3 | 624 | 1052 | 0.007 | 0.008* | 9.878 (1.83-53.322) |
| BA vs. AA | Caucasian | 3 | 624 | 1052 | <0.001 | 0.044* | 3.156 (1.034-9.634) |
| $B B+B A$ vs. $A A$ | Caucasian | 3 | 624 | 1052 | <0.001 | 0.034* | 3.555 (1.098-11.51) |
| $B B$ vs. $B A+A A$ | Caucasian | 3 | 624 | 1052 | 0.029 | 0.006* | 7.294 (1.752-30.369) |
| B vs. $A$ | African | 4 | 512 | 860 | 0.653 | 0.159 | 1.163 (0.943-1.436) |
| BB vs. AA | African | 4 | 512 | 860 | 0.796 | 0.746 | 1.076 (0.693-1.67) |
| BA vs. AA | African | 4 | 512 | 860 | 0.652 | 0.075 | 1.296 (0.974-1.724) |
| $B B+B A$ vs. $A A$ | African | 4 | 512 | 860 | 0.72 | 0.106 | 1.232 (0.956-1.586) |
| $B B$ vs. $B A+A A$ | African | 4 | 512 | 860 | 0.755 | 0.897 | 1.029 (0.666-1.59) |
| B vs. A | PB | 14 | 2904 | 3782 | <0.001 | 0.001* | 1.576 (1.193-2.08) |
| BB vs. AA | PB | 14 | 2904 | 3782 | <0.001 | 0.001* | 2.274 (1.43-3.616) |
| BA vs. AA | PB | 14 | 2904 | 3782 | <0.001 | 0.005* | 1.543 (1.143-2.081) |
| $B B+B A$ vs. $A A$ | PB | 14 | 2904 | 3782 | <0.001 | 0.002* | 1.624 (1.186-2.223) |
| $B B$ vs. $B A+A A$ | PB | 14 | 2904 | 3782 | 0.001 | 0.001* | 2.011 (1.317-3.07) |
| $B$ vs. $A$ | HB | 4 | 1039 | 2612 | 0.016 | 0.502 | 0.92 (0.721-1.173) |
| BB vs. AA | HB | 4 | 1039 | 2612 | 0.048 | 0.552 | 0.866 (0.54-1.39) |
| BA vs. AA | HB | 4 | 1039 | 2612 | 0.122 | 0.841 | 0.984 (0.837-1.156) |
| $B B+B A$ vs. $A A$ | HB | 4 | 1039 | 2612 | 0.038 | 0.716 | 0.942 (0.684-1.298) |
| $B B$ vs. $B A+A A$ | HB | 4 | 1039 | 2612 | 0.121 | 0.43 | 0.917 (0.739-1.138) |
| $B$ vs. $A$ | Gastric cancer | 6 | 1640 | 2983 | <0.001 | 0.194 | 1.22 (0.904-1.647) |
| BB vs. AA | Gastric cancer | 6 | 1640 | 2983 | <0.001 | 0.176 | 1.565 (0.818-2.995) |
| BA vs. AA | Gastric cancer | 6 | 1640 | 2983 | 0.002 | 0.309 | 1.171 (0.864-1.586) |
| $B B+B A$ vs. $A A$ | Gastric cancer | 6 | 1640 | 2983 | <0.001 | 0.216 | 1.246 (0.879-1.764) |
| $B B$ vs. $B A+A A$ | Gastric cancer | 6 | 1640 | 2983 | <0.001 | 0.223 | 1.401 (0.814-2.411) |
| B vs. A | Breast cancer | 3 | 795 | 1350 | <0.001 | 0.212 | 2.31 (0.621-8.593) |
| BB vs. AA | Breast cancer | 3 | 795 | 1350 | <0.001 | 0.2 | 4.049 (0.478-34.306) |
| BA vs. AA | Breast cancer | 3 | 795 | 1350 | <0.001 | 0.197 | 2.347 (0.642-8.58) |
| $B B+B A$ vs. $A A$ | Breast cancer | 3 | 795 | 1350 | <0.001 | 0.2 | 2.52 (0.613-10.36) |
| $B B$ vs. $B A+A A$ | Breast cancer | 3 | 795 | 1350 | <0.001 | 0.233 | 3.176 (0.476-21.196) |
| $B$ vs. $A$ | Cervical cancer | 4 | 504 | 770 | 0.474 | 0.269 | 1.121 (0.916-1.372) |
| BB vs. AA | Cervical cancer | 4 | 504 | 770 | 0.453 | 0.782 | 1.061 (0.696-1.618) |
| BA vs. AA | Cervical cancer | 4 | 504 | 770 | 0.554 | 0.177 | 1.215 (0.916-1.613) |
| $B B+B A$ vs. $A A$ | Cervical cancer | 4 | 504 | 770 | 0.586 | 0.207 | 1.177 (0.914-1.515) |
| $B B$ vs. $B A+A A$ | Cervical cancer | 4 | 504 | 770 | 0.456 | 0.848 | 1.041 (0.692-1.566) |
| B vs. A | Y | 15 | 3459 | 5620 | <0.001 | 0.008* | 1.447 (1.103-1.897) |
| BB vs. AA | Y | 15 | 3459 | 5620 | <0.001 | 0.004* | 1.915 (1.227-2.991) |
| BA vs. AA | Y | 15 | 3459 | 5620 | <0.001 | 0.02* | 1.422 (1.057-1.915) |
| $B B+B A$ vs. $A A$ | Y | 15 | 3459 | 5620 | <0.001 | 0.013* | 1.494 (1.088-2.052) |
| $B B$ vs. $B A+A A$ | Y | 15 | 3459 | 5620 | <0.001 | 0.009* | 1.673 (1.137-2.461) |
| B vs. A | N | 3 | 484 | 774 | 0.709 | 0.14 | 1.168 (0.951-1.434) |
| BB vs. AA | N | 3 | 484 | 774 | 0.597 | 0.84 | 1.05 (0.655-1.681) |

Continued over

Table 2 Results of pooled analysis for TLR2 polymorphism and cancer susceptibility (Continued)

| Comparison | Subgroup | $n$ | Cases | Controls | $P_{H}$ | $P_{z}$ | HR (95\% CI) |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| BA vs. AA | N | 3 | 484 | 774 | 0.872 | 0.039* | 1.335 (1.015-1.757) |
| $B B+B A$ vs. AA | N | 3 | 484 | 774 | 0.839 | 0.07 | 1.258 (0.981-1.613) |
| $\begin{gathered} \text { BB vs. BA+AA } \\ \text { rs3804099 } \end{gathered}$ | N | 3 | 484 | 774 | 0.615 | 0.959 | 0.988 (0.62-1.575) |
| B vs. A | Overall | 9 | 1901 | 2618 | 0.001 | 0.723 | 0.967 (0.806-1.162) |
| BB vs. AA | Overall | 9 | 1901 | 2618 | 0.029 | 0.29 | 0.84 (0.609-1.16) |
| BA vs. AA | Overall | 9 | 1901 | 2618 | 0.643 | 0.008* | 0.827 (0.717-0.952) |
| $B B+B A$ vs. $A A$ | Overall | 9 | 1901 | 2618 | 0.446 | 0.016* | 0.85 (0.744-0.97) |
| $B B$ vs. $B A+A A$ | Overall | 10 | 3456 | 4574 | 0.001 | 0.946 | 0.991 (0.768-1.28) |
| B vs. A | Asian | 5 | 783 | 1288 | 0.013 | 0.177 | 0.838 (0.648-1.083) |
| BB vs. AA | Asian | 5 | 783 | 1288 | 0.721 | 0.005* | 0.65 (0.482-0.877) |
| BA vs. AA | Asian | 5 | 783 | 1288 | 0.892 | 0.001* | 0.69 (0.55-0.867) |
| $B B+B A$ vs. $A A$ | Asian | 5 | 783 | 1288 | 0.994 | <0.001 | 0.684 (0.555-0.843) |
| $B B$ vs. $B A+A A$ | Asian | 5 | 783 | 1288 | 0.005 | 0.559 | 0.869 (0.542-1.393) |
| $B$ vs. $A$ | Caucasian | 4 | 1118 | 1330 | 0.025 | 0.3 | 1.147 (0.885-1.486) |
| BB vs. AA | Caucasian | 4 | 1118 | 1330 | 0.024 | 0.455 | 1.283 (0.667-2.47) |
| BA vs. AA | Caucasian | 4 | 1118 | 1330 | 0.819 | 0.425 | 0.929 (0.774-1.114) |
| $B B+B A$ vs. $A A$ | Caucasian | 4 | 1118 | 1330 | 0.87 | 0.866 | 0.985 (0.829-1.171) |
| $B B$ vs. $B A+A A$ | Caucasian | 5 | 2673 | 3286 | 0.01 | 0.647 | 1.082 (0.771-1.518) |
| $B$ vs. $A$ | Breast cancer | 2 | 214 | 235 | 0.647 | 0.364 | 0.885 (0.68-1.152) |
| BB vs. AA | Breast cancer | 2 | 214 | 235 | 0.611 | 0.399 | 0.796 (0.47-1.351) |
| BA vs. AA | Breast cancer | 2 | 214 | 235 | 0.887 | 0.302 | 0.792 (0.509-1.233) |
| $B B+B A$ vs. AA | Breast cancer | 2 | 214 | 235 | 0.765 | 0.276 | 0.793 (0.523-1.203) |
| $B B$ vs. $B A+A A$ | Breast cancer | 2 | 214 | 235 | 0.621 | 0.713 | 0.921 (0.592-1.432) |
| B vs. A | Gastric Cancer | 2 | 336 | 808 | 0.831 | 0.002* | 0.728 (0.594-0.893) |
| BB vs. AA | Gastric Cancer | 2 | 336 | 808 | 0.75 | 0.026* | 0.605 (0.389-0.942) |
| BA vs. AA | Gastric Cancer | 2 | 336 | 808 | 0.926 | 0.018* | 0.706 (0.529-0.942) |
| $B B+B A$ vs. $A A$ | Gastric Cancer | 2 | 336 | 808 | 0.956 | 0.004* | 0.681 (0.524-0.886) |
| $B B$ vs. $B A+A A$ | Gastric Cancer | 2 | 336 | 808 | 0.928 | 0.083 | 0.683 (0.444-1.051) |
| $B B$ vs. $B A+A A$ | Colon Cancer | 2 | 1666 | 2058 | 0.243 | 0.034* | 0.841 (0.716-0.987) |
| $B$ vs. $A$ | PB | 5 | 1172 | 1400 | 0.004 | 0.985 | 0.997 (0.759-1.311) |
| BB vs. AA | PB | 5 | 1172 | 1400 | 0.01 | 0.762 | 0.912 (0.502-1.658) |
| BA vs. AA | PB | 5 | 1172 | 1400 | 0.764 | 0.252 | 0.901 (0.754-1.077) |
| $B B+B A$ vs. $A A$ | PB | 5 | 1172 | 1400 | 0.468 | 0.385 | 0.928 (0.785-1.098) |
| $B B$ vs. $B A+A A$ | PB | 6 | 2727 | 3356 | 0.021 | 0.549 | 0.915 (0.683-1.225) |
| $B$ vs. $A$ | HB | 4 | 729 | 1218 | 0.007 | 0.658 | 0.934 (0.691-1.263) |
| BB vs. AA | HB | 4 | 729 | 1218 | 0.29 | 0.155 | 0.794 (0.577-1.091) |
| BA vs. AA | HB | 4 | 729 | 1218 | 0.624 | 0.005* | 0.713 (0.564-0.902) |
| $B B+B A$ vs. $A A$ | HB | 4 | 729 | 1218 | 0.679 | 0.005* | 0.734 (0.591-0.912) |
| $B B$ vs. $B A+A A$ | HB | 4 | 729 | 1218 | 0.012 | 0.782 | 1.073 (0.65-1.772) |
| B vs. A | Y | 5 | 1327 | 1792 | 0.13 | 0.036* | 0.895 (0.807-0.993) |
| BB vs. AA | Y | 5 | 1327 | 1792 | 0.233 | 0.087 | 0.828 (0.668-1.028) |
| BA vs. AA | Y | 5 | 1327 | 1792 | 0.484 | 0.058 | 0.856 (0.729-1.005) |
| $B B+B A$ vs. $A A$ | Y | 5 | 1327 | 1792 | 0.258 | 0.028* | 0.844 (0.725-0.982) |
| $B B$ vs. $B A+A A$ | Y | 5 | 1327 | 1792 | 0.437 | 0.265 | 0.898 (0.742-1.086) |
| B vs. $A$ | N | 4 | 574 | 826 | 0.004 | 0.37 | 1.179 (0.823-1.688) |
| BB vs. AA | N | 4 | 574 | 826 | 0.008 | 0.596 | 1.262 (0.534-2.98) |
| BA vs. AA | N | 4 | 574 | 826 | 0.628 | 0.042* | 0.73 (0.54-0.988) |
| $B B+B A$ vs. $A A$ | N | 4 | 574 | 826 | 0.469 | 0.315 | 0.87 (0.663-1.142) |
| $B B$ vs. $B A+A A$ | N | 4 | 574 | 826 | 0.002 | 0.242 | 1.564 (0.739-3.308) |
| rs3804100 |  |  |  |  |  |  |  |
| B vs. A | Overall | 8 | 2842 | 3081 | 0.422 | 0.254 | 1.076 (0.949-1.219) |
| BB vs. AA | Overall | 8 | 2842 | 3081 | 0.682 | 0.412 | 0.823 (0.516-1.311) |
| BA vs. AA | Overall | 8 | 2842 | 3081 | 0.487 | 0.603 | 1.041 (0.896-1.209) |
| $B B+B A$ vs. $A A$ | Overall | 8 | 2842 | 3081 | 0.758 | 0.641 | 1.035 (0.894-1.199) |
| $B B$ vs. $B A+A A$ | Overall | 8 | 2842 | 3081 | 0.243 | 0.061 | 1.343 (0.987-1.827) |

