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Association of the vitamin D metabolism gene GC and CYP27B1 polymorphisms with cancer susceptibility: a meta-analysis and trial sequential analysis

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Abstract

Nowadays, vitamin D is known to have functions beyond bone formation, including inhibiting angiogenesis and promoting tumor apoptosis. CYP27B1 and group-specific component (GC), the main enzyme responsible for the degradation and transport of active vitamin D, play important role in many cancer related cellular processes. Relationships between CYP27B1 and GC polymorphisms and cancer susceptibility have been widely investigated, whereas the results are inconsistent. We strictly searched on EMBASE, PubMed, Web of Science, Wan Fang and CNKI electronic databases for relevant studies exploring the associations of GC (rs4588 and rs7041) and CYP27B1 (rs4646537, rs3782130) polymorphisms with cancer risks according to search strategy. Thirty-two studies published in thirteen articles involving 15,713 cases and 17,304 controls were included. Our analyses suggested that rs4588 and rs7041 polymorphisms were significantly associated with overall cancer risk. Stratification analyses of ethnicity indicated that rs4588 polymorphism significantly increased cancer risk in Caucasians and Asians, while rs7041 polymorphism significantly increased cancer risk in Asians. When studies were stratified by cancer type, our results indicated that rs4588 significantly increased the risk of breast cancer and digestive system tumor, but not in prostate cancer and non-small cell lung cancer, while rs7041 significantly increased the risk of non-small cell lung cancer. Above associations were noteworthy findings as evaluated by false-positive report probabilities (FPRP). There were no associations of rs4646537 and rs3782130 with overall cancer risks. Associations between CYP27B1 and GC polymorphisms and cancer risks were examined, and additional large samples are necessary to validate our results.

Keywords: cancer susceptibility; vitamin D-binding proteins; CYP27B1; group-specific

component; polymorphism; meta-analysis

Introduction

Cancer remains a major global burden of public health. According to the GLOBOCAN 2018, there will be an estimated 18.1 million new cancer cases and 9.6 million deaths in 2018 worldwide [1]. Various causes involving a variety of environmental and genetic factors lead to the development of cancer, although the exact mechanism of carcinogenesis has not been fully understood.

Vitamin D is a fat-soluble vitamin that is closely related to health [2]. They have the following three characteristics: (1) they are found in some natural foods; (2) humans store 7-dehydrocholesterol from cholesterol, which can be converted to vitamin D_3 after exposure to ultraviolet light; (3) proper sunbathing is enough to satisfy the body's vitamin D need [2]. Vitamin D deficiency is a ubiquitous phenomenon. Nowadays, vitamin D is known to have functions beyond bone formation, including enhancing immune defense [3], inhibiting cell proliferation [4], inhibiting angiogenesis [5], inhibiting cell metastasis [6], and promoting tumor apoptosis [4]. In addition, vitamin D can reduce mortality in several malignancies [7]. Numerous studies have shown that vitamin D deficiency may be the reason why thousands of patients die prematurely from colon, breast, ovarian and other cancers each year [8-10].

Vitamin D is synthesized by a series of reactions catalyzed by many enzymes. CYP2R1 and CYP27A1 are 25-hydroxylase enzymes that first convert pro-vitamin D absorbed from the diet or produced in the skin after exposure to sunlight [11]. Next, CYP27B1, 1a-hydroxylase converts 25(OH)D into 1,25-dihydroxyvitamin D [$1,25(OH)_2D_3$] in the kidney [11]. Both vitamin D metabolites bind to vitamin D-binding proteins, also known as group-specific component (GC),

which aid in the transport of vitamin D [11]. Genetic polymorphisms involving the vitamin D pathway may affect its activity, so if vitamin D does play a role in carcinogenesis, it may be associated with cancer.

Recently, genome-wide association studies (GWASs) have identified CYP27B1 and GC polymorphisms significantly associated with 25(OH)D concentrations [12]. The worldwide variation of CYP27B1 gene (Chromosome 12: 58,156,117-58,162,769 reverse strand) and of its polymorphism SNP rs4646537 (Chromosome 12:58157281 forward strand) and SNP rs3782130 (Chromosome 12:58161898 forward strand), and GC gene (Chromosome 4: 72,607,410-72,669,758 reverse strand) and of its polymorphism SNP rs4588 (Chromosome 4:72618323 forward strand) and SNP rs7041 (Chromosome 4:72618334 forward strand) were analysed with data obtained from the public database 1000 Genomes Phase 3 Browser. According to the 1000 Genomes Project Phase 3 allele frequencies, the minor allele frequency (MAF) for rs4646537 is 4% in the combined population, the MAF for rs3782130 is 35% in the combined population, the MAF for rs4588 is 21% in the combined population, and the MAF for rs7041 is 38% in the combined population. Up to now, two common CYP27B1 polymorphisms (rs4646537, rs3782130) and two common GC polymorphisms (rs4588 and rs7041) were found to be associated with cancer risks, including breast cancer, non-small cell lung cancer, prostate cancer, hepatocellular carcinoma, esophageal cancer, gastric cancer and colorectal cancer. However, the results are inconsistent, probably because of the limited sample size. To better explore the precise relationship, we performed a meta-analysis and trial sequential analysis to characterize the associations of GC (rs4588 and rs7041) and CYP27B1 (rs4646537, rs3782130) polymorphisms with cancer susceptibility.

Material and methods

Literature retrieval

We strictly searched on EMBASE, PubMed, Web of Science, Wan Fang and CNKI electronic databases (up to Dec 1, 2018) for relevant studies exploring the associations of GC (rs4588 and rs7041) and CYP27B1 (rs4646537, rs3782130) polymorphisms with cancer risks according to the search strategy (Table S1). Four authors (Man Zhu, Zhenzhao Luo, Zheqiong Tan and Hui Wang) independently searched and screened the search.

Inclusion and exclusion criteria

Enrolled studies should meet the following inclusion criteria: (A) Human-based research; (B) Case-control/cohort studies; (C) Effective data were available to compute odds ratio (OR), 95% confidence interval (CI) and P value; (D) Involved in the associations of GC (rs4588 and rs7041) or CYP27B1 (rs4646537, rs3782130) polymorphisms (at least one polymorphism involved) with cancer risk; (E) The control group met Hardy-Weinberg Equilibrium (HWE). When $P>0.05$, the genetic balance of the population genes is indicated, indicating that the data is from the same Mendelian population [13]. In addition, the enrolled studies also need to meet the following exclusion criteria: (A) Case only or non-cancer subject only studies; (B) Duplicate publications; (C) Conference abstracts.

Data extraction

Two researchers (Tangwei Wu and Hui Hu) independently screened the detailed data from all enrolled studies. The following data was collected: first author name, issuing time, country, ethnicity, type of cancer, control source, genotyping method, numbers of cases and controls.

Quality assessment

Two researchers (Tangwei Wu and Hui Hu) assessed the quality of each investigation using the quality assessment criteria (Table S2), which was derived from previously published meta-analysis of molecular association studies [14]. The quality assessment criteria cover the methodology for the ascertainment of cancer case (0-2 point), case representation (0-2 point), control representation (0-3 point), control selection (0-2 point), genotyping examination (0-2 point), conform to HWE (0-1 point) and total sample size (0-3 point). Total scores ranged from 0 to 15, and studies with scores > 9 point were classified as high quality.

Statistical analysis

Stata software (Stata, College Station, TX, USA), version 12.0, was used for statistical analysis. Associations of GC (rs4588 and rs7041) and CYP27B1 (rs4646537, rs3782130) polymorphisms with cancer risks were estimated by odds ratio (OR) and 95% confidence interval (CI). Five different genetic models (dominant, recessive, homozygote, heterozygote, and allele model) were used in current study. Statistical heterogeneity was counted by Cochrane Q-test and P-values, and random-effect model was used if $P \leq 0.10$ or $I^2 \geq 50\%$, otherwise, fixed-effect model was used. Stratification analysis was performed based on ethnicity, cancer type and the detection method of genotype. Publication bias (Begg's test and Egger's test) analyses and sensitivity analyses were used to evaluate the reliability of current study. $P<0.05$ was considered statistically significant. For each significant finding, false positive report probability (FPRP) analysis was performed using the method reported by Wacholder et al. [15]. We calculated FPRP assuming a prior probability of 0.1 as previously proposed [16]. We set 0.2 as an FPRP threshold and only result with FPRP value < 0.2 was referred as noteworthy [16].

Trial sequential analysis (TSA)

The poor effect of systematic or random errors may increase due to sparse data, which may eventually mislead result in meta-analyses [17]. In order to get more comprehensive results, trial sequential analysis (TSA, Copenhagen Trial Unit, Denmark, 2011) was utilized. In our current study, an overall type–I error of 5%, a statistical test power of 80% and a 20% relative risk reduction was set up.

Results

Screening process and characteristics of enrolled studies

A total of 342 articles were obtained based on our search strategy. After reading titles and abstracts, thirty-four articles conformed to our inclusion criteria. After reading full-text, twenty-one articles were excluded, including ten that did not describe GC (rs4588 and rs7041) or CYP27B1 (rs4646537, rs3782130) polymorphisms and cancer susceptibility, two that did not meet HWE, four case only or non-cancer subject only articles, and five that not provide detailed genotyping data. Finally, thirteen eligible articles including thirty-two studies (15,713 cases and 17,304 controls) were enrolled in our current meta-analysis [18-30]. Fig. 1 describes the screening process.

In general, sixteen studies included Caucasian populations, fourteen studies included Asian populations and two studies included African populations. TaqMan method was used in nine studies, PCR-RFLP method was used in eighteen studies, Illumina method was used in three studies and two studies used the SNPlex assay method. Ten studies reported the effects of GC polymorphisms in breast cancer, eight reported in digestive system tumor, three in non-small cell

lung cancer and two in prostate cancer. Six studies reported the effects of CYP27B1 polymorphisms in prostate cancer, two reported in non-small cell lung cancer and one in digestive system tumor. The characteristics of these studies were listed in Table 1.

Meta-analysis and TSA of rs7041

Nine publications including thirteen studies with 6,916 cases and 7,870 controls examined rrs7041 polymorphism. As shown in Table 2, we found that rs7041 polymorphism significantly increased cancer risk in four models: dominant (OR=1.22, 95% CI=1.03-1.44, *P*=0.019), recessive (OR=1.27, 95% CI=1.02-1.58, *P*=0.030), homozygote (OR=1.41, 95% CI=1.06–1.88, *P*=0.017, Fig.2A), and allele (OR=1.17, 95% CI=1.02–1.33, *P*=0.022) models. When studies were stratified by ethnicity, significant associations were found in Asians (recessive, OR=1.40, 95% CI=1.11–1.77, *P*=0.005; homozygote, OR=1.52, 95% CI=1.19–1.93, *P*=0.001; heterozygote, OR=1.28, 95% CI=1.00–1.63, *P*=0.047; Allele, OR=1.20, 95% CI=1.09–1.32, *P*=0.000). Stratification analyses of cancer type indicated that rs7041 polymorphism increased the risk of non-small cell lung cancer (recessive, OR=1.73, 95% CI=1.05–2.84, *P*=0.031, Fig. 2B; homozygote, OR=1.97, 95% CI=1.38–2.81, *P*=0.000; allele, OR=1.32, 95% CI=1.09–1.60, *P*=0.004). Moreover, our data indicated that rs7041 polymorphism was also significantly associated with an increased risk of cancer in the studies with publication-based controls. The FPRP values for significant findings at different prior probability levels are shown in Table S3. With the assumption of prior probability of 0.1, these statistically significant associations were noteworthy (FPRP value< 0.2) for overall cancer risk (dominant and allele models), Asians (recessive, homozygote and allele models), non-small cell lung cancer (homozygote and allele models) and PCR-RFLP (heterozygote model) subgroups.

As shown in Fig. 3A, although the total number of cases did not exceed the O'Brien-Fleming boundary, the cumulative Z-curve exceeded the test sequence monitoring boundary, which verified that rs7041 was significantly associated with cancer susceptibility.

Meta-analysis and TSA of rs4588

Seven publications including ten studies with 4,759 cases and 5,262 controls examined rs4588 polymorphism. As shown in Table 3, we found that rs4588 polymorphism significantly increased cancer risk in all five models: dominant (OR=1.10, 95% CI=1.02-1.19, *P*=0.016), recessive (OR=1.27, 95% CI=1.11-1.46, *P*=0.001), homozygote (OR=1.31, 95% CI=1.13–1.51, *P*=0.000, Fig. 4A), heterozygote (OR=1.23, 95% CI=1.06–1.42, *P*=0.005), and allele (OR=1.11, 95% CI=1.05–1.18, *P*=0.001) models. Stratification analyses indicated that rs4588 polymorphism significantly increased cancer risk in Caucasians (dominant, OR=1.10, 95% CI=1.01–1.21, P=0.040; recessive, OR=1.17, 95% CI=1.00–1.39, *P*=0.049; homozygote, OR=1.22, 95% CI=1.02–1.45, *P*=0.026; allele, OR=1.10, 95% CI=1.02–1.18, *P*=0.015) and Asians (recessive, OR=1.51, 95% CI=1.18–1.94, *P*=0.001; homozygote, OR=1.56, 95% CI=1.06–2.29, *P*=0.024; heterozygote, OR=1.51, 95% CI=1.16–1.96, *P*=0.002, Fig. 4B). When studies were stratified by cancer type, significant associations were found in breast cancer (dominant, OR=1.10, 95% CI=1.00–1.21, *P*=0.046; homozygote, OR=1.20, 95% CI=1.00–1.43, *P*=0.047; allele, OR=1.09, 95% CI=1.01–1.17, *P*=0.030) and digestive system tumor (recessive, OR=1.58, 95% CI=1.02–2.46, *P*=0.042; heterozygote, OR=1.54, 95% CI=1.15–2.08, *P*=0.004), but not in prostate cancer and non-small cell lung cancer. Moreover, when studies were stratified by quality score, an increased cancer risk was observed in high quality subgroup in all five genetic models. When studies were stratified by control source and genotyping method, significant associations were

found in publication-based controls, hospital-based controls and PCR-RFLP method, but not in TaqMan method. The FPRP values for significant findings at different prior probability levels are shown in Table S4. With the assumption of prior probability of 0.1, these statistically significant associations were noteworthy for overall cancer risk (in all five models), Caucasians (homozygote and allele models), Asians (recessive and heterozygote models), digestive system tumor (heterozygote model), breast cancer (allele model) publication-based controls (homozygote and allele models), PCR-RFLP (recessive, homozygote, heterozygote and allele models) and high quality (in all five models) subgroups.

To analyze the reliability of our results, we performed a TSA analysis. As shown in Fig. 3B, the cumulative number of cases did not meet the O'Brien-Fleming boundary and test sequence monitoring boundary. Current TSA results suggested that more sample size was still needed for more robust results.

Meta-analysis and TSA of rs4646537 and rs3782130

Two publications including three studies with 1,403 cases and 1,325 controls examined rs4646537 polymorphism; five publications including six studies with 2,721 cases and 2,761 controls examined rs3782130 polymorphism. As shown in Table S5, we found these two polymorphisms were not associated with cancer risk.

As for rs4646537 and rs3782130, the cumulative number of cases did not exceed the O'Brien-Fleming boundary and test sequence monitoring boundary (Fig. 3C and Fig. 3D). Therefore, more sample size was still needed for more robust results.

Publication bias and Sensitivity analysis

As showed in Figure S1 and Table 4, Begg's and Egger's tests indicated that there was no

evidence of significant publication bias in our current meta-analysis. Sensitivity analysis found that none of the single study significantly changed the final conclusion (Figure S2).

Discussion

It has long been clear that genetics has the ability to intervene in the cancer risk in the coming decades. Since polymorphism is the most important cause of human genetic material and information variation, the specific relationship between polymorphisms and cancer susceptibility has attracted widespread attention. With the rapid development of medical science and technology, the field of tumor genetic susceptibility has gradually attracted great interest, and the research on tumor genetic polymorphism is also increasing. Genetic polymorphisms involving the vitamin D pathway has become an important class of genes in the extensive study of polymorphisms in risk factors associated with malignant tumors.

CYP27B1 and GC are two important enzymes involved in vitamin D binding and transport. Nowadays, a growing body of evidence suggests that differential expression of CYP27B1 and GC may play an important role in carcinogenesis development. Reduced CYP27B1 gene expression level has been found in various tumors, including prostate cancer [31-32], non-small cell lung cancer [23]. Whitlatch and colleagues [32] investigated CYP27B1 expression in normal prostate, prostatic hyperplasia, and prostate cancer, and they found that normal prostate exhibited the highest expression of CYP27B1, while its expression was decreased in the following order: prostatic hyperplasia and prostate cancer. These findings suggest that the malignant progression of prostate tissue certainly reduces CYP27B1 expression. Furthermore, Kong et al. [23] found that non-small cell lung cancer patients with high CYP27B1 expression had better overall survival than those

with low CYP27B1, which indicated that low CYP27B1 expression was also correlated with a poorer prognosis. In addition, there are two common single nucleotide polymorphisms (rs7041 and rs4588) in GC gene. In the previous reports, genetic variants in the GC gene, including rs7041 and rs4588, have been investigated in breast cancer [18-19, 22, 25], non-small cell lung cancer [21], prostate cancer [26] and digestive system tumor [27]. However, to date, there is no systematic evaluation on how CYP27B1 and GC polymorphisms are involved in development of cancers.

Our data found that rs4588 was significantly associated with an increased risk of cancer susceptibility, and current result was confirmed by FPRP and TSA analyses. Among these studies, there were four studies on breast cancer, four on digestive system tumor, one on prostate cancer and one on non-small cell lung cancer. Stratified analyses by cancer type revealed a significant association between rs4588 and breast cancer and digestive system tumor, but not in prostate cancer and non-small cell lung cancer. However, our outcomes were different to the results shown by Anderson et al. [18], McCullough et al. [19], Reimers et al. [22], and Deschasaux et al. [25], which demonstrated that rs4588 polymorphism was not associated with breast cancer. This discrepancy may be caused by the limited sample size. Anderson et al. [18] included only 3143 subjects (1535 cases and 1608 controls), McCullough et al. [19] included only 966 subjects (490 cases and 476 controls), Reimers et al. [22] included only 1931 subjects (940 cases and 991 controls), Deschasaux et al. [25] included only 670 subjects (220 cases and 450 controls), which may lack sufficient power to support or deny an association. Previous studies also focused on the relationship between the rs4588 and digestive system tumor. However, our outcomes were different to previous study [27], which indicated that rs4588 polymorphism was not associated with hepatocellular carcinoma, esophageal cancer and gastric cancer. Possible reasons for this difference could be explained as the

limited sample size. There was only one study for hepatocellular carcinoma, esophageal cancer and gastric cancer, which was far from enough to obtain trustworthy results. Based on current TSA results, more studies by standardized unbiased methods are required to offer more detailed data.

As for rs7041, we found that this polymorphism significantly increased cancer risk. Stratification analyses of ethnicity suggested rs7041 increased cancer risk in Asians, but not in Caucasians. Possible reasons can be explained as the different genetic backgrounds of cancer across ethnicities. In this meta-analysis, the pooled rs7041 C allele frequency of the controls showed a large difference across ethnicities (Asians: 30.2%; Caucasians: 45.4%), which may possibly affect the relationships between rs7041 polymorphism and cancer risk among different racial subgroups. Moreover, when studies were stratified by cancer type, we also found that rs7041 polymorphism was significantly associated with an increased risk in the non-small cell lung cancer. However, most subgroups had insufficient numbers, which may attenuate the statistical power. Our results were partially consistent with the consequence of the study by Wang et al. [20], which reported that there was no significant association between rs7041 and breast cancer in Asians and Caucasians. However, study by Reimers et al [22]. suggested that rs7041 was associated with an increased risk of breast cancer in Caucasians. It is noteworthy that Yao et al. [33] indicated that increased polymorphism may be related to the higher prevalence of estrogen receptor (ER)-negative but not ER-positive breast cancer. At present, a large number of researches indicated that there were important differences in genetic susceptibility between ER-negative and ER-positive breast cancer [11]. Therefore, it is reasonable to hypothesize that rs7041 polymorphism may have a specific effect on the susceptibility to ER-negative breast cancer. Of note, due to limited data, lack of further evaluation between rs7041 and ER-negative and ER-positive breast

cancer prevented our comprehensive understanding. Further large-cohort and well-designed studies are necessary to identify the possible association between them. With respect to the remaining two polymorphisms, we failed to find any associations between rs4646537 and rs3782130 and cancer risk. Given the limited sample size, our results should be interpreted with caution.

In general, current analysis has the following advantages: (1) Our research results were validated based on TSA analysis to ensure the reliability of the results. (2) All included studies were consistent with the HWE balance law, which may improve the reliability of our study. (3): This system evaluation is the first analysis of reviewing the relationships between CYP27B1 (rs4646537, rs3782130) and GC (rs4588 and rs7041) polymorphisms with cancer susceptibility. (4): To avoid false positive findings, FPRP analyses were used for all significant findings observed in our study. However, current study still has the following shortcomings: (1) The subjects we included were limited to Caucasians and Asians, and the results of this study still lack information from other ethnic groups, which may lead to publication bias. (2) The number of studies on rs4646537, rs3782130, rs4588 and rs7041 was relatively small in some subgroups, which may create significant or insignificant results by chance. (3) In some included studies, detailed information (e.g., radiation exposure, carcinogen, smoking and other risk factors) was not gathered, which further prevented the stratification analyses. Thus, a larger sample size, multi-racial, multi-center standardized research is needed to provide more detailed data in the future.