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Table 2 Results of pooled analysis for TLR2 polymorphism and cancer susceptibility (Continued)

| Comparison | Subgroup | $n$ | Cases | Controls | $\boldsymbol{P}_{\mathrm{H}}$ | $P_{Z}$ | HR (95\% CI) |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| B vs. A | Asian | 5 | 622 | 1005 | 0.152 | 0.71 | 1.037 (0.856-1.257) |
| BB vs. AA | Asian | 5 | 622 | 1005 | 0.66 | 0.153 | 0.655 (0.366-1.17) |
| BA vs. AA | Asian | 5 | 622 | 1005 | 0.276 | 0.543 | 0.917 (0.692-1.213) |
| $B B+B A$ vs. $A A$ | Asian | 5 | 622 | 1005 | 0.688 | 0.391 | 0.888 (0.677-1.165) |
| $B B$ vs. $B A+A A$ | Asian | 5 | 622 | 1005 | 0.105 | 0.079 | 1.346 (0.966-1.875) |
| B vs. A | Caucasian | 3 | 2220 | 2076 | 0.937 | 0.237 | 1.105 (0.937-1.304) |
| BB vs. AA | Caucasian | 3 | 2220 | 2076 | 0.618 | 0.494 | 1.337 (0.582-3.075) |
| BA vs. AA | Caucasian | 3 | 2220 | 2076 | 0.87 | 0.317 | 1.095 (0.917-1.308) |
| $B B+B A$ vs. $A A$ | Caucasian | 3 | 2220 | 2076 | 0.908 | 0.268 | 1.104 (0.927-1.315) |
| $B B$ vs. $B A+A A$ | Caucasian | 3 | 2220 | 2076 | 0.612 | 0.51 | 1.323 (0.576-3.039) |
| $B$ vs. A | PB | 4 | 2269 | 2142 | 0.365 | 0.555 | 1.049 (0.896-1.228) |
| BB vs. AA | PB | 4 | 2269 | 2142 | 0.471 | 0.91 | 0.959 (0.465-1.977) |
| BA vs. AA | PB | 4 | 2269 | 2142 | 0.402 | 0.495 | 1.061 (0.894-1.26) |
| $B B+B A$ vs. $A A$ | PB | 4 | 2269 | 2142 | 0.384 | 0.514 | 1.057 (0.894-1.251) |
| $B B$ vs. BA+ AA | PB | 4 | 2269 | 2142 | 0.479 | 0.911 | 0.96 (0.466-1.978) |
| B vs. A | HB | 4 | 573 | 939 | 0.308 | 0.266 | 1.124 (0.915-1.381) |
| BB vs. AA | HB | 4 | 573 | 939 | 0.512 | 0.336 | 0.74 (0.4-1.368) |
| BA vs. AA | HB | 4 | 573 | 939 | 0.346 | 0.872 | 0.975 (0.715-1.329) |
| $B B+B A$ vs. $A A$ | HB | 4 | 573 | 939 | 0.83 | 0.829 | 0.967 (0.715-1.308) |
| $B B$ vs. $B A+A A$ | HB | 4 | 573 | 939 | 0.146 | $0.033^{*}$ | 1.449 (1.031-2.036) |
| $B$ vs. $A$ | Breast cancer | 2 | 213 | 241 | 0.429 | 0.886 | 0.968 (0.617-1.517) |
| BA vs. AA | Breast cancer | 2 | 213 | 241 | 0.663 | 0.662 | 1.118 (0.679-1.839) |
| $B B+B A$ vs. $A A$ | Breast cancer | 2 | 213 | 241 | 0.533 | 0.867 | 1.042 (0.641-1.695) |
| B vs. A | Gastric cancer | 2 | 173 | 524 | 0.493 | 0.598 | 0.918 (0.669-1.261) |
| BB vs. AA | Gastric cancer | 2 | 173 | 524 | 0.259 | 0.168 | 0.481 (0.17-1.362) |
| BA vs. AA | Gastric cancer | 2 | 173 | 524 | 0.88 | 0.531 | 1.129 (0.772-1.652) |
| $B B+B A$ vs. $A A$ | Gastric cancer | 2 | 173 | 524 | 0.675 | 0.927 | 1.018 (0.703-1.473) |
| $B B$ vs. $B A+A A$ | Gastric cancer | 2 | 173 | 524 | 0.27 | 0.142 | 0.463 (0.165-1.295) |
| $B \mathrm{vs}$. A | Y | 6 | 2543 | 2537 | 0.666 | 0.546 | 1.045 (0.905-1.207) |
| BB vs. AA | Y | 6 | 2543 | 2537 | 0.706 | 0.824 | 0.935 (0.516-1.695) |
| BA vs. AA | Y | 6 | 2543 | 2537 | 0.683 | 0.436 | 1.065 (0.909-1.248) |
| $B B+B A$ vs. $A A$ | Y | 6 | 2543 | 2537 | 0.688 | 0.467 | 1.059 (0.907-1.237) |
| $B B$ vs. $B A+A A$ | Y | 6 | 2543 | 2537 | 0.693 | 0.771 | 0.916 (0.508-1.653) |
| B vs. A | N | 2 | 299 | 544 | 0.075 | 0.741 | 1.091 (0.652-1.824) |
| BB vs. AA | N | 2 | 299 | 544 | 0.188 | 0.308 | 0.674 (0.316-1.439) |
| BA vs. AA | N | 2 | 299 | 544 | 0.108 | 0.507 | 0.855 (0.537-1.36) |
| $B B+B A$ vs. $A A$ | N | 2 | 299 | 544 | 0.563 | 0.499 | 0.855 (0.543-1.346) |
| $B B$ vs. BA+AA | N | 2 | 299 | 544 | 0.073 | 0.789 | 0.716 (0.062-8.24) |
| rs4696480 |  |  |  |  |  |  |  |
| B vs. A | Overall | 4 | 492 | 500 | 0.323 | 0.03* | 1.216 (1.019-1.452) |
| BB vs. AA | Overall | 4 | 492 | 500 | 0.344 | $0.032^{*}$ | 1.463 (1.034-2.069) |
| BA vs. AA | Overall | 4 | 492 | 500 | 0.059 | 0.167 | 1.407 (0.867-2.281) |
| $B B+B A$ vs. $A A$ | Overall | 4 | 492 | 500 | 0.076 | 0.115 | 1.415 (0.919-2.179) |
| $B B$ vs. $B A+A A$ | Overall | 4 | 492 | 500 | 0.836 | 0.296 | 1.169 (0.872-1.568) |
| $B$ vs. $A$ | Asian | 2 | 232 | 230 | 0.628 | 0.772 | 1.039 (0.801-1.348) |
| BB vs. AA | Asian | 2 | 232 | 230 | 0.563 | 0.692 | 1.106 (0.671-1.824) |
| BA vs. AA | Asian | 2 | 232 | 230 | 0.711 | 0.77 | 0.939 (0.616-1.433) |
| $B B+B A$ vs. $A A$ | Asian | 2 | 232 | 230 | 0.981 | 0.968 | 0.992 (0.672-1.465) |
| $B B$ vs. $B A+A A$ | Asian | 2 | 232 | 230 | 0.382 | 0.596 | 1.125 (0.728-1.738) |
| $B$ vs. $A$ | Caucasian | 2 | 260 | 270 | 0.424 | 0.007* | 1.393 (1.094-1.775) |
| BB vs. AA | Caucasian | 2 | 260 | 270 | 0.406 | 0.009* | 1.903 (1.171-3.091) |
| BA vs. AA | Caucasian | 2 | 260 | 270 | 0.252 | 0.001* | 1.984 (1.307-3.012) |
| $B B+B A$ vs. $A A$ | Caucasian | 2 | 260 | 270 | 0.261 | 0.001* | 1.95 (1.317-2.887) |
| $B B$ vs. $B A+A A$ | Caucasian | 2 |  |  | 0.848 | 0.351 | 1.208 (0.812-1.798) |
| B vs. A | PB | 3 | 307 | 319 | 0.21 | 0.176 | 1.167 (0.933-1.458) |
| BB vs. AA | PB | 3 | 307 | 319 | 0.217 | 0.152 | 1.369 (0.891-2.105) |