Conclusions

In conclusion, this systematical meta-analysis indicated that rs4588 and rs7041

polymorphisms play important roles in cancer pathogenesis, especially in non-small cell lung cancer, breast cancer and digestive system tumor, which were noteworthy findings as evaluated by FPRP. However, the other two polymorphisms (rs4646537 and rs3782130) are not associated with cancer risk. Further well-designed studies are necessary to validate our results.

Conflict of interest

The authors have no competing interests to declare.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

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Author contributions

M. Z., Z.Z. L., Z. T. H. W. and Z.X. L. performed the research design; T. W. and H. H. assessed the studies quality and data collection; M. Z. and S. F. did the sensitive analysis and publication bias test. M. Z., Z. T. and Z.X. L. wrote the paper. All authors confirmed the final edition.

References

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68(6):394-424.

2. Jukic AMZ, Hoofnagle AN, Lutsey PL. Measurement of Vitamin D for Epidemiologic and Clinical Research: Shining Light on a Complex Decision. *Am J Epidemiol*. 2018;187(4):879-890.

3. Abdo J, Rai V, Agrawal DK. Interplay of Immunity and Vitamin D: Interactions and Implications with Current IBD Therapy. *Curr Med Chem*. 2017;24(9):852-867.

4. Gao Y, Um CY, Fedirko V, et al. Effects of supplemental vitamin D and calcium on markers of proliferation, differentiation, and apoptosis in the normal colorectal mucosa of colorectal adenoma patients. *PLoS One*. 2018;13(12):e0208762.

5. Berger MD, Stintzing S, Heinemann V, et al. A Polymorphism within the Vitamin D Transporter Gene Predicts Outcome in Metastatic Colorectal Cancer Patients Treated with FOLFIRI/Bevacizumab or FOLFIRI/Cetuximab. *Clin Cancer Res*. 2018;24(4):784-793.

6. Chiang KC, Yeh TS, Chen SC, et al. The Vitamin D Analog, MART-10, Attenuates Triple Negative Breast Cancer Cells Metastatic Potential. *Int J Mol Sci*. 2016;17(4): E606.

7. Brenner H, Jansen L, Saum KU, et al. Vitamin D Supplementation Trials Aimed at Reducing Mortality Have Much Higher Power When Focusing on People with Low Serum 25-Hydroxyvitamin D Concentrations. *J Nutr*. 2017;147(7):1325-1333.

8. de La Puente-Yagüe M, Cuadrado-Cenzual MA, Ciudad-Cabañas MJ, et al. Vitamin D: And its role in breast cancer. *Kaohsiung J Med Sci*. 2018;34(8):423-427.

9. Cho YA, Lee J, Oh JH, et al. Vitamin D receptor FokI polymorphism and the risks of colorectal cancer, inflammatory bowel disease, and colorectal adenoma. *Sci Rep*. 2018;8(1):12899.

10. Ong JS, Gharahkhani P, An J, et al. Vitamin D and overall cancer risk and cancer mortality: a Mendelian randomization study. *Hum Mol Genet*. 2018;27(24):4315-4322.

11. Zhu M, Qiu S, Zhang X, et al. The associations between CYP24A1 polymorphisms and cancer susceptibility: A meta-analysis and trial sequential analysis. *Pathol Res Pract*. 2018;214(1):53-63.

12. Wang S, Huo D, Kupfer S, et al. Genetic variation in the vitamin D related pathway and breast

cancer risk in women of African ancestry in the root consortium. *Int J Cancer*. 2018;142(1):36-43.

13. Meng J, Wang S, Zhang M, et al. TP73 G4C14-A4T14 polymorphism and cancer susceptibility: evidence from 36 case-control studies. *Biosci Rep*. 2018;38(6): BSR20181452.

14. He J, Liao XY, Zhu JH, et al. Association of MTHFR C677T and A1298C polymorphisms with non-Hodgkin lymphoma susceptibility: evidence from a meta-analysis. *Sci Rep*. 2014;4:6159.

15. Wacholder S, Chanock S, Garcia-Closas M, et al. Assessing the probability that a positive report is false: an approach for molecular epidemiology studies. *J Natl Cancer Inst*. 2004;96(6):434-442.

16. He J, Wang MY, Qiu LX, et al. Genetic variations of mTORC1 genes and risk of gastric cancer in an Eastern Chinese population. *Mol Carcinog*. 2013;52 Suppl 1:E70-79.

17. Khan S, Dar SA, Mandal RK, et al. Angiotensin-Converting Enzyme Gene I/D Polymorphism Is Associated With Systemic Lupus Erythematosus Susceptibility: An Updated Meta-Analysis and Trial Sequential Analysis. *Front Physiol*. 2018;9:1793.

18. Anderson LN, Cotterchio M, Cole DE, et al. Vitamin D-related genetic variants, interactions with vitamin D exposure, and breast cancer risk among Caucasian women in Ontario. *Cancer Epidemiol Biomarkers Prev*. 2011; 20(8):1708-1717.

19. McCullough ML, Stevens VL, Diver WR, et al. Vitamin D pathway gene polymorphisms, diet, and risk of postmenopausal breast cancer: a nested case-control study. *Breast Cancer Res*. 2007;9(1):9.

20. Wang W, Ingles SA, Torres-Mejía G, et al. Genetic variants and non-genetic factors predict circulating vitamin D levels in Hispanic and non-Hispanic White women: the Breast Cancer Health Disparities Study. *Int J Mol Epidemiol Genet*. 2014;5(1):31-46.

21. Wu X, Cheng J, Yang K, et al. Vitamin D-Related Gene Polymorphisms, Plasma 25-Hydroxy-Vitamin D, Cigarette Smoke and Non-Small Cell Lung Cancer (NSCLC) Risk. *Int J Mol Sci*. 2016;17(10): E1597.

22. Reimers LL, Crew KD, Bradshaw PT, et al. Vitamin D-related gene polymorphisms, plasma 25-hydroxyvitamin D, and breast cancer risk. *Cancer Causes Control*. 2015;26(2):187-203.

23. Kong J, Xu F, Qu J, et al. Genetic polymorphisms in the vitamin D pathway in relation to lung cancer risk and survival. *Oncotarget*. 2015;6(4):2573-2582.

24. Clendenen TV, Ge W, Koenig KL, et al. Genetic Polymorphisms in Vitamin D Metabolism and Signaling Genes and Risk of Breast Cancer: A Nested Case-Control Study. *PLoS One*. 2015;10(10):e0140478.

25. Deschasaux M, Souberbielle JC, Latino-Martel P, et al. Weight Status and Alcohol Intake Modify the Association between Vitamin D and Breast Cancer Risk. *J Nutr*. 2016;146(3):576-585.

26. Deschasaux M, Souberbielle JC, Latino-Martel P, et al. A prospective study of plasma 25-hydroxyvitamin D concentration and prostate cancer risk. *Br J Nutr*. 2016;115(2):305-14.

27. Zhou L, Zhang X, Chen X, et al. GC Glu416Asp and Thr420Lys polymorphisms contribute to gastrointestinal cancer susceptibility in a Chinese population. *Int J Clin Exp Med*. 2012;5(1):72-79.

28. Holick CN, Stanford JL, Kwon EM, et al. Comprehensive association analysis of the vitamin D pathway genes, VDR, CYP27B1, and CYP24A1, in prostate cancer. *Cancer Epidemiol Biomarkers Prev*. 2007;16(10):1990-1999.

29. Holt SK, Kwon EM, Peters U, et al. Vitamin D pathway gene variants and prostate cancer risk. *Cancer Epidemiol Biomarkers Prev*. 2009;18(6):1929-1933.

30. Mahmoudi T, Karimi K, Arkani M, et al. Lack of associations between Vitamin D metabolism-related gene variants and risk of colorectal cancer. *Asian Pac J Cancer Prev*. 2014;15(2):957-961.

31. Susa T, Iizuka M, Okinaga H, et al.Without 1α-hydroxylation, the gene expression profile of 25(OH)D3 treatment overlaps deeply with that of 1,25(OH)2D3 in prostate cancer cells. *Sci Rep*. 2018;8(1):9024.

32. Whitlatch LW, Young MV, Schwartz GG, et al. 25-Hydroxyvitamin D-1alpha-hydroxylase activity is diminished in human prostate cancer cells and is enhanced by gene transfer. *J Steroid Biochem Mol Biol*. 2002;81(2):135-140.

33. Yao S, Zirpoli G, Bovbjerg DH, et al. Variants in the vitamin D pathway, serum levels of vitamin D, and estrogen receptor negative breast cancer among African-American women: a case-control study. *Breast Cancer Res*. 2012;14(2):58.

Figure legends

Figure 1. Flow chart of the process for study identification and selection

Figure 2. Meta-analysis for the association between rs7041 polymorphism and cancer risk. A overall comparison (homozygote model); **B** stratification analysis by cancer type (recessive model)

Figure 3. Trial sequential analyses of the association between rs4588, rs7041, rs3782130 and rs4646537 polymorphisms (dominant model) and cancer risk. A rs7041; **B** rs4588; **C** rs3782130; **D** rs4646537

Figure 4. Meta-analysis for the association between rs4588 polymorphism and cancer risk. A overall comparison (homozygote model); **B** stratification analysis by ethnicity (heterozygote model)

Tables

Table 1. Characteristics of included studies

Table 2. Meta-analysis of associations between the rs7041 polymorphism and cancer risk

Table 3. Meta-analysis of associations between the rs4588 polymorphism and cancer risk

Table 4. Begg's and Egger's tests for publication bias

Table 1. Characteristics of included studies

First Author	Year	Country	Ethnicity	Cancer type	Control source	Genotyping method	Cases (AA/AB/BB)	Controls (AA/AB/BB)	HWE	Score
GC (rs4588)										
McCullough	2007	USA	Caucasian	Breast cancer	PB	TaqMan	240/202/48	246/186/44	0.307	12
Anderson	2011	Canada	Caucasian	Breast cancer	PB	PCR-RFLP	792/608/135	846/642/120	0.906	10
Zhou-1	2012	China	Asian	Hepatocellular carcinoma	HB	PCR-RFLP	101/111/25	142/148/25	0.110	7
Zhou-2	2012	China	Asian	Esophageal cancer	HB	PCR-RFLP	148/108/33	159/144/34	0.868	7
Zhou-3	2012	China	Asian	Gastric cancer	HB	PCR-RFLP	74/89/29	88/92/24	0.995	6
Zhou-4	2012	China	Asian	Colorectal cancer	HB	PCR-RFLP	113/100/33	182/134/15	0.117	7
Reimers	2015	USA	Caucasian	Breast cancer	PB	TaqMan	456/402/82	514/393/84	0.471	10
Deschasaux	2016	France	Caucasian	Breast cancer	PB	TaqMan	101/89/30	227/181/42	0.498	8
Deschasaux	2016	France	Caucasian	Prostate cancer	PB	TaqMan	82/63/20	71/43/10	0.344	7
Wu	2016	China	Asian	Non-small cell lung cancer	PB	PCR-RFLP	235/173/37	230/170/26	0.462	10
GC (rs7041)										
McCullough	2007	USA	Caucasian	Breast cancer	PB	TaqMan	154/237/103	149/235/106	0.460	12
Anderson	2011	Canada	Caucasian	Breast cancer	PB	PCR-RFLP	288/782/558	486/760/309	0.703	10
Zhou-1	2012	China	Asian	Hepatocellular carcinoma	HB	PCR-RFLP	117/98/22	152/139/24	0.311	7
Zhou-2	2012	China	Asian	Esophageal cancer	HB	PCR-RFLP	148/119/22	188/128/21	0.899	7