[^0]Table 2 Results of pooled analysis for TLR2 polymorphism and cancer susceptibility (Continued)

| Comparison | Subgroup | $n$ | Cases | Controls | $P_{H}$ | $P_{Z}$ | HR (95\% CI) |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| BA vs. AA | PB | 3 | 307 | 319 | 0.044 | 0.421 | 1.322 (0.67-2.611) |
| $B B+B A$ vs. $A A$ | PB | 3 | 307 | 319 | 0.056 | 0.349 | 1.336 (0.729-2.449) |
| $B B$ vs. $B A+A A$ | PB | 3 | 307 | 319 | 0.652 | 0.408 | 1.167 (0.809-1.681) |
| B vs. A | Y | 3 | 417 | 411 | 0.463 | 0.158 | 1.15 (0.947-1.396) |
| BB vs. AA | Y | 3 | 417 | 411 | 0.502 | 0.163 | 1.31 (0.897-1.916) |
| BA vs. AA | Y | 3 | 417 | 411 | 0.183 | 0.238 | 1.211 (0.881-1.665) |
| $B B+B A$ vs. $A A$ | Y | 3 | 417 | 411 | 0.227 | 0.158 | 1.239 (0.921-1.666) |
| $\begin{gathered} \text { BB vs. BA+AA } \\ \text { rs5743708 } \end{gathered}$ | Y | 3 | 427 | 411 | 0.677 | 0.412 | 1.146 (0.827-1.588) |
| B vs. A | Overall | 2 | 309 | 572 | <0.001 | 0.321 | 4.076 (0.255-65.24) |
| BA vs. AA | Overall | 2 | 309 | 572 | 0.022 | 0.338 | 1.697 (0.575-5.011) |
| $\begin{gathered} \text { BB+BA vs. AA } \\ \text { rs1898830 } \end{gathered}$ | Overall | 4 | 2618 | 3487 | <0.001 | 0.312 | 1.651 (1.348-2.022) |
| B vs. A | Overall | 3 | 2520 | 3146 | 0.391 | 0.939 | 1.003 (0.928-1.085) |
| BB vs. AA | Overall | 3 | 2520 | 3146 | 0.323 | 0.646 | 0.961 (0.809-1.14) |
| BA vs. AA | Overall | 3 | 2520 | 3146 | 0.056 | 0.806 | 0.971 (0.768-1.227) |
| $B B+B A$ vs. AA | Overall | 3 | 2520 | 3146 | 0.075 | 0.813 | 0.975 (0.791-1.202) |
| $B B$ vs. $B A+A A$ | Overall | 3 | 2520 | 3146 | 0.998 | 0.77 | 0.977 (0.835-1.143) |
| B vs. A | Caucasian | 2 | 2309 | 2914 | 0.623 | 0.655 | 1.019 (0.939-1.106) |
| BB vs. AA | Caucasian | 2 | 2309 | 2914 | 0.779 | 0.972 | 1.003 (0.837-1.202) |
| BA vs. AA | Caucasian | 2 | 2309 | 2914 | 0.515 | 0.355 | 1.056 (0.941-1.187) |
| $B B+B A$ vs. $A A$ | Caucasian | 2 | 2309 | 2914 | 0.518 | 0.433 | 1.045 (0.936-1.167) |
| $B B$ vs. $B A+A A$ | Caucasian | 2 | 2309 | 2914 | 0.955 | 0.777 | 0.975 (0.822-1.158) |
| $B$ vs. $A$ | PB | 2 | 2309 | 2914 | 0.623 | 0.655 | 1.019 (0.939-1.106) |
| BB vs. AA | PB | 2 | 2309 | 2914 | 0.779 | 0.972 | 1.003 (0.837-1.202) |
| BA vs. AA | PB | 2 | 2309 | 2914 | 0.515 | 0.355 | 1.056 (0.941-1.187) |
| $B B+B A$ vs. $A A$ | PB | 2 | 2309 | 2914 | 0.518 | 0.433 | 1.045 (0.936-1.167) |
| $B B$ vs. $B A+A A$ | PB | 2 | 2309 | 2914 | 0.955 | 0.777 | 0.975 (0.822-1.158) |

vs. $\mathrm{AA}(\mathrm{OR}=1.903,95 \% \mathrm{Cl}=1.171-3.091, P=0.009)$, BA vs. $\mathrm{AA}(\mathrm{OR}=1.984,95 \% \mathrm{Cl}=1.307-3.012, P=0.001)$, $\mathrm{BB}+\mathrm{BA}$ vs. $\mathrm{AA}(\mathrm{OR}=1.95,95 \% \mathrm{Cl}=1.317-2.887, P=0.001)]$. Thus, we can conclude that a subgroup analysis by ethnicity suggests that rs4696480 is related to cancer risk in Caucasians, but not in other ethnic groups (Table 2 and Supplementary Figure S1).

For rs3804100 polymorphism, we collected eight publications which contained 2842 cases and 3081 controls [1,13-16,18,38,41]. But only in hospital-based analysis we found the model of BB vs. BA+AA (OR $=1.449,95 \%$ $\mathrm{Cl}=1.031-2.036, P=0.033$ ) added to the risk of cancer. None of the other models showed any association between rs3804100 and cancer risk, either in the analysis of overall group or in other subgroups (Table 2 and Supplementary Figure S2).

As for rs5743708 [6,37,42] and rs1898830 [16,37], they were found to have no significant correlation with cancer, either in overall analysis or in other subgroup analysis (Table 2 and Supplementary Figures S3 and S4).

## Sensitivity analysis and publication bias

By the way, we removed individual study one by one when conducted the sensitivity analysis. We did not observe any significant changes in the OR and corresponding $95 \%$ CI values, so the stability of our results was confirmed. All the details of sensitivity analysis are shown in the Supplementary Table S2 and Figure S5.

We used the Begg's test to evaluate publication bias for selected literature. These funnel plots in Figure 4 showed the relationship between the cancer risk and the TLR2 polymorphism in this meta-analysis. Among the various polymorphic sites, the funnel plots were symmetrically distributed. This showed that there was no publication bias. The Egger's test further analyzed the publication bias, and showed that no significant evidence of publication bias was


Figure 5. TSA for TLR2 polymorphism under the allele contrast model (B vs. A)
observed in our study ( $P=0.937$ for SNP rs4696480; $P=0.291$ for -196 to -174 del polymorphism; $P=0.991$ for SNP rs3804099) (Supplementary Table S3).

## Results of FPRP and TSA

The FPRP values for positive findings at different prior probability levels are shown in Table 3. For -196 to -174del variant, almost all the statistical power high than 0.2 , for the FPRP values, under the prior probability of 0.25 , the FPRP values for each group is less than 0.2 , except the five genetic models about Caucasian subgroup. Which means that the results on Caucasian subgroup are not stable, more studies are needed to illustrate the results. For the other positive results on rs3804099, rs3804100 and rs4696480, almost all the statistical power was higher than 0.5 , and under the prior probability of 0.25 , the FPRP values for each group is less than 0.2 , which means that the results are reliable. The results of TSA are shown in Figure 5, we analyzed the required sample size of each polymorphism. The required sample size of -196 to -174 del variant is approximately 39020 , although the sample size in the current study did not meet the required number, we observed that the cumulative z -curve crossed the trial sequential monitoring boundary and the traditional significant boundary ( $Z=1.96, \alpha=0.05$ ), which means that our conclusions were robust with the sufficient evidence. For rs3804100 (required sample size: 9162) and rs4696480 (required sample size: 1984), we observed that the cumulative z-curve crossed the trial sequential monitoring boundary and the traditional significant boundary, and meet the required number. The TSA result about rs 1898830 showed that the mutant allele performed the similar impact on cancer risk compare with the wild allele, no more samples are needed to confirm