Zhou-3	2012	China	Asian	Gastric cancer	HB	PCR-RFLP	99/89/16	98/86/10	0.105	6
Zhou-4	2012	China	Asian	Colorectal cancer	HB	PCR-RFLP	123/107/16	171/132/28	0.724	7
Kong	2014	China	Asian	Non-small cell lung cancer	PB	TaqMan	272/339/50	329/240/34	0.254	10
Wang-1	2014	Spain	Caucasian	Breast cancer	PB	Illumina	203/402/221	216/362/201	0.050	13
Wang-2	2014	Non-Spain	Caucasian	Breast cancer	PB	Illumina	42/61/27	73/116/35	0.320	11
Clendenen	2015	Sweden	Caucasian	Breast cancer	PB	Illumina	265/348/121	546/658/229	0.193	9
Reimers	2015	USA	Caucasian	Breast cancer	PB	TaqMan	239/470/186	311/474/193	0.609	10
Deschasaux	2016	France	Caucasian	Prostate cancer	PB	TaqMan	19/63/45	39/76/50	0.337	7
Wu	2016	China	Asian	Non-small cell lung cancer	PB	PCR-RFLP	173/225/47	175/230/61	0.281	10
CYP27B1 (rs4646537)										
Holick	2007	USA	Caucasian	Prostate cancer	PB	SNPlex assay	546/38/0	497/43/2	0.310	14
Holt-1	2009	USA	Caucasian	Prostate cancer	PB	PCR-RFLP	319/324/61	314/325/77	0.601	10
Holt-2	2009	USA	African	Prostate cancer	PB	PCR-RFLP	85/28/2	50/16/1	0.826	7
CYP27B1 (rs3782130)										
Holick	2007	USA	Caucasian	Prostate cancer	PB	SNPlex assay	260/251/75	260/229/61	0.327	14
Holt-1	2009	USA	Caucasian	Prostate cancer	PB	PCR-RFLP	637/50/2	636/52/0	0.303	10
Holt-2	2009	USA	African	Prostate cancer	PB	PCR-RFLP	97/15/2	54/8/1	0.298	7
Kong	2014	China	Asian	Non-small cell lung cancer	PB	TaqMan	229/297/77	230/371/120	0.150	10

Mahmoudi	2014	Iran	Asian	Colorectal cancer	HB	PCR-RFLP	144/125/34	180/138/36	0.216	6
Wu	2016	China	Asian	Non-small cell lung cancer	PB	PCR-RFLP	194/149/83	187/163/45	0.300	10

Abbreviation: PB: publication-based controls; HB: hospital-based controls; HWE, Hardy-Weinberg Equilibrium; A: wild type; B: mutated type

Table 2. Meta-analysis of associations between the rs7041 polymorphism and cancer risk

Model	Overall and Stratification analyses	No. of study	No. of cases/controls	OR (95% CI)	*P*-value	Random/Fixed effect model	*P* for heterogeneity	I^2 (%)
Dominant	Overall	13	6916/7870	**1.22(1.03, 1.44)**	**0.019**	Random	0.000	80.0
	Caucasian	7	4834/5624	1.25(0.96, 1.63)	0.092	Random	0.000	87.3
	Asian	6	2082/2246	1.19(0.98, 1.45)	0.077	Random	0.030	59.7
	Breast cancer	6	4707/5459	1.21(0.92, 1.60)	0.179	Random	0.000	89.2
	Digestive system tumor	4	976/1177	1.08(0.91, 1.28)	0.364	Fixed	0.811	0
	Non-small cell lung cancer	2	1106/1069	1.38(0.89, 2.14)	0.150	Random	0.012	84.1
	Prostate cancer	1	127/165	1.76(0.96, 3.22)	0.067	Fixed	-	-
	PB	9	5940/6693	**1.28(1.04, 1.59)**	**0.023**	Random	0.000	85.2
	HB	4	976/1177	1.08(0.91, 1.28)	0.364	Fixed	0.811	0
	PCR-RFLP	6	3049/3198	1.23(0.90, 1.68)	0.198	Random	0.000	86.2
	TaqMan	4	2177/2236	1.29(0.95, 1.75)	0.102	Random	0.002	79.3
	Illumina	3	1690/2436	1.11(0.97, 1.28)	0.119	Fixed	0.796	0
	High quality (> 9)	7	5079/5095	1.28(0.99, 1.64)	0.057	Random	0.000	87.5
	Low quality (≤ 9)	6	1837/2775	1.11(0.98, 1.25)	0.104	Fixed	0.653	0
Recessive	Overall	13	6916/7870	**1.27(1.02, 1.58)**	**0.030**	Random	0.000	79.2
	Caucasian	7	4834/5624	1.21(0.91, 1.62)	0.192	Random	0.000	88.0
	Asian	6	2082/2246	**1.40(1.11, 1.77)**	**0.005**	Fixed	0.179	35.2
	Breast cancer	6	4707/5459	1.21(0.88, 1.66)	0.248	Random	0.000	90.0
	Digestive system tumor	4	976/1177	1.16(0.84, 1.61)	0.377	Fixed	0.356	7.4
	Non-small cell lung cancer	2	1106/1069	**1.73(1.05, 2.84)**	**0.031**	Random	0.153	51.1
	Prostate cancer	1	127/165	1.26(0.77, 2.07)	0.354	Fixed	-	-
	PB	9	5940/6693	**1.30(1.01, 1.68)**	**0.045**	Random	0.000	85.1
	HB	4	976/1177	1.16(0.84, 1.61)	0.377	Fixed	0.356	7.4

	PCR-RFLP	6	3049/3198	**1.55(1.10, 2.19)**	**0.013**	Random	0.017	63.8
	TaqMan	4	2177/2236	1.06(0.90, 1.24)	0.497	Fixed	0.498	0
	Illumina	3	1690/2436	1.07(0.91, 1.25)	0.400	Fixed	0.589	0
	High quality (> 9)	7	5079/5095	1.35(0.99, 1.85)	0.055	Random	0.000	87.6
	Low quality (≤ 9)	6	1837/2775	1.10(0.92, 1.32)	0.298	Fixed	0.571	0
Homozygote	Overall	13	6916/7870	**1.41(1.06, 1.88)**	**0.017**	Random	0.000	84.5
	Caucasian	7	4834/5624	1.38(0.92, 2.07)	0.124	Random	0.000	91.5
	Asian	6	2082/2246	**1.52(1.19, 1.93)**	**0.001**	Fixed	0.203	31.1
	Breast cancer	6	4707/5459	1.33(0.85, 2.06)	0.213	Random	0.000	92.9
	Digestive system tumor	4	976/1177	1.19(0.85, 1.67)	0.315	Fixed	0.420	0
	Non-small cell lung cancer	2	1106/1069	**1.97(1.38, 2.81)**	**0.000**	Fixed	0.514	0
	Prostate cancer	1	127/165	1.85(0.94, 3.65)	0.077	Fixed	-	-
	PB	9	5940/6693	**1.49(1.05, 2.09)**	**0.024**	Random	0.000	89.0
	HB	4	976/1177	1.19(0.85, 1.67)	0.315	Fixed	0.420	51.1
	PCR-RFLP	6	3049/3198	**1.66(1.03, 2.69)**	**0.039**	Random	0.000	79.7
	TaqMan	4	2177/2236	1.25(0.92, 1.69)	0.157	Random	0.078	56
	Illumina	3	1690/2436	1.14(0.96, 1.37)	0.145	Fixed	0.816	0
	High quality (> 9)	7	5079/5095	1.52(0.99, 2.30)	0.052	Random	0.000	90.7
	Low quality (≤ 9)	6	1837/2775	1.17(0.96, 1.43)	0.116	Fixed	0.435	0
Heterozygote	Overall	13	6916/7870	1.18(0.98, 1.43)	0.081	Random	0.000	68.4
	Caucasian	7	4834/5624	1.14(0.90, 1.45)	0.279	Random	0.000	79.1
	Asian	6	2082/2246	**1.28(1.00, 1.63)**	**0.047**	Fixed	0.103	45.3
	Breast cancer	6	4707/5459	1.15(0.88, 1.49)	0.303	Random	0.000	82.5
	Digestive system tumor	4	976/1177	1.12(0.80, 1.58)	0.508	Fixed	0.322	14.0
	Non-small cell lung cancer	2	1106/1069	1.52(0.70, 3.29)	0.285	Random	0.032	78.4
	Prostate cancer	1	127/165	1.09(0.64, 1.83)	0.758	Fixed	-	-

	PB	9	5940/6693	1.20(0.96, 1.49)	0.110	Random	0.000	76.6
	HB	4	976/1177	1.12(0.80, 1.58)	0.508	Fixed	0.322	14.0
	PCR-RFLP	6	3049/3198	**1.48(1.09, 2.01)**	**0.013**	Random	0.071	50.7
	TaqMan	4	2177/2236	0.99(0.84, 1.17)	0.904	Fixed	0.975	0
	Illumina	3	1690/2436	1.03(0.87, 1.21)	0.769	Fixed	0.463	0
	High quality (> 9) Low	7	5079/5095	1.25(0.96, 1.63)	0.103	Random	0.000	80.6
	quality (≤ 9)	6	1837/2775	1.05(0.86, 1.27)	0.639	Fixed	0.580	0
Allele	Overall	13	6916/7870	**1.17(1.02, 1.33)**	**0.022**	Random	0.000	85.2
	Caucasian	7	4834/5624	1.17(0.95, 1.44)	0.133	Random	0.000	91.7
	Asian	6	2082/2246	**1.20(1.09, 1.32)**	**0.000**	Fixed	0.137	40.2
	Breast cancer	6	4707/5459	1.15(0.92, 1.44)	0.217	Random	0.000	93.1
	Digestive system tumor	4	976/1177	1.08(0.94, 1.23)	0.283	Fixed	0.750	0
	Non-small cell lung cancer	2	1106/1069	**1.32(1.09, 1.60)**	**0.004**	Random	0.144	53.1
	Prostate cancer	1	127/165	1.33(0.95, 1.85)	0.096	Fixed	-	-
	PB	9	5940/6693	**1.20(1.02, 1.42)**	**0.029**	Random	0.000	89.4
	HB	4	976/1177	1.08(0.94, 1.23)	0.283	Fixed	0.750	0
	PCR-RFLP	6	3049/3198	1.21(0.95, 1.53)	0.121	Random	0.000	87.0
	TaqMan	4	2177/2236	1.16(0.96, 1.41)	0.130	Random	0.004	77.6
	Illumina	3	1690/2436	1.07(0.98, 1.17)	0.128	Fixed	0.919	0
	High quality (> 9)	7	5079/5095	1.21(0.99, 1.48)	0.057	Random	0.000	91.1
	Low quality (≤ 9)	6	1837/2775	1.08(0.99, 1.18)	0.086	Fixed	0.728	0

Abbreviation: OR: Odds ratio; CI: Confidence interval; PB: Publication-based controls; HB: Hospital-based controls. Bold values are statistically significant (P<0.05).