Table 3 FPRP values for associations between the risk of cancer and the frequency of genotypes

| Comparison | Subgroup | $n$ | $\mathrm{P}_{\mathbf{z}}$ | OR (95\% CI) | Statistical power |  |  |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  |  |  |  |  |  | 0.25 | 0.1 | 0.01 | 0.001 |
| (-196 to -174del) |  |  |  |  |  |  |  |  |  |
| B vs. A | Overall | 18 | 0.005* | 1.468 (1.129-1.91) | 0.564 | $0.022^{\dagger}$ | $0.064^{\dagger}$ | 0.427 | 0.883 |
| BB vs. AA | Overall | 18 | 0.005* | 1.716 (1.178-2.5) | 0.237 | $0.054^{\dagger}$ | $0.146^{\dagger}$ | 0.652 | 0.950 |
| BA vs. AA | Overall | 18 | 0.008* | 1.408 (1.092-1.816) | 0.683 | $0.035^{\dagger}$ | 0.099 ${ }^{\dagger}$ | 0.547 | 0.924 |
| $B B+B A$ vs. $A A$ | Overall | 18 | 0.007* | 1.449 (1.107-1.897) | 0.597 | $0.034{ }^{\dagger}$ | $0.096{ }^{\dagger}$ | 0.539 | 0.922 |
| $B B$ vs. $B A+A A$ | Overall | 18 | $0.013^{*}$ | 1.517 (1.092-2.107) | 0.468 | $0.073^{\dagger}$ | $0.192^{\dagger}$ | 0.723 | 0.963 |
| $B$ vs. A | Asian | 11 | 0.043* | 1.169 (1.005-1.361) | 0.999 | $0.117^{\dagger}$ | 0.285 | 0.814 | 0.978 |
| $B B+B A$ vs. $A A$ | Asian | 11 | 0.033* | 1.203 (1.015-1.427) | 0.994 | $0.106^{\dagger}$ | 0.262 | 0.796 | 0.975 |
| B vs. A | Caucasian | 3 | 0.028* | 3.291 (1.139-9.51) | 0.073 | 0.532 | 0.773 | 0.974 | 0.997 |
| BB vs. AA | Caucasian | 3 | 0.008* | 9.878 (1.83-53.322) | 0.014 | 0.621 | 0.831 | 0.982 | 0.998 |
| BA vs. AA | Caucasian | 3 | $0.044^{*}$ | 3.156 (1.034-9.634) | 0.096 | 0.577 | 0.804 | 0.978 | 0.998 |
| $B B+B A$ vs. $A A$ | Caucasian | 3 | 0.034* | 3.555 (1.098-11.51) | 0.075 | 0.579 | 0.805 | 0.978 | 0.998 |
| $B B$ vs. $B A+A A$ | Caucasian | 3 | 0.006* | 7.294 (1.752-30.369) | 0.015 | 0.561 | 0.793 | 0.977 | 0.998 |
| $B$ vs. $A$ | PB | 14 | 0.001 * | 1.576 (1.193-2.08) | 0.364 | $0.011{ }^{\dagger}$ | $0.031{ }^{\dagger}$ | 0.263 | 0.783 |
| BB vs. AA | PB | 14 | $0.001^{*}$ | 2.274 (1.43-3.616) | 0.040 | $0.039{ }^{\dagger}$ | $0.108^{\dagger}$ | 0.571 | 0.931 |
| BA vs. AA | PB | 14 | 0.005* | 1.543 (1.143-2.081) | 0.427 | $0.031{ }^{\dagger}$ | $0.086^{\dagger}$ | 0.510 | 0.913 |
| $B B+B A$ vs. $A A$ | PB | 14 | $0.002^{*}$ | 1.624 (1.186-2.223) | 0.310 | $0.023^{\dagger}$ | $0.067^{\dagger}$ | 0.441 | 0.888 |
| $B B$ vs. $B A+A A$ | PB | 14 | 0.001* | 2.011 (1.317-3.07) | 0.087 | $0.040^{\dagger}$ | $0.111^{\dagger}$ | 0.578 | 0.933 |
| $B$ vs. $A$ | Y | 15 | 0.008* | 1.447 (1.103-1.897) | 0.603 | $0.036{ }^{\dagger}$ | $0.101{ }^{\dagger}$ | 0.551 | 0.925 |
| BB vs. AA | Y | 15 | 0.004* | 1.915 (1.227-2.991) | 0.141 | $0.083^{\dagger}$ | 0.214 | 0.750 | 0.968 |
| BA vs. AA | Y | 15 | 0.02* | 1.422 (1.057-1.915) | 0.637 | $0.088^{\dagger}$ | 0.224 | 0.760 | 0.970 |
| $B B+B A$ vs. $A A$ | Y | 15 | $0.013^{*}$ | 1.494 (1.088-2.052) | 0.510 | $0.072^{\dagger}$ | 0.189 | 0.719 | 0.963 |
| $B B$ vs. $B A+A A$ | Y | 15 | 0.009* | 1.673 (1.137-2.461) | 0.290 | $0.085^{\dagger}$ | 0.218 | 0.754 | 0.969 |
| BA vs. AA | N | 3 | 0.039* | 1.335 (1.015-1.757) | 0.797 | $0.129^{\dagger}$ | 0.307 | 0.830 | 0.980 |
| rs3804099 |  |  |  |  |  |  |  |  |  |
| BA vs. AA | Overall | 9 | 0.008* | 0.827 (0.717-0.952) | 0.999 | $0.024^{\dagger}$ | $0.069^{\dagger}$ | 0.448 | 0.891 |
| $B B+B A$ vs. $A A$ | Overall | 9 | 0.016* | 0.85 (0.744-0.97) | 1.000 | $0.045^{\dagger}$ | $0.125^{\dagger}$ | 0.611 | 0.941 |
| BB vs. AA | Asian | 5 | 0.005* | 0.65 (0.482-0.877) | 0.434 | $0.032^{\dagger}$ | $0.091{ }^{\dagger}$ | 0.524 | 0.917 |
| BA vs. AA | Asian | 5 | $0.001^{*}$ | 0.69 (0.55-0.867) | 0.287 | $0.064^{\dagger}$ | $0.170^{\dagger}$ | 0.692 | 0.958 |
| B vs. A | Gastric cancer | 2 | $0.002^{*}$ | 0.728 (0.594-0.893) | 0.801 | $0.009{ }^{\dagger}$ | $0.025^{\dagger}$ | 0.223 | 0.743 |
| BB vs. AA | Gastric cancer | 2 | 0.026* | 0.605 (0.389-0.942) | 0.334 | $0.190^{\dagger}$ | 0.413 | 0.886 | 0.987 |
| BA vs. AA | Gastric cancer | 2 | 0.018* | 0.706 (0.529-0.942) | 0.652 | $0.076{ }^{\dagger}$ | $0.199{ }^{\dagger}$ | 0.732 | 0.965 |
| $B B+B A$ vs. $A A$ | Gastric cancer | 2 | 0.004* | 0.681 (0.524-0.886) | 0.563 | $0.022^{\dagger}$ | $0.063^{\dagger}$ | 0.426 | 0.882 |
| $B B$ vs. $B A+A A$ | Colon cancer | 2 | 0.034* | 0.841 (0.716-0.987) | 0.998 | $0.093^{\dagger}$ | 0.235 | 0.771 | 0.971 |
| BA vs. AA | HB | 4 | 0.005* | 0.713 (0.564-0.902) | 0.712 | $0.020^{\dagger}$ | $0.057^{\dagger}$ | 0.400 | 0.871 |
| $B B+B A$ vs. $A A$ | HB | 4 | 0.005* | 0.734 (0.591-0.912) | 0.807 | $0.019^{\dagger}$ | $0.055^{\dagger}$ | 0.391 | 0.867 |
| $B$ vs. A | Y | 5 | 0.036* | 0.895 (0.807-0.993) | 1.000 | $0.098^{\dagger}$ | 0.247 | 0.783 | 0.973 |
| $B B+B A$ vs. $A A$ | Y | 5 | 0.028* | 0.844 (0.725-0.982) | 0.999 | $0.078^{\dagger}$ | 0.202 | 0.736 | 0.966 |
| BA vs. AA | N | 4 | 0.042* | 0.73 (0.54-0.988) | 0.722 | $0.147^{\dagger}$ | 0.341 | 0.851 | 0.983 |
| rs3804100 |  |  |  |  |  |  |  |  |  |
| BB vs. BA+ AA | HB | 4 | 0.033* | 1.449 (1.031-2.036) | 0.579 | $0.144^{\dagger}$ | 0.336 | 0.848 | 0.983 |
| rs4696480 |  |  |  |  |  |  |  |  |  |
| B vs. A | Overall | 4 | 0.03* | 1.216 (1.019-1.452) | 0.990 | $0.085^{\dagger}$ | 0.218 | 0.754 | 0.969 |
| BB vs. AA | Overall | 4 | $0.032^{*}$ | 1.463 (1.034-2.069) | 0.556 | $0.145^{\dagger}$ | 0.337 | 0.848 | 0.983 |
| B vs. A | Caucasian | 2 | 0.007* | 1.393 (1.094-1.775) | 0.725 | $0.029{ }^{\dagger}$ | $0.084^{\dagger}$ | 0.501 | 0.910 |
| BB vs. AA | Caucasian | 2 | 0.009* | 1.903 (1.171-3.091) | 0.168 | $0.143^{\dagger}$ | 0.333 | 0.846 | 0.982 |
| BA vs. AA | Caucasian | 2 | $0.001^{*}$ | 1.984 (1.307-3.012) | 0.095 | $0.040^{\dagger}$ | $0.110^{\dagger}$ | 0.576 | 0.932 |
| $B B+B A$ vs. $A A$ | Caucasian | 2 | 0.001* | 1.95 (1.317-2.887) | 0.095 | $0.026^{\dagger}$ | $0.075^{\dagger}$ | 0.470 | 0.899 |

Statistical power was calculated using the number of observations in the subgroup and the OR and $P$ values in this table. Abbreviations: Cl , confidence interval; H-B, hospital based; HWE (Y), polymorphisms conformed to HWE in the control group.

* $P$-value less than 0.05 was considered as statistically significant.
${ }^{\dagger}$ The significant result with the FPRP values less than 0.2 was considered a worthy finding.