Table 3. Meta-analysis of associations between the rs4588 polymorphism and cancer risk

Model	Overall and Stratification analyses	No. of study	No. of cases/controls	OR (95% CI)	*P*-value	Random/ Fixed effect	*P* for heterogeneity	I^2 (%)
Dominant	Overall	10	4759/5262	**1.10(1.02, 1.19)**	**0.016**	Fixed	0.614	0
	Caucasian	5	3350/3649	**1.10(1.01, 1.21)**	**0.040**	Fixed	0.770	0
	Asian	5	1409/1613	1.10(0.95, 1.27)	0.214	Fixed	0.248	26.0
	Breast cancer	4	3185/3525	**1.10(1.00, 1.21)**	**0.046**	Fixed	0.791	0
	Digestive system	4	964/1187	1.12(0.94, 1.32)	0.210	Fixed	0.154	42.9
	tumor Prostate cancer	1	165/124	1.36(0.85, 2.17)	0.203	Fixed	-	-
	Non-small cell lung cancer	1	445/426	1.05(0.80, 1.37)	0.727	Fixed	-	-
	PB	6	3795/4075	**1.10(1.00, 1.20)**	**0.040**	Fixed	0.857	0
	HB	4	964/1187	1.12(0.94, 1.32)	0.210	Fixed	0.154	42.9
	PCR-RFLP	6	2944/3221	1.07(0.97, 1.18)	0.202	Fixed	0.342	11.4
	TaqMan	4	1815/2041	1.16(0.98, 1.32)	0.083	Fixed	0.899	0
	High quality (> 9)	4	3410/3501	**1.16(1.02, 1.32)**	**0.047**	Fixed	0.314	15.5
	Low quality (≤ 9)	6	1349/1761	1.08(0.98, 1.19)	0.109	Fixed	0.859	0
Recessive	Overall	10	4759/5262	**1.27(1.11, 1.46)**	**0.001**	Fixed	0.204	26.1
	Caucasian	5	3350/3649	**1.17(1.00, 1.39)**	**0.049**	Fixed	0.652	0
	Asian	5	1409/1613	**1.51(1.18, 1.94)**	**0.001**	Fixed	0.128	44.1
	Breast cancer	4	3185/3525	1.16(0.98, 1.37)	0.092	Fixed	0.588	0
	Digestive system tumor	4	964/1187	**1.58(1.02, 2.46)**	**0.042**	Random	0.070	57.5
	Prostate cancer	1	165/124	1.57(0.71, 3.49)	0.266	Fixed	-	-
	Non-small cell lung cancer	1	445/426	1.40(0.83, 2.35)	0.210	Fixed	-	-
	PB	6	3795/4075	**1.19(1.02, 1.40)**	**0.029**	Fixed	0.724	0
	HB	4	964/1187	**1.58(1.02, 2.46)**	**0.042**	Random	0.070	57.5
	PCR-RFLP	6	2944/3221	**1.35(1.13, 1.61)**	**0.001**	Fixed	0.121	42.6

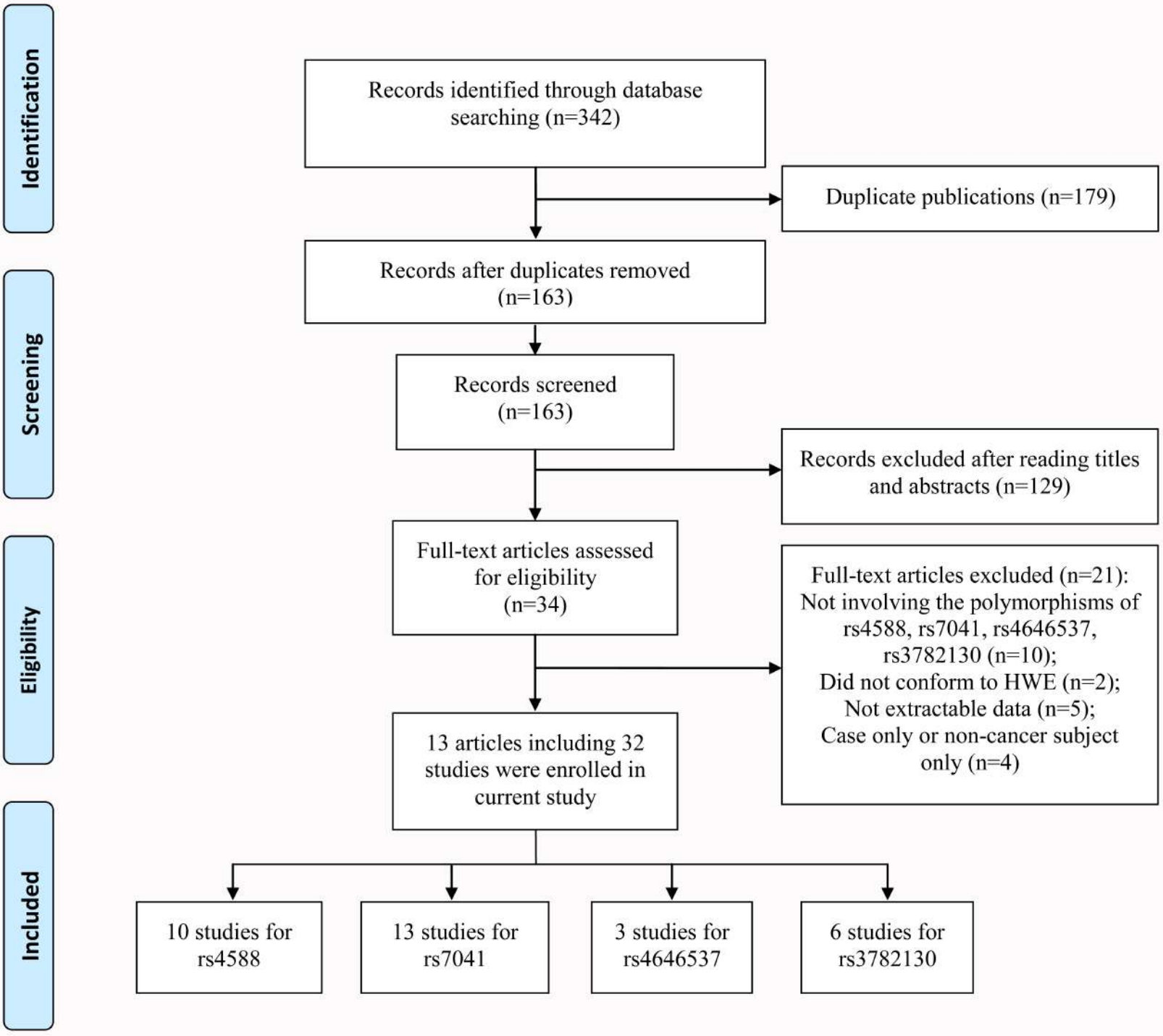
	TaqMan	4	1815/2041	1.16(0.93, 1.44)	0.189	Fixed	0.488	0
	High quality (> 9)	4	3410/3501	**1.55(1.23, 1.96)**	**0.000**	Fixed	0.216	29.2
	Low quality (≤ 9)	6	1349/1761	1.14(0.96, 1.36)	0.121	Fixed	0.758	0
Homozygote	Overall	10	4759/5262	**1.31(1.13, 1.51)**	**0.000**	Fixed	0.173	29.6
	Caucasian	5	3350/3649	**1.22(1.02, 1.45)**	**0.026**	Fixed	0.683	0
	Asian	5	1409/1613	**1.56(1.06, 2.29)**	**0.024**	Random	0.072	53.4
	Breast cancer	4	3185/3525	**1.20(1.00, 1.43)**	**0.047**	Fixed	0.671	0
	Digestive system	4	964/1187	1.62(0.98, 2.68)	0.061	Random	0.037	64.5
	tumor Prostate cancer	1	165/124	1.73(0.76, 3.94)	0.191	Fixed	-	-
	Non-small cell lung cancer	1	445/426	1.39(0.82, 2.38)	0.224	Fixed	-	-
	PB	6	3795/4075	**1.23(1.05, 1.45)**	**0.013**	Fixed	0.775	0
	HB	4	964/1187	1.62(0.98, 2.68)	0.061	Random	0.037	64.5
	PCR-RFLP	6	2944/3221	**1.45(1.08, 1.94)**	**0.014**	Random	0.072	50.5
	TaqMan	4	1815/2041	1.23(0.98, 1.54)	0.077	Fixed	0.518	0
	High quality (> 9)	4	3410/3501	**1.59(1.25, 2.04)**	**0.000**	Fixed	0.130	41.3
	Low quality (≤ 9)	6	1349/1761	1.18(0.99, 1.40)	0.069	Fixed	0.892	0
Heterozygote	Overall	10	4759/5262	**1.23(1.06, 1.42)**	**0.005**	Fixed	0.314	14.0
	Caucasian	5	3350/3649	1.12(0.94, 1.34)	0.203	Fixed	0.662	0
	Asian	5	1409/1613	**1.51(1.16, 1.96)**	**0.002**	Fixed	0.305	17.2
	Breast cancer	4	3185/3525	1.11(0.93, 1.33)	0.251	Fixed	0.534	0
	Digestive system tumor	4	964/1187	**1.54(1.15, 2.08)**	**0.004**	Fixed	0.191	36.8
	Prostate cancer	1	165/124	1.37(0.58, 3.20)	0.474	Fixed	-	-
	Non-small cell lung cancer	1	445/426	1.40(0.81, 2.41)	0.227	Fixed	-	-
	PB	6	3795/4075	1.15(0.97, 1.35)	0.113	Fixed	0.704	0
	HB	4	964/1187	1.24(0.99, 1.65)	0.127	Fixed	0.191	36.8
	PCR-RFLP	6	2944/3221	**1.34(1.12, 1.62)**	**0.002**	Fixed	0.279	20.5

	TaqMan	4	1815/2041	1.07(0.85, 1.35)	0.546	Fixed	0.552	0
	High quality (> 9)	4	3410/3501	**1.51(1.18, 1.93)**	**0.001**	Fixed	0.438	0
	Low quality (≤ 9)	6	1349/1761	1.11(0.92, 1.32)	0.272	Fixed	0.593	0
Allele	Overall	10	4759/5262	**1.11(1.05, 1.18)**	**0.001**	Fixed	0.284	17.3
	Caucasian	5	3350/3649	**1.10(1.02, 1.18)**	**0.015**	Fixed	0.685	0
	Asian	5	1409/1613	1.15(0.99, 1.35)	0.077	Random	0.086	50.9
	Breast cancer	4	3185/3525	**1.09(1.01, 1.17)**	**0.030**	Fixed	0.764	0
	Digestive system	4	964/1187	1.18(0.95, 1.45)	0.131	Random	0.049	61.8
	tumor Prostate cancer	1	165/124	1.33(0.92, 1.93)	0.127	Fixed	-	-
	Non-small cell lung cancer	1	445/426	1.09(0.88, 1.35)	0.425	Fixed	-	-
	PB	6	3795/4075	**1.10(1.02, 1.17)**	**0.010**	Fixed	0.809	0
	HB	4	964/1187	1.18(0.95, 1.45)	0.131	Random	0.049	61.8
	PCR-RFLP	6	2944/3221	**1.10(1.02, 1.19)**	**0.014**	Fixed	0.104	45.3
	TaqMan	4	1815/2041	1.13(0.97, 1.25)	0.087	Random	0.085	50.6
	High quality (> 9)	4	3410/3501	**1.19(1.07, 1.33)**	**0.001**	Fixed	0.137	40.0
	Low quality (≤ 9)	6	1349/1761	1.08(0.99, 1.16)	0.054	Fixed	0.988	0

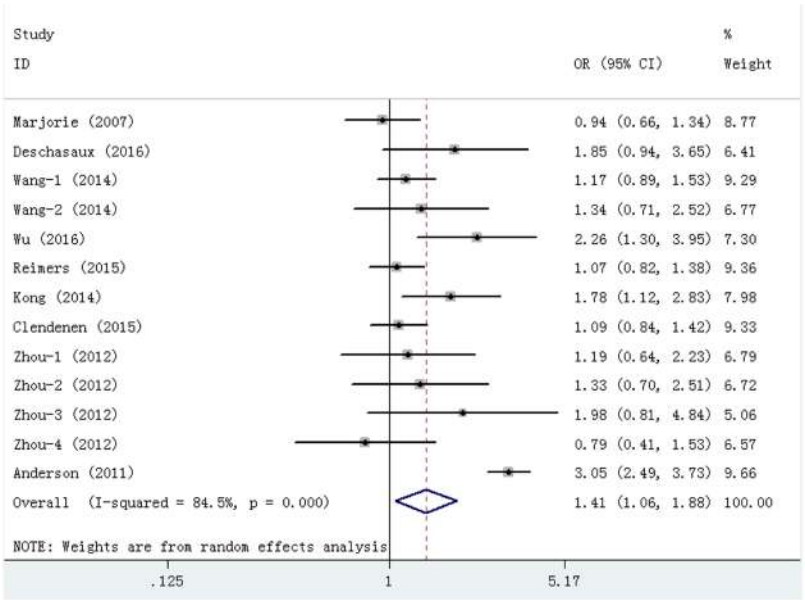
Abbreviation: OR: Odds ratio; CI: Confidence interval; PB: Publication-based controls; HB: Hospital-based controls. Bold values are statistically significant (P<0.05).

Table 4. Begg's and Egger's tests for publication bias

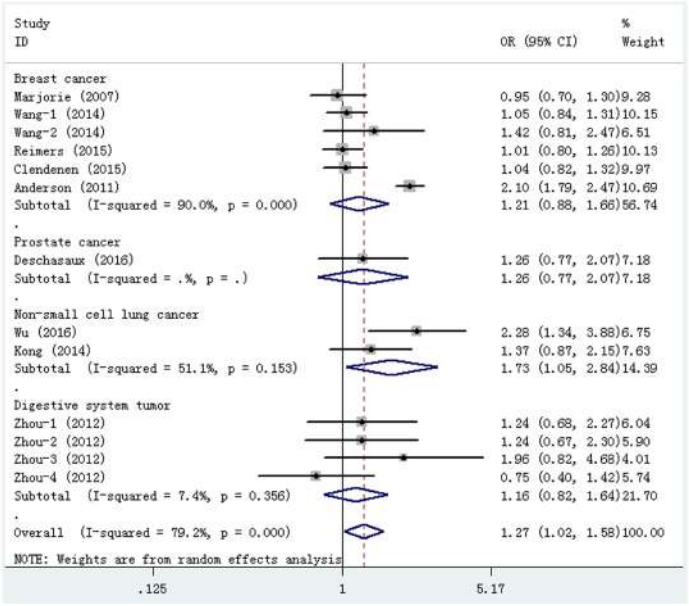
Model	rs4588		rs7041		rs4646537		rs3782130	
	P_{Begg}	P_{Egger}	P_{Begg}	P_{Egger}	P_{Begg}	P_{Egger}	P_{Begg}	P_{Egger}
Dominant	0.669	0.573	0.502	0.221	0.602	0.838	0.707	0.727
Recessive	0.132	0.119	0.200	0.498	0.546	0.588	0.310	0.945
Homozygote	0.231	0.124	0.161	0.362	0.573	0.597	0.452	0.833
Heterozygote	0.107	0.132	0.127	0.722	1.000	0.562	0.348	0.736
Allele	0.208	0.130	0.200	0.166	0.609	0.721	0.851	0.947

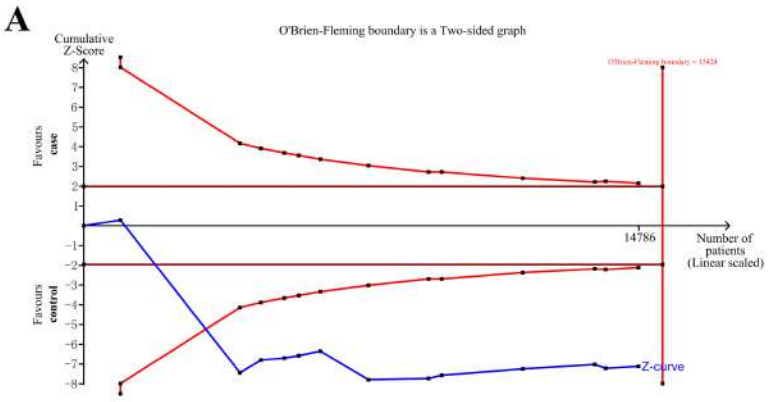

Identification
Screening
Eligibility
Included
Records identified through database searching (n=342)
Duplicate publications (n=179)
Records after duplicates removed (n=163)
Records screened (n=163)
Records excluded after reading titles and abstracts (n=129)
Full-text articles assessed for eligibility (n=34)
Full-text articles excluded (n=21):
Not involving the polymorphisms of rs4588, rs7041, rs4646537, rs3782130 (n=10);
Did not conform to HWE (n=2);
Not extractable data (n=5);
Case only or non-cancer subject only (n=4)
13 articles including 32 studies were enrolled in current study
10 studies for rs4588
13 studies for rs7041
3 studies for rs4646537
6 studies for rs3782130

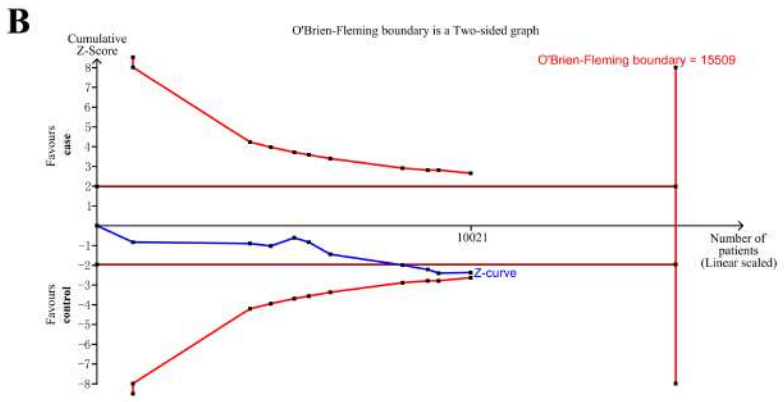
A

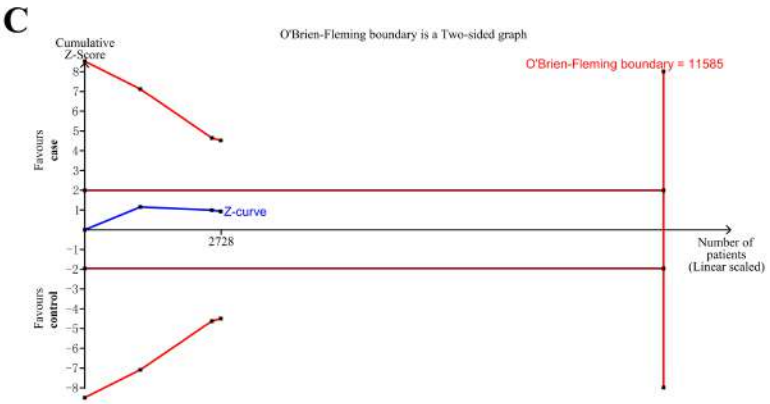

Study
ID
OR (95% CI)
%
Weight
Marjorie (2007) 0.94 (0.66, 1.34) 8.77
Deschasaux (2016) 1.85 (0.94, 3.65) 6.41
Wang-1 (2014) 1.17 (0.89, 1.53) 9.29
Wang-2 (2014) 1.34 (0.71, 2.52) 6.77
Wu (2016) 2.26 (1.30, 3.95) 7.30
Reimers (2015) 1.07 (0.82, 1.38) 9.36
Kong (2014) 1.78 (1.12, 2.83) 7.98
Clendenen (2015) 1.09 (0.84, 1.42) 9.33
Zhou-1 (2012) 1.19 (0.64, 2.23) 6.79
Zhou-2 (2012) 1.33 (0.70, 2.51) 6.72
Zhou-3 (2012) 1.98 (0.81, 4.84) 5.06
Zhou-4 (2012) 0.79 (0.41, 1.53) 6.57
Anderson (2011) 3.05 (2.49, 3.73) 9.66
Overall (I-squared = 84.5%, p = 0.000) 1.41 (1.06, 1.88) 100.00
NOTE: Weights are from random effects analysis
.125
1
5.17