CEU

$\mathrm{CHB}+\mathrm{CHS}$


ESN


JPT


YRI

Figure 6. LD analyses for TLR2 polymorphisms in populations from 1000 genomes Phase 3
The number of each cell represents $r^{2}$ and white color cells show no LD between polymorphisms.
the result (Figure 5). However, The TSA results of rs3804099 and rs5743708 indicated that more objects are need to drag out the robust conclusion (Supplementary Figure S6).

## LD analyses and in-silico analysis of TLR2 expression

LD analysis was conducted to evaluate the presence of bins in different TLR2 polymorphisms, aiming to understand the internal linkages, the results of which are shown in Figure 6. Highlighted, there is significant LD between rs4696480 and rs1898830 in CEU, CHB and CHS, and JPT populations (CEU: $\mathrm{r}^{2}=0.52$; CHB and CHS: $\mathrm{r}^{2}=0.90$; JPT: $r^{2}=1.0$ ). The LD between rs3804099 and rs3804100 is also remarkable in CHB and CHS and JPT populations (CHB and CHS: $\mathrm{r}^{2}=0.85$; JPT: $\mathrm{r}^{2}=0.86$ ) (Supplementary Table S4). According to the result on GTEx portal data, we found that the mutant allele leads to an increase expression of TLR2 mRNA in rs1898830 $\left(P=3.5^{\star} 10^{-17}\right)$, while the mutant allele of rs3804099 $\left(P=2.5^{*} 10^{-14}\right)$, rs3804100 $\left(P=9.7^{*} 10^{-5}\right)$ and rs4696480 $\left(P=1.2^{*} 10^{-5}\right)$ lead to a decreased expression of TLR2 (Figure 7).

## Discussion

TLRs are expressed in mast cells and several other cell types, which could recognize microbial components and trigger inflammatory response. TLR2 is type I transmembrane transporter which plays an important role in immune inflammatory response [43], and have been shown to influence host defense and disease progression [44]. There have been four previous meta-analyses on TLR2. But two of the studies were limited to gastric cancer [45,46]. One of these articles suggested that - 196 to -174 del was associated with the rise of cancer risk and the rs3804099 can decrease cancer risk [47]. Another article suggested that -196 to -174 del had no relationship with cervical cancer [48]. For assessing


Figure 7. In-silico analysis of TLR2 expression concerned to its polymorphisms
the real influence of TLR2 on cancer risk, we collected more samples than before. And our meta-analysis combines many types of cancers to study the relationship between TLR2 polymorphism and cancer risk as comprehensively as possible.

For -196 to -174 del , it is a 22 -bp deletion at the promoter region of TLR2 gene. Transcriptional reduction in the TLR2 gene due to this substitution may significantly alter the function of the promoter [49]. Chen et al.'s meta-analysis [45] thought that this polymorphism is not associated with gastric cancer. Yang et al. [48] published a meta-analysis in 2018 suggesting that -196 to -174 del had nothing to do with cervical cancer. And in our calculations, we revealed that the deletion of these 22 genes does increase the risk of cancer, especially among Caucasians. However, the subgroup calculations of gastric, breast and cervical cancers had no obvious significance.

Synonymous mutations are associated with disease, such as rs3804099 and rs3804100 of TLR2 [16]. We found that rs3804099 is protective against gastric cancer which is consistent with Wang et al. [47]. As for rs3804100, unfortunately, we only came to the conclusions related to cancer in the subgroup of hospital-based. This conclusion is extremely contingent because of the small number of samples and the limitations of the source of the sample. Taking into account the vast majority of calculations and references, we reserve the conclusion that rs3804100 is not related to cancer. And we are the first meta-analysis involving rs 4696480 . The overall analysis of $B$ vs. $A$ and $B B$ vs. AA shown
that rs4696480 has increased the risk of cancer. At the same time, the calculation results also show that its influence on cancer is particularly obvious among the Caucasian population.

Although our conclusions about -196 to -174del, rs3804099 and rs3804100 are consistent with the previous two meta-analyses, we included more case-control studies, so our meta-analysis is more convincing. And we also clearly observe that 'ethnic' factors are critical in assessing the role of TLR2 in cancer risk. The calculation of -196 to -174del and rs 4696480 both found that Caucasians make a significant increase in the cancer risk. And in the model of BB vs. AA and BA vs. AA, rs3804099 deduce the cancer risk in Asians. Furthermore, as the results showing - 196 to -174del and rs4696480 are associated with the tumorigenesis, so that these polymorphisms could be a potential biomarker to remind people with the polymorphism pay more attention to the occurrence of cancer, and solve the problem as soon as possible. In the current study, we also evaluated the LD between different polymorphisms of TLR2, we found that there are significantly LD among rs4696480 and rs1898830, rs3804099 and rs3804100. Based on the results, it could guide the researchers to put these polymorphisms together when assess their effect on cancer risks or other bioscience mechanisms. At the same time, we should also be aware of some of the limitations of our article. First of all, based on the results of TSA, we found that the sample size of -196 to - 174 del, rs3804100 and rs4696480 is enough to generate the reliable conclusion in the current study, however, larger number of patients are needed to confirm the effect of rs3804099, rs1898830 and rs5743708 to cancer risks. Second, we lack in-depth studies of the effects of environment, lifestyle, bacterial infections and other factors of cancer risk.

## Conclusion

Our meta-analysis suggested that -196 to -174del increased the risk of cancer; rs4696480 increases the risk of cancer in Caucasians; rs3804099 reduced the risk of cancer, especially gastric cancer. While there is no direct evidence showing that rs5743708,3804100 and rs1898830 are related to cancer.

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## Competing Interests

The authors declare that there are no competing interests associated with the manuscript.

## Author Contribution

Conception and design: S.-L.G. and Y.-D.C. Collection and assembly of data: C.Y., J.C. and L.-F.Z. Data analysis and interpretation: S.-L.G., Y.-D.C. and L.Z. Manuscript writing: S.-L.G., YD.C. and S.-M.W. Final approval of manuscript: all authors.

## Abbreviations

CEU, Utah residents with Northern and Western European ancestry from the CEPH collection; CHB, Han Chinese in Beijing, China; CHS, Southern Han Chinese, China; FPRP, false-positive report probability; HWE, Hardy-Weinberg equilibrium; JPT, Japanese in Tokyo, Japan; LD, linkage disequilibrium; NOS, Newcastle-Ottawa Scale; OR, odds ratio; TLR2, Toll-like receptor-2; TSA, trial sequential analysis; $95 \% \mathrm{CI}, 95 \%$ confidence interval.

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Supplementary table 1. Methodological quality of the included studies according to the Newcastle-Ottawa Scale.

| SNP | Author | Year | Adequacy of Case Definition | Representativ eness of the Cases | Selectio <br> $n$ of <br> Controls | Definition of Controls | Comparability Cases/Controls | Ascertainment of Exposure | Same Method <br> of <br> Ascertainment | Non-response rate |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| (-196 to -174del) | Tahara et al. | 2007 | * | * | * | * |  | * | * | NA |
| (-196 to -174del) | Pandey et al. | 2009 | * | * | * | * | * | * | * | NA |
| (-196 to -174del) | Hishida et al. | 2010 | * | * |  |  | * | * | * | NA |
| (-196 to -174del) | Srivastava et al. | 2010 | * | * | * | * | * | * | * | NA |
| (-196 to -174del) | Nischalk et al. | 2011 | * |  | * | * |  | * | * | NA |
| (-196 to -174del) | Oliveira et al. | 2012 | * | * | * | * |  | * | * | NA |
| (-196 to -174del) | Mandal et al. | 2012 | * | * | * | * | * | * | * | NA |
| (-196 to -174del) | Theodoropoulos et al. | 2012 | * |  | * | * | * | * | * | NA |
| (-196 to -174del) | Singh et al. | 2013 | * | * | * | * | * | * | * | NA |
| (-196 to -174del) | Bi et al. | 2014 | * | * | * | * |  | * | * | NA |
| (-196 to -174del) | Castano-Rodriguez et al. | 2014 | * | * |  |  | * | * | * | NA |
| (-196 to -174del) | Zidi et al. | 2014 | * | * | * | * |  | * | * | NA |
| (-196 to -174del) | Devi et al. | 2015 | * | * | * | * | * | * | * | NA |
| (-196 to -174del) | Proença et al. | 2015 | * | * | * | * |  | * | * | NA |
| (-196 to -174del) | Zidi et al. | 2015 | * | * | * | * | * | * | * | NA |
| (-196 to -174del) | AL-Harras et al. | 2016 | * | * | * | * |  | * | * | NA |
| (-196 to -174del) | Huang et al. | 2018 | * | * | * | * | * | * | * | NA |
| (-196 to -174del) | Messaritakis et al. | 2018 | * | * | * | * |  | * | * | NA |
| (-196 to -174del) | Zeng et al. | 2011a | * | * |  |  | ** | * | * | NA |
| rs3804099 | Etokebe et al. | 2009 | * | * | * | * |  | * | * | NA |
| rs3804099 | Zeng et al. | 2011b | * | * |  |  | ** | * | * | NA |
| rs3804099 | Xie et al. | 2012 | * | * |  |  | * | * | * | NA |
| rs3804099 | Slattery et al. | 2012 | * | * | * | * | * | * | * | NA |
| rs3804099 | Slattery et al. | 2012 | * | * | * | * | * | * | * | NA |
| rs3804099 | Miedema et al. | 2012 | * | * | * | * |  | ** | * | NA |
| rs3804099 | Zeljic et al. | 2013 | * | * | * | * | ** | * | * | NA |
| rs3804099 | Semlali et al. | 2017 | * | * | * | * | * | * | * | NA |
| rs3804099 | Semlali et al. | 2018 | * | * | * | * | * | * | * | NA |


| rs3804099 | Tongtawee et al. | 2018 | * | * |  |  | * | * | * | NA |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| rs3804100 | Purdu et al. | 2008 | * |  | * | * | * |  | * | NA |
| rs3804100 | Etokebe et al. | 2009 | * | * | * | * |  | * | * | NA |
| rs3804100 | Xie et al. | 2012 | * | * |  |  | * | * | * | NA |
| rs3804100 | Miedema et al. | 2012 | * | * | * | * |  | ** | * | NA |
| rs3804100 | Castaño-Rodríguez et al. | 2014 | * | * |  |  | * | * | * | NA |
| rs3804100 | Semlali et al. | 2017 | * | * | * | * | * | * | * | NA |
| rs3804100 | Semlali et al. | 2018 | * | * | * | * | * | * | * | NA |
| rs3804100 | Tongtawee et al. | 2018 | * | * |  |  | * | * | * | NA |
| rs4696480 | Miedema et al. | 2012 | * | * | * | * |  | ** | * | NA |
| rs4696480 | Gallo et al. | 2017 | * | * | * | * |  | * | * | NA |
| rs4696480 | Semlali et al. | 2017 | * | * | * | * | * | * | * | NA |
| rs4696480 | Semlali et al. | 2018 | * | * | * | * | * | * | * | NA |
| rs5743708 | Nischalk et al. | 2011 | * |  | * | * |  | * | * | NA |
| rs5743708 | Slattery et al. | 2012 | * | * | * | * | * | * | * | NA |
| rs5743708 | Slattery et al. | 2012 | * | * | * | * | * | * | * | NA |
| rs5743708 | Kına et al. | 2018 | * | * | * | * | * | * | * | NA |
| rs1898830 | Xie et al. | 2012 | * | * |  |  | * | * | * | NA |
| rs1898830 | Slattery et al. | 2012 | * | * | * | * | * | * | * | NA |
| rs1898830 | Slattery et al. | 2012 | * | * | * | * | * | * | * | NA |

This table identifies "high" quality choices with a "star". A study can be awarded a maximum of 1 star for each numbered item within the Selection and Exposure categories. A
maximum of 2 stars can be given for Comparability. *, Yes; NA, not applicable. (http://www.ohri.ca/programs/clinical epidemiology/oxford.htm).

Supplementary table 2. Details of the sensitivity analyses for TLR2 polymorphism and cancer risk.

| SNP | Comparison | Study omitted | Estimate (95\% Confident Interval) | Effect Model |
| :---: | :---: | :---: | :---: | :---: |
| (-196 to -174del) | B vs. A | Tahara et al. (2007) | 1.3842176 (1.0833399-1.7686585) | Random |
|  |  | Pandey et al. (2009) | 1.3852967 (1.0883054-1.7633349) |  |
|  |  | Hishida et al. (2010) | 1.4153796 (1.0891982-1.8392425) |  |
|  |  | Srivastava et al. (2010) | 1.3988788 (1.0941139-1.7885357) |  |
|  |  | Zeng et al. (2011a) | 1.4531407 (1.1535394-1.8305556) |  |
|  |  | Nischalk et al. (2011) | 1.3801254 (1.0811518-1.761775) |  |
|  |  | Oliveira et al. (2012) | 1.3466114 (1.0639657-1.7043427) |  |
|  |  | Mandal et al. (2012) | 1.389533 (1.0895275-1.7721463) |  |
|  |  | Theodoropoulos et al. (2012) | 1.2380068 (1.0824547-1.4159125) |  |
|  |  | Singh et al. (2013) | 1.4060576 (1.1006653-1.7961845) |  |
|  |  | Bi et al. (2014) | 1.4226668 (1.1177661-1.8107371) |  |
|  |  | Castano-Rodriguez et al. (2014) | 1.4321136 (1.1263661-1.8208549) |  |
|  |  | Zidi et al. (2014) | 1.4113173 (1.1074009-1.798641) |  |
|  |  | Devi et al. (2015) | 1.3978628 (1.0823373-1.8053708) |  |
|  |  | Proenca et al. (2015) | 1.3872203 (1.0892484-1.7667044) |  |
|  |  | Zidi et al. (2015) | 1.4134914 (1.1091279-1.8013773) |  |
|  |  | AL-Harras et al. (2016) | 1.4114381 (1.109862-1.7949597) |  |
|  |  | Huang et al. (2018) | 1.3877288 (1.0831736-1.7779155) |  |
|  |  | Combined | 1.3920354(1.1039533-1.7552939) |  |
|  | BB vs. AA | Tahara et al. (2007) | 1.6191133 (1.1074116-2.3672569) | Random |
|  |  | Pandey et al. (2009) | 1.6689134 (1.1418774-2.4392042) |  |
|  |  | Hishida et al. (2010) | 1.8226418 (1.1751486-2.8268964) |  |
|  |  | Srivastava et al. (2010) | 1.7162418 (1.1617243-2.5354433) |  |
|  |  | Zeng et al. (2011a) | 1.8692523 (1.3004427-2.6868577) |  |
|  |  | Nischalk et al. (2011) | 1.6466268 (1.1200988-2.4206614) |  |
|  |  | Oliveira et al. (2012) | 1.6287422 (1.1182092-2.372366) |  |
|  |  | Mandal et al. (2012) | 1.7230891 (1.1648878-2.5487742) |  |
|  |  | Theodoropoulos et al. (2012) | 1.4391873 (1.0632966-1.9479607) |  |
|  |  | Singh et al. (2013) | 1.7411302 (1.1714258-2.5879016) |  |
|  |  | Bi et al. (2014) | 1.7911378 (1.2046455-2.6631689) |  |


|  | Castano-Rodriguez et al. (2014) | 1.7924392 (1.2086339-2.6582394) |  |
| :---: | :---: | :---: | :---: |
|  | Zidi et al. (2014) | 1.7909669 (1.1981788-2.6770315) |  |
|  | Devi et al. (2015) | 1.7879089 (1.1870695-2.6928654) |  |
|  | Proenca et al. (2015) | 1.7214299 (1.1655397-2.5424454) |  |
|  | Zidi et al. (2015) | 1.8113037 (1.217249-2.6952751) |  |
|  | AL-Harras et al. (2016) | 1.7418679 (1.1769091-2.5780275) |  |
|  | Huang et al. (2018) | 1.6676577 (1.1255744-2.4708116) |  |
|  | Combined | $1.7159047(1.1779598-2.4995155)$ |  |
| BA vs. AA | Tahara et al. (2007) | 1.4379952 (1.1013559-1.8775312) | Random |
|  | Pandey et al. (2009) | 1.4099357 (1.0802039-1.8403181) |  |
|  | Hishida et al. (2010) | 1.4325813 (1.0812083-1.8981441) |  |
|  | Srivastava et al. (2010) | 1.4125484 (1.0770715-1.8525165) |  |
|  | Zeng et al. (2011a) | 1.475433 (1.1450467-1.9011475) |  |
|  | Nischalk et al. (2011) | 1.4035684 (1.0712777-1.8389293) |  |
|  | Oliveira et al. (2012) | 1.3656155 (1.0514834-1.7735951) |  |
|  | Mandal et al. (2012) | 1.4033546 (1.0730686-1.8353013) |  |
|  | Theodoropoulos et al. (2012) | 1.249367 (1.0883496-1.4342062) |  |
|  | Singh et al. (2013) | 1.4239892 (1.088258-1.8632944) |  |
|  | Bi et al. (2014) | 1.446191 (1.112655-1.8797095) |  |
|  | Castano-Rodriguez et al. (2014) | 1.4140229 (1.0890495-1.8359689) |  |
|  | Zidi et al. (2014) | 1.4204854 (1.0901513-1.8509163) |  |
|  | Devi et al. (2015) | 1.400021 (1.0571072-1.8541719) |  |
|  | Proenca et al. (2015) | 1.4025673 (1.0742663-1.8311986) |  |
|  | Zidi et al. (2015) | 1.404094 (1.0766704-1.8310896) |  |
|  | AL-Harras et al. (2016) | 1.4375898 (1.1057117-1.8690807) |  |
|  | Huang et al. (2018) | 1.4095417 (1.0742522-1.8494798) |  |
|  | Combined | $1.4082073(1.0920892-1.8158295)$ |  |
| BB+BA vs. AA | Tahara et al. (2007) | 1.4584963 (1.0969443-1.9392155) | Random |
|  | Pandey et al. (2009) | 1.4463475 (1.0912107-1.9170641) |  |
|  | Hishida et al. (2010) | 1.4739951 (1.0930413-1.9877213) |  |
|  | Srivastava et al. (2010) | 1.4542896 (1.0920157-1.936747) |  |
|  | Zeng et al. (2011a) | 1.5263284 (1.1706467-1.9900784) |  |
|  | Nischalk et al. (2011) | 1.4389279 (1.0814754-1.9145266) |  |



Xie et al. (2012)
Miedema et al. (2012)
Slattery et al. (2012)
Zeljic et al. (2013)
Semlali et al. (2017)
Semlali et al. (2018)
Tongtawee et al. (2018)
Zeng et al. (2011b)
Combined
Etokebe et al. (2009)
Xie et al. (2012)
Miedema et al. (2012)
Slattery et al. (2012)
Zeljic et al. (2013)
Semlali et al. (2017)
Semlali et al. (2018)
Tongtawee et al. (2018)
Zeng et al. (2011b)
Combined
Etokebe et al. (2009)
Xie et al. (2012)
Miedema et al. (2012)
Slattery et al. (2012)
Zeljic et al. (2013)
Semlali et al. (2017)
Semlali et al. (2018)
Tongtawee et al. (2018)
Zeng et al. (2011b)