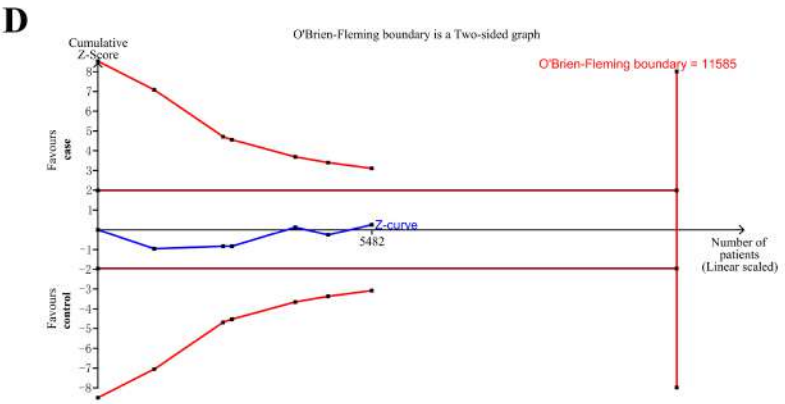
B


Study
ID
OR (95% CI)
%
Weight
Breast cancer
Marjorie (2007) 0.95 (0.70, 1.30) 9.28
Wang-1 (2014) 1.05 (0.84, 1.31) 10.15
Wang-2 (2014) 1.42 (0.81, 2.47) 6.51
Reimers (2015) 1.01 (0.80, 1.26) 10.13
Clendenen (2015) 1.04 (0.82, 1.32) 9.97
Anderson (2011) 2.10 (1.79, 2.47) 10.69
Subtotal (I-squared = 90.0%, p = 0.000) 1.21 (0.88, 1.66) 56.74
Prostate cancer
Deschasaux (2016) 1.26 (0.77, 2.07) 7.18
Subtotal (I-squared = .%, p = .) 1.26 (0.77, 2.07) 7.18
Non-small cell lung cancer
Wu (2016) 2.28 (1.34, 3.88) 6.75
Kong (2014) 1.37 (0.87, 2.15) 7.63
Subtotal (I-squared = 51.1%, p = 0.153) 1.73 (1.05, 2.84) 14.39
Digestive system tumor
Zhou-1 (2012) 1.24 (0.68, 2.27) 6.04
Zhou-2 (2012) 1.24 (0.67, 2.30) 5.90
Zhou-3 (2012) 1.96 (0.82, 4.68) 4.01
Zhou-4 (2012) 0.75 (0.40, 1.42) 5.74
Subtotal (I-squared = 7.4%, p = 0.356) 1.16 (0.82, 1.64) 21.70
Overall (I-squared = 79.2%, p = 0.000) 1.27 (1.02, 1.58) 100.00
NOTE: Weights are from random effects analysis
.125
1
5.17

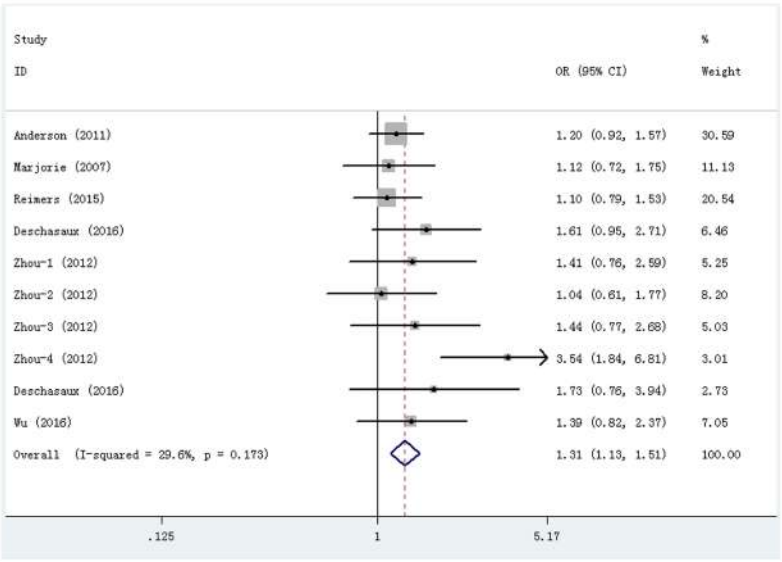

A
O'Brien-Fleming boundary is a Two-sided graph
Cumulative Z-Score
O'Brien-Fleming boundary = 15424
Favours case
Favours control
14786
Number of patients (Linear scaled)
Z-curve


B
O'Brien-Fleming boundary is a Two-sided graph
Cumulative Z-Score
O'Brien-Fleming boundary = 15509
Favours case
Favours control
10021
Number of patients (Linear scaled)
Z-curve

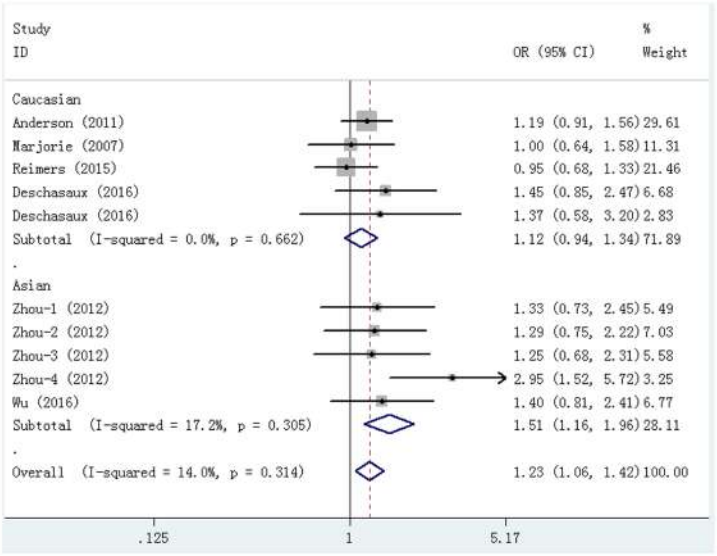

C
O'Brien-Fleming boundary is a Two-sided graph
Cumulative Z-Score
O'Brien-Fleming boundary = 11585
Favours case
Favours control
Z-curve
2728
Number of patients (Linear scaled)


D
O'Brien-Fleming boundary is a Two-sided graph
Cumulative Z-Score
O'Brien-Fleming boundary = 11585
Favours case
Favours control
Z-curve
5482
Number of patients (Linear scaled)

A


Study
ID
OR (95% CI)
%
Weight
Anderson (2011) 1.20 (0.92, 1.57) 30.59
Marjorie (2007) 1.12 (0.72, 1.75) 11.13
Reimers (2015) 1.10 (0.79, 1.53) 20.54
Deschasaux (2016) 1.61 (0.95, 2.71) 6.46
Zhou-1 (2012) 1.41 (0.76, 2.59) 5.25
Zhou-2 (2012) 1.04 (0.61, 1.77) 8.20
Zhou-3 (2012) 1.44 (0.77, 2.68) 5.03
Zhou-4 (2012) 3.54 (1.84, 6.81) 3.01
Deschasaux (2016) 1.73 (0.76, 3.94) 2.73
Wu (2016) 1.39 (0.82, 2.37) 7.05
Overall (I-squared = 29.6%, p = 0.173) 1.31 (1.13, 1.51) 100.00
.125
1
5.17

B


Study
ID
OR (95% CI)
%
Weight
Caucasian
Anderson (2011) 1.19 (0.91, 1.56) 29.61
Marjorie (2007) 1.00 (0.64, 1.58) 11.31
Reimers (2015) 0.95 (0.68, 1.33) 21.46
Deschasaux (2016) 1.45 (0.85, 2.47) 6.68
Deschasaux (2016) 1.37 (0.58, 3.20) 2.83
Subtotal (I-squared = 0.0%, p = 0.662) 1.12 (0.94, 1.34) 71.89
.
Asian
Zhou-1 (2012) 1.33 (0.73, 2.45) 5.49
Zhou-2 (2012) 1.29 (0.75, 2.22) 7.03
Zhou-3 (2012) 1.25 (0.68, 2.31) 5.58
Zhou-4 (2012) 2.95 (1.52, 5.72) 3.25
Wu (2016) 1.40 (0.81, 2.41) 6.77
Subtotal (I-squared = 17.2%, p = 0.305) 1.51 (1.16, 1.96) 28.11
.
Overall (I-squared = 14.0%, p = 0.314) 1.23 (1.06, 1.42) 100.00
.125
1
5.17

Supplementary Materials

Supplementary Tables

Table S1 The detailed search strategies of the associations between GC (rs4588, rs7041), CYP27B1 (rs4646537, and rs3782130) polymorphisms and cancer risk

Database	Search strategy	
Pubmed	#1: Polymorphism, genetic #2: Polymorphism* #3: SNP #4: Single nucleotide polymorphism #5: Variant #6: Mutation #7: #1 OR #2 OR #3 OR #4 OR #5 OR #6 #8: rs4588 #9: rs7041 #10: rs4646537 #11: rs3782130 #12: vitamin D-binding protein #13: CYP27B1 #14: #8 OR #9 OR #10 OR #11 OR #12 OR #13 #15: Neoplasms #16: Cancer #17: Carcino* #18: #15 OR #16 OR #17 #19: #7 AND #14 AND #18	((Polymorphism, genetic) OR Polymorphism* OR SNP OR (Single nucleotide polymorphism) OR Variant OR Mutation) AND (rs4588 OR rs7041 OR rs4646537 OR rs3782130 OR CYP24A1 OR vitamin D-binding protein OR CYP27B1) AND (Neoplasms OR Cancer OR Carcino*))
Embase	#1: 'neoplasm'/exp #2: cancer #3: tumor #4: carcinoma #5: carcinogenesis #6: #1 OR #2 OR #3 OR #4 OR #5 #7: rs4588 #8: rs7041 #9: rs4646537 #10: rs3782130 #11: vitamin D-binding protein #12: CYP27B1 #13: #7 OR #8 OR #9 OR #10 OR #11 OR #12 #14: 'single nucleotide polymorphism'/exp #15: SNP	(('neoplasm'/exp OR cancer OR tumor OR carcinoma OR carcinogenesis) AND (rs4588 OR rs7041 OR rs4646537 OR rs3782130 OR CYP24A1 OR vitamin D-binding protein OR CYP27B1) AND ('single nucleotide polymorphism'/exp OR SNP OR polymorphism OR variant OR mutation))

	#16: polymorphism
	#17: variant
	#18: mutation
	#19: #14 OR #15 OR #16 OR #17 OR #18
	#20: #6 AND #13 AND #19

Table S2. Score of quality assessment

Criteria	Score
Representativeness of case	
Selected from population cancer	2
registry Selected from hospital	1
No method of selection described	0
Representativeness of control	
Population-based	3
Blood donors	2
Hospital-based	1
Not described	0
Ascertainment of cancer case	
Histopathologic	2
confirmation By patient	1
medical record Not described	0
Control selection	
Controls matched with cases by age and sex	2
Controls matched with cases only by age or by sex	1
Not matched or not descried	0
Genotyping examination	
Genotyping done blindly and quality control	2
Only genotyping done blindly or quality control	1
Unblinded and without quality control	0
HWE	
HWE in the control group	1
HWD in the control group or not	0
mentioned Total sample size	
> 1000	3
501 - 1000	2
201 - 500	1
≤ 200	0

Table S3. False-positive report probability values for associations between the rs7041 polymorphism and cancer risk