## Combined

$\mathrm{BB}+\mathrm{BA}$ vs. AA

Etokebe et al. (2009)
Xie et al. (2012)
Miedema et al. (2012)
Slattery et al. (2012)
$0.92676383(0.7667833-1.1201224)$
$0.95441699(0.77630502-1.1733943)$
$0.96444345(0.76220924-1.2203357)$
$0.90798628(0.77780855-1.0599512)$
0.98396611(0.80367553-1.2047018)
1.0058529(0.83297974-1.2146034) $1.0002049(0.82552308-1.2118498)$ 1.007781(0.83084249-1.2224008) 0.96741525(0.805536-1.1618255)
$0.83248496(0.58359981-1.1875111)$ 0.83050156(0.57751393-1.1943139)
$0.79650563(0.55756348-1.1378456)$
$0.82188183(0.54482174-1.2398363)$
$0.83790469(0.67976439-1.0328348)$
0.86173928(0.59840006-1.2409668)
$0.89638388(0.64419699-1.2472955)$
0.87157202(0.60786855-1.2496743)
0.89229125(0.62907434-1.2656432)
0.84045512(0.60901101-1.1598556)
$0.82675534(0.71513367-0.95579952)$
$0.84389544(0.73035383-0.97508842)$
$0.8227998(0.70942289-0.95429611)$
0.72886878(0.60421723-0.87923628)
$0.83129221(0.71871334-0.96150529)$
0.83012533(0.71732771-0.96066004)
$0.83351672(0.72058511-0.96414721)$
$0.83189094(0.7195071-0.96182865)$
$0.86057824(0.73464006-1.0081059)$
$0.8265341(0.71730049-0.95240227)$
$0.84955496(0.74180108-0.97296107)$
$0.85593086(0.74777192-0.97973406)$
$0.84141642(0.7326141-0.96637726)$
$0.76597619(0.64349884-0.91176468)$

Random

FIXED

FIXED

|  |  | Zeljic et al. (2013) | $0.83369786(0.72757339-0.9553017)$ |  |
| :---: | :---: | :---: | :---: | :---: |
|  |  | Semlali et al. (2017) | 0.856233(0.74684209-0.98164654) |  |
|  |  | Semlali et al. (2018) | $0.86472785(0.75451595-0.99103838)$ |  |
|  |  | Tongtawee et al. (2018) | $0.86316466(0.75228989-0.99038053)$ |  |
|  |  | Zeng et al. (2011b) | 0.89538008(0.77273506-1.0374907) |  |
|  |  | Combined | $0.84974157(0.74417662-0.97028139)$ |  |
|  | BB vs. $\mathrm{BA}+\mathrm{AA}$ | Etokebe et al. (2009) | $0.98531634(0.75018847-1.2941391)$ | Random |
|  |  | Slattery et al. (2012) | $1.0224282(0.73720181-1.4180096)$ |  |
|  |  | Xie et al. (2012) | $0.90305895(0.71781307-1.1361111)$ |  |
|  |  | Miedema et al. (2012) | $0.95622373(0.72741711-1.2570007)$ |  |
|  |  | Slattery et al. (2012) | $0.99512035(0.7201038-1.375169)$ |  |
|  |  | Zeljic et al. (2013) | $0.96521997(0.77944446-1.195274)$ |  |
|  |  | Semlali et al. (2017) | $1.0094388(0.76200932-1.3372103)$ |  |
|  |  | Semlali et al. (2018) | $1.0407708(0.79820967-1.3570417)$ |  |
|  |  | Tongtawee et al. (2018) | $1.0242591(0.77977443-1.3453976)$ |  |
|  |  | Zeng et al. (2011b) | $1.0333945(0.78642559-1.3579214)$ |  |
|  |  | Combined | $0.99117113(0.76757505-1.2799012)$ |  |
| rs3804100 | B vs. A | Purdu et al. (2008) | 1.0509363(0.87773889-1.2583095) | FIXED |
|  |  | Etokebe et al. (2009) | $1.0712918(0.94372904-1.216097)$ |  |
|  |  | Xie et al. (2012) | 1.023598(0.8918919-1.174753) |  |
|  |  | Miedema et al. (2012) | $1.0755367(0.94661063-1.2220222)$ |  |
|  |  | Castano-Rodriguez et al. (2014) | $1.0826485(0.94917309-1.2348937)$ |  |
|  |  | Semlali et al. (2017) | $1.0897315(0.95792955-1.239668)$ |  |
|  |  | Semlali et al. (2018) | $1.0973544(0.96575099-1.2468916)$ |  |
|  |  | Tongtawee et al. (2018) | $1.098178(0.96446925-1.2504234)$ |  |
|  |  | Combined | $1.0757035(0.94900288-1.2193197)$ |  |
|  | BB vs. AA | Purdu et al. (2008) | $0.69224417(0.39371327-1.2171344)$ | FIXED |
|  |  | Etokebe et al. (2009) | $0.82257968(0.51609141-1.3110803)$ |  |
|  |  | Xie et al. (2012) | 0.78167593(0.444442-1.3747964) |  |
|  |  | Miedema et al. (2012) | $0.79560041(0.49527037-1.2780495)$ |  |
|  |  | Castano-Rodriguez et al. (2014) | $0.84008753(0.50456429-1.3987256)$ |  |
|  |  | Semlali et al. (2017) | $0.87610734(0.54209089-1.4159324)$ |  |
|  |  | Semlali et al. (2018) | $0.82225353(0.50898784-1.3283241)$ |  |


|  |  | Tongtawee et al. (2018) | 0.92980087(0.57338297-1.5077701) |  |
| :---: | :---: | :---: | :---: | :---: |
|  |  | Combined | 0.82257966(0.51609141-1.3110803) |  |
|  | BA vs. AA | Purdu et al. (2008) | 0.95118934(0.74209517-1.2191983) | FIXED |
|  |  | Etokebe et al. (2009) | $1.0331113(0.88734871-1.202818)$ |  |
|  |  | Xie et al. (2012) | $1.0672268(0.9164629-1.2427924)$ |  |
|  |  | Miedema et al. (2012) | $1.0441124(0.8955912-1.2172638)$ |  |
|  |  | Castano-Rodriguez et al. (2014) | $1.0305344(0.88151097-1.2047508)$ |  |
|  |  | Semlali et al. (2017) | 1.0410093(0.8920272-1.2148736) |  |
|  |  | Semlali et al. (2018) | $1.0668006(0.91554779-1.2430412)$ |  |
|  |  | Tongtawee et al. (2018) | $1.0363233(0.88703543-1.2107363)$ |  |
|  |  | Combined | $1.040501(0.89578847-1.2085915)$ |  |
|  | BB+BA vs. AA | Purdu et al. (2008) | 0.93218386(0.73226815-1.1866783) | FIXED |
|  |  | Etokebe et al. (2009) | $1.0282626(0.88614511-1.1931726)$ |  |
|  |  | Xie et al. (2012) | $1.0493138(0.90400296-1.2179821)$ |  |
|  |  | Miedema et al. (2012) | 1.0359852(0.8916021-1.2037492) |  |
|  |  | Castano-Rodriguez et al. (2014) | $1.0301102(0.88389486-1.2005129)$ |  |
|  |  | Semlali et al. (2017) | $1.0422701(0.8959319-1.2125105)$ |  |
|  |  | Semlali et al. (2018) | $1.061036(0.9134236-1.2325029)$ |  |
|  |  | Tongtawee et al. (2018) | 1.0438291(0.89639461-1.215513) |  |
|  |  | Combined | 1.0354481 (0.89429472-1.1988809) |  |
|  | BB vs. $\mathrm{BA}+\mathrm{AA}$ | Purdu et al. (2008) | $1.3592938(0.97788465-1.889466)$ | FIXED |
|  |  | Etokebe et al. (2009) | $1.3427418(0.98680955-1.8270552)$ |  |
|  |  | Xie et al. (2012) | $0.76624233(0.43729138-1.3426455)$ |  |
|  |  | Miedema et al. (2012) | $1.3311722(0.97659153-1.814494)$ |  |
|  |  | Castano-Rodriguez et al. (2014) | $1.4226214(1.0304278-1.9640886)$ |  |
|  |  | Semlali et al. (2017) | $1.4013143(1.0246511-1.9164394)$ |  |
|  |  | Semlali et al. (2018) | 1.3562951 (0.99298555-1.852531) |  |
|  |  | Tongtawee et al. (2018) | $1.4469726(1.0552281-1.9841487)$ |  |
|  |  | Combined | $1.3427418(0.98680954-1.8270552)$ |  |
| rs4696480 | B vs. A | Miedema et al. (2012) | $1.1666657(0.93330896-1.4583688)$ | FIXED |
|  |  | Gallo et al. (2017) | 1.1498516 (0.94730139-1.3957106) |  |
|  |  | Semlali et al. (2017) | $1.2602687(1.0255111-1.5487664)$ |  |
|  |  | Semlali et al. (2018) | $1.2888148(1.0570656-1.5713724)$ |  |

Combined
Miedema et al. (2012)
Gallo et al. (2017)
Semlali et al. (2017)
Semlali et al. (2018)
Combined
Miedema et al. (2012)
Gallo et al. (2017)
Semlali et al. (2017)
Semlali et al. (2018) Combined
Miedema et al. (2012)
Gallo et al. (2017)
Semlali et al. (2017)
Semlali et al. (2018) Combined
Miedema et al. (2012)
Gallo et al. (2017)
Semlali et al. (2017)
Semlali et al. (2018)
Combined
rs5743708
B vs. A

BA vs. AA
$\mathrm{BB}+\mathrm{BA}$ vs. AA
1.2160064(1.0187157-1.4515055)
1.3694062(0.89078385-2.1051946)
1.3104771(0.89652187-1.9155701)
1.5451926(1.0297643-2.3186085)
1.6503272(1.115391-2.4418161)
1.4627797(1.0342395-2.0688868)
1.3224006(0.66976017-2.6109993)
1.1872793(0.77804178-1.8117695)
1.6747332(0.99755496-2.8116057)
$1.5634577(0.83154303-2.9395955)$
$1.4065839(0.86725762-2.2813039)$
$1.3358485(0.72868836-2.4489083)$
1.2201217(0.84528029-1.7611873)
1.6279997(0.9715367-2.7280316)
$1.5861192(0.92640245-2.7156382)$
1.4149311(0.91863568-2.1793514)
1.1666807(0.80948448-1.6814948)
$1.1461788(0.82732379-1.5879225)$
1.1172881(0.79788733-1.5645475)
1.2501878(0.89752364-1.7414242)
$1.1693906(0.87195311-1.5682888)$
16.521536(11.041318-24.721792)
$0.98288077(0.51824826-1.8640767)$
4.0756825(0.25461694-65.239915)
2.9571428(1.4962763-5.8443046)
0.98214287(0.51079553-1.8884357) $1.6968818(0.57462964-5.0108935)$
2.2095497(0.50451875-9.6767654)
2.4511757(0.53151315-11.304071)
2.0795665(0.33308411-12.983498)
$1.0068018(0.73271269-1.3834208)$
$1.8129221(0.57173252-5.7486434)$

FIXED

## Random

Random

FIXED

Random

Random

Random

Xie et al. (2012)
Slattery et al. (2012)
Slattery et al. (2012)

## Combined

Xie et al. (2012)
Slattery et al. (2012)
Slattery et al. (2012)
Combined
Xie et al. (2012)
Slattery et al. (2012)
Slattery et al. (2012)
Combined
Xie et al. (2012)
Slattery et al. (2012)
Slattery et al. (2012)
Combined
Xie et al. (2012)
Slattery et al. (2012)
Slattery et al. (2012)
Combined
1.0188407(0.93886125-1.1056333)

FIXED 0.9835791(0.89551055-1.0803088)
$1.0013056(0.88363576-1.134645)$
1.0030393(0.9276129-1.0845988)
1.0031921(0.83704913-1.2023121)
$0.92918319(0.75771797-1.1394496)$
0.9231993(0.70171112-1.2145981)
0.96050464(0.80895557-1.1404448)
1.0563735(0.94049549-1.1865287)
$0.80378997(0.4504793-1.4342021)$
$0.82878494(0.42668638-1.6098112)$
0.97101493(0.76821406-1.2273532)
1.0449898(0.93609422-1.1665533)
$0.82465678(0.4953464-1.3728954)$
$0.84786361(0.46967152-1.5305862)$
0.97508254(0.79100631-1.2019954)
$0.97547317(0.82177967-1.1579112)$

FIXED
FIXED

Random

Random
五

## Supplementary table 3. P values of the Egger's test for TLR2 polymorphism.

| Polymorphisms | Subgroup | Egger's test P > \|t| |
| :---: | :---: | :---: |
| (-196 to -174del) | Overall | 0.291 |
|  | Asian | 0.593 |
|  | Caucasian | 0.983 |
|  | African | 0.889 |
|  | PB | 0.791 |
|  | HB | 0.598 |
|  | Gastric Cancer | 0.459 |
|  | Breast cancer | 0.768 |
|  | Cervical cancer | 0.14 |
|  | Y | 0.261 |
|  | N | 0.108 |
| rs3804099 | Overall | 0.991 |
|  | Asian | 0.772 |
|  | Caucasian | 0.405 |
|  | PB | 0.939 |
|  | HB | 0.94 |
|  | Y | 0.236 |
|  | N | 0.996 |
| rs3804100 | Overall | 0.279 |
|  | Asian | 0.003 |
|  | Caucasian | 0.578 |
|  | PB | 0.423 |
|  | HB | 0.297 |
|  | Y | 0.312 |
| rs4696480 | Overall | 0.937 |


|  | PB | 0.553 |
| :--- | :--- | :--- |
|  | Y | 0.029 |
| rs 1898830 | Overall | 0.494 |

## Supplementary table 4. Details of the linkage disequilibrium analysis for disequilibrium analysis for TLR2 polymorphisms in populations from 1000

genomes Phase 3.

| L1 | $\mathbf{L 2}$ | $\mathbf{D}^{\prime}$ | $\mathbf{L O D}$ | $\mathbf{R}^{\mathbf{2}}$ | $\mathbf{C I}_{\text {low }}$ | $\mathbf{C I}_{\text {high }}$ | Dist | T-int |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| CHB+CHS |  |  |  |  |  |  |  |  |
| rs4696480 | rs1898830 | 0.98 | 74.79 | 0.905 | 0.94 | 1 | 1327 | 105.94 |
| rs4696480 | rs3804099 | 0.945 | 16.58 | 0.279 | 0.83 | 0.99 | 17530 | - |
| rs4696480 | rs3804100 | 0.938 | 14.51 | 0.241 | 0.8 | 0.98 | 18283 | - |
| rs4696480 | rs5743708 | 1 | 0.06 | 0.003 | 0.04 | 0.97 | 19191 | - |
| rs1898830 | rs3804099 | 0.948 | 18.09 | 0.298 | 0.84 | 0.99 | 16203 | 64.48 |
| rs1898830 | rs3804100 | 0.94 | 15.19 | 0.257 | 0.81 | 0.99 | 16956 | - |
| rs1898830 | rs5743708 | 1 | 0.05 | 0.003 | 0.04 | 0.97 | 17864 | - |
| rs3804099 | rs3804100 | 0.987 | 58.89 | 0.853 | 0.94 | 1 | 753 | 88.94 |
| rs3804099 | rs5743708 | 1 | 0.24 | 0.006 | 0.05 | 0.97 | 1661 | - |
| rs3804100 | rs5743708 | 1 | 0.28 | 0.007 | 0.06 | 0.98 | 908 | 0.63 |
| CEU |  |  |  |  |  |  |  |  |
| rs4696480 | rs1898830 | 1 | 18.31 | 0.528 | 0.9 | 1 | 1327 | 25.77 |
| rs4696480 | rs3804099 | 0.44 | 3.63 | 0.152 | 0.26 | 0.58 | 17530 | - |
| rs4696480 | rs3804100 | 1 | 2.36 | 0.085 | 0.43 | 1 | 18283 | - |
| rs4696480 | rs5743708 | 1 | 1.47 | 0.047 | 0.25 | 1 | 19191 | - |
| rs1898830 | rs3804099 | 1 | 13.87 | 0.415 | 0.88 | 1 | 16203 | 25.14 |
| rs1898830 | rs3804100 | 1 | 1.24 | 0.045 | 0.2 | 1 | 16956 | - |
| rs1898830 | rs5743708 | 1 | 2.57 | 0.088 | 0.45 | 1 | 17864 | - |
| rs3804099 | rs3804100 | 1 | 3.35 | 0.108 | 0.56 | 1 | 753 | 12.02 |
| rs3804099 | rs5743708 | 1 | 1.03 | 0.037 | 0.16 | 0.99 | 1661 | - |


| rs3804100 | rs5743708 | 0.635 | 0.03 | 0.002 | 0.04 | 0.96 | 908 | 5.1 |
| :--- | :--- | :--- | :---: | :---: | :---: | :---: | :---: | :---: |
| ESN |  |  |  |  |  |  |  |  |
| rs4696480 | rs1898830 | 1 | 1.99 | 0.064 | 0.36 | 1 | 1327 | 3.42 |
| rs4696480 | rs3804099 | 0.008 | 0 | 0 | -0.01 | 0.22 | 17530 | - |
| rs4696480 | rs3804100 | 1 | 1.43 | 0.075 | 0.24 | 1 | 18283 | - |
| rs1898830 | rs3804099 | 1 | 4.89 | 0.154 | 0.67 | 1 | 16203 | 6.4 |
| rs1898830 | rs3804100 | 0.922 | 0.08 | 0.004 | 0.04 | 0.97 | 16956 | - |
| rs3804099 | rs3804100 | 1 | 0.81 | 0.031 | 0.12 | 0.99 | 753 | 2.32 |
| JPT |  |  |  |  |  |  |  |  |
| rs4696480 | rs1898830 | 1 | 42.41 | 1 | 0.97 | 1 | 1327 | 56.01 |
| rs4696480 | rs3804099 | 0.897 | 7 | 0.3 | 0.69 | 0.97 | 17530 | - |
| rs4696480 | rs3804100 | 0.939 | 6.6 | 0.285 | 0.72 | 0.99 | 18283 | - |
| rs1898830 | rs3804099 | 0.897 | 7 | 0.3 | 0.69 | 0.97 | 16203 | 27.2 |
| rs1898830 | rs3804100 | 0.939 | 6.6 | 0.285 | 0.72 | 0.99 | 16956 | - |
| rs3804099 | rs3804100 | 1 | 29.6 | 0.864 | 0.93 | 1 | 753 | 42.8 |
| YRI |  |  |  |  |  |  |  |  |
| rs4696480 | rs1898830 | 1 | 1.56 | 0.047 | 0.27 | 1 | 1327 | 5.39 |
| rs4696480 | rs3804099 | 0.004 | 0 | 0 | -0.01 | 0.19 | 17530 | - |
| rs4696480 | rs3804100 | 1 | 3.83 | 0.117 | 0.6 | 1 | 18283 | - |
| rs1898830 | rs3804099 | 1 | 3.4 | 0.122 | 0.57 | 1 | 16203 | 7.42 |
| rs1898830 | rs3804100 | 1 | 0.19 | 0.006 | 0.05 | 0.97 | 16956 | - |
| rs3804099 | rs3804100 | 1 | 1.75 | 0.046 | 0.31 | 1 | 753 | 5.77 |

The linkage disequilibrium values were calculated using $r 2$ and $D^{\prime}$ statistic CI (Confidence Interval); LOD: Log odds score.


Fig.S1 Meta-analysis of the association between TLR2 rs4696480 polymorphism and cancer risk.

$B$ vs. $A$

$B B$ vs. $A A$

$B A$ vs. $A A$

$B B+B A$ vs. $A A$

$B B$ vs. $B A+A A$

Fig.S2 Meta-analysis of the association between TLR2 rs3804100 polymorphism and cancer risk.


Fig.S3 Meta-analysis of the association between TLR2 rs5743708 polymorphism and cancer risk.


Fig.S4 Meta-analysis of the association between TLR2 rs1898830 polymorphism and cancer risk.


Fig.S5 Sensitivity analysis for TLR2 polymorphism and overall cancer susceptibility ( $B$ vs. $A, r s 5743708, B B+B A$ vs. $A A$ )


Fig. S6. Trial sequential analysis for TLR2 polymorphism (rs3804099, rs5743708) under the allele contrast model (B vs. A).


[^0]:    Continued over