Significant association	OR (95%CI)	*P* [a]	Statistical power [b]	Prior probability				
				0.25	0.1	0.01	0.001	0.0001
Dominant								
Overall	1.22(1.03, 1.44)	0.019	0.993	**0.054**	**0.145**	0.651	0.950	0.995
PB	1.28(1.04, 1.59)	0.023	0.924	**0.077**	0.200	0.733	0.965	0.996
Recessive								
Overall	1.27(1.02, 1.58)	0.030	0.932	**0.093**	0.236	0.772	0.972	0.997
Asian	1.40(1.11, 1.77)	0.005	0.718	**0.020**	**0.058**	**0.404**	**0.873**	**0.986**
Non-small cell lung cancer	1.73(1.05, 2.84)	0.031	0.286	0.240	0.487	0.913	0.991	0.999
PB	1.30(1.01, 1.68)	0.045	0.863	**0.135**	0.319	0.837	0.981	0.998
PCR-RFLP	1.55(1.10, 2.19)	0.013	0.426	**0.084**	0.215	0.750	0.968	0.997
Homozygote								
Overall	1.41(1.06, 1.88)	0.017	0.663	**0.080**	0.207	0.742	0.967	0.997
Asian	1.52(1.19, 1.93)	0.001	0.457	**0.004**	**0.011**	**0.113**	0.563	0.928
Non-small cell lung cancer	1.97(1.38, 2.81)	0.000	0.066	**0.008**	**0.024**	0.214	0.734	0.965
PB	1.49(1.05, 2.09)	0.024	0.515	**0.108**	0.267	0.801	0.976	0.998
PCR-RFLP	1.66(1.03, 2.69)	0.039	0.340	0.259	0.512	0.920	0.991	0.999
Heterozygote								
Asian	1.28(1.00, 1.63)	0.047	0.901	**0.131**	0.312	0.833	0.980	0.998
PCR-RFLP	1.48(1.09, 2.01)	0.013	0.534	**0.063**	**0.169**	0.691	0.958	0.996
Allele								
Overall	1.17(1.02, 1.33)	0.022	1.000	**0.047**	**0.128**	0.618	0.942	0.994
Asian	1.20(1.09, 1.32)	0.000	1.000	**0.001**	**0.002**	**0.017**	**0.150**	0.639
Non-small cell lung cancer	1.32(1.09, 1.60)	0.004	0.904	**0.015**	**0.044**	0.339	0.838	0.981

PB	1.20(1.02, 1.42)	0.029	0.995	**0.092**	0.234	0.771	0.971	0.997

The results in false-positive report probability analysis were in bold, if the prior probability <0.2. OR: odds ratio; CI: confidence interval; [a] *P* value for significant test; [b] Statistical power was calculated using the number of observations in the meta-analysis and the OR and *P* value in this table.

Table S4. False-positive report probability values for associations between the rs4588 polymorphism and cancer risk

Significant association	OR (95%CI)	*P* [a]	Statistical power [b]	Prior probability				
				0.25	0.1	0.01	0.001	0.0001
Dominant								
Overall	1.10(1.02, 1.19)	0.016	1.000	**0.050**	**0.136**	0.634	0.946	0.994
Caucasian	1.10(1.01, 1.21)	0.040	1.000	**0.130**	0.310	0.832	0.980	0.998
Breast cancer	1.10(1.00, 1.21)	0.046	1.000	**0.130**	0.310	0.832	0.980	0.998
PB	1.10(1.00, 1.20)	0.040	1.000	**0.087**	0.223	0.759	0.969	0.997
High quality (> 9)	1.16(1.02, 1.32)	0.047	1.000	**0.068**	**0.180**	0.707	0.961	0.996
Recessive								
Overall	1.27(1.11, 1.46)	0.001	0.990	**0.002**	**0.007**	**0.072**	0.440	0.887
Caucasian	1.17(1.00, 1.39)	0.049	0.998	**0.182**	0.401	0.880	0.987	0.999
Asian	1.51(1.18, 1.94)	0.001	0.479	**0.008**	**0.023**	0.207	0.725	0.964
Digestive system	1.58(1.02, 2.46)	0.042	0.409	0.239	0.485	0.912	0.991	0.999
tumor PB	1.19(1.02, 1.40)	0.029	0.997	**0.097**	0.245	0.781	0.973	0.997
HB	1.58(1.02, 2.46)	0.042	0.409	0.239	0.485	0.912	0.991	0.999
PCR-RFLP	1.35(1.13, 1.61)	0.001	0.879	**0.003**	**0.009**	**0.086**	0.488	0.905
High quality (> 9)	1.55(1.23, 1.96)	0.000	0.392	**0.002**	**0.006**	**0.060**	0.391	0.865
Homozygote								
Overall	1.31(1.13, 1.51)	0.000	0.969	**0.001**	**0.002**	**0.020**	**0.168**	0.668
Caucasian	1.22(1.02, 1.45)	0.026	0.990	**0.068**	**0.179**	0.706	0.960	0.996
Asian	1.56(1.06, 2.29)	0.024	0.421	**0.142**	0.331	0.845	0.982	0.998
Breast cancer	1.20(1.00, 1.43)	0.047	0.994	**0.111**	0.273	0.805	0.977	0.998
PB	1.23(1.05, 1.45)	0.013	0.991	**0.040**	**0.110**	0.577	0.932	0.993
PCR-RFLP	1.45(1.08, 1.94)	0.014	0.590	**0.059**	**0.159**	0.675	0.954	0.995

High quality (> 9)	1.59(1.25, 2.04)	0.000	0.323	**0.002**	**0.007**	**0.075**	0.450	0.891
Heterozygote Overall								
Asian	1.23(1.06, 1.42)	0.005	0.997	**0.014**	**0.041**	0.320	0.826	0.979
Digestive system	1.51(1.16, 1.96)	0.002	0.480	**0.012**	**0.035**	0.287	0.803	0.976
tumor PCR-RFLP	1.54(1.15, 2.08)	0.004	0.432	**0.033**	**0.092**	0.528	0.918	0.991
High quality (> 9)	1.34(1.12, 1.62)	0.002	0.878	**0.008**	**0.025**	0.220	0.740	0.966
Allele	1.51(1.18, 1.93)	0.001	0.479	**0.006**	**0.018**	**0.171**	0.675	0.954
Overall								
Caucasian	1.11(1.05, 1.18)	0.001	1.000	**0.002**	**0.007**	**0.075**	0.451	0.892
Breast cancer	1.10(1.02, 1.18)	0.015	1.000	**0.023**	**0.066**	0.436	0.886	0.987
PB	1.09(1.01, 1.17)	0.030	1.000	**0.049**	**0.133**	0.628	0.945	0.994
PCR-RFLP	1.10(1.02, 1.17)	0.010	1.000	**0.007**	**0.022**	**0.196**	0.711	0.961
High quality (> 9)	1.10(1.02, 1.19)	0.014	1.000	**0.050**	**0.136**	0.634	0.946	0.994
	1.19(1.07, 1.33)	0.001	1.000	**0.006**	**0.019**	**0.177**	0.685	0.956

The results in false-positive report probability analysis were in bold, if the prior probability <0.2. OR: odds ratio; CI: confidence interval; [a] *P* value for significant test; [b] Statistical power was calculated using the number of observations in the meta-analysis and the OR and *P* value in this table.

Table S5. Meta-analysis of associations between rs4646537 and rs3782130 polymorphisms and cancer risk

Variables	N	Dominant model OR(95%CI)/I^2 %/P_Q	Recessive model OR(95%CI)/I^2 %/P_Q	Homozygote model OR(95%CI)/I^2 %/P_Q	Heterozygote model OR(95%CI)/I^2 %/P_Q	Allele model OR(95%CI)/I^2 %/P_Q
rs4646537						
Overall	3	0.92(0.76, 1.10)/0/0.675	0.77(0.55, 1.09)/0/0.615	0.76(0.53, 1.10)/0/0.610	0.78(0.54, 1.12)/0/0.695	0.91(0.79, 1.05)/0/0.591
Caucasian	2	0.91(0.75, 1.10)/0/0.419	0.77(0.54, 1.09)/0/0.353	0.76(0.52, 1.09)/0/0.351	0.78(0.54, 1.12)/0/0.424	0.90(0.78, 1.04)/0/0.357
African	1	1.04(0.52, 2.07)	1.17(0.10, 13.13)	1.18(0.10, 13.31)	1.14(0.10, 13.62)	1.04(0.56, 1.94)
Prostate cancer	3	0.92(0.76, 1.10)/0/0.675	0.77(0.55, 1.09)/0/0.615	0.76(0.53, 1.10)/0/0.610	0.78(0.54, 1.12)/0/0.695	0.91(0.79, 1.05)/0/0.591
PCR-RFLP	2	0.95(0.78, 1.16)/0/0.793	0.79(0.56, 1.13)/0/0.752	0.79(0.55, 1.14)/0/0.743	0.80(0.56, 1.15)/0/0.776	0.93(0.80, 1.08)/0/0.710
SNPlex assay	1	0.77(0.49, 1.20)	0.19(0.01, 3.86)	0.18(0.01, 3.80)	0.23(0.01, 4.85)	0.74(0.48, 1.15)
High quality (> 9)	2	0.91(0.75, 1.10)/0/0.419	0.77(0.54, 1.09)/0/0.353	0.76(0.52, 1.09)/0/0.351	0.78(0.54, 1.12)/0/0.424	0.90(0.78, 1.04)/0/0.357
Low quality (≤ 9)	1	1.04(0.52, 2.07)	1.17(0.10, 13.13)	1.18(0.10, 13.31)	1.14(0.10, 13.62)	1.04(0.56, 1.94)
rs3782130						
Overall	6	0.99(0.87, 1.11)/0/0.533	1.14(0.95, 1.38)/0/0.417	1.11(0.91, 1.35)/0/0.526	1.19(0.97, 1.44)/1.4/0.407	1.02(0.94, 1.12)/0/0.665
Caucasian	2	1.09(0.89, 1.33)/0/0.616	1.21(0.85, 1.73)/0/0.353	1.27(0.87, 1.84)/0/0.369	1.16(0.80, 1.69)/0/0.329	1.10(0.94, 1.29)/0/0.760
African	1	1.05(0.44, 2.52)	1.11(0.10, 12.46)	1.11(0.10, 12.56)	1.07(0.08, 13.65)	1.06(0.47, 2.34)
Asian	3	0.93(0.79, 1.10)/13/0.317	1.13(0.82, 1.55)/50/0.134	1.06(0.84, 1.33)/28/0.251	1.18(0.84, 1.67)/51/0.130	0.99(0.89, 1.11)/3/0.357
Prostate cancer	3	1.09(0.89, 1.33)/0/0.879	1.21(0.85, 1.72)/0/0.648	1.26(0.87, 1.83)/0/0.665	1.16(0.80, 1.68)/0/0.620	1.10(0.94, 1.28)/0/0.950
NSCLC	2	0.87(0.73, 1.04)/0/0.976	1.14(0.70, 1.85)/75/0.045	1.04(0.68, 1.57)/61/0.111	1.24(0.75, 2.05)/73/0.053	0.96(0.85, 1.09)/0/0.331
Colorectal cancer	1	1.14(0.84, 1.55)	1.12(0.68, 1.83)	1.18(0.70, 1.98)	1.04(0.62, 1.77)	1.11(0.88, 1.40)
PCR-RFLP	4	0.98(0.83, 1.17)/0/0.616	0.98(0.74, 1.28)/0/0.638	0.96(0.72, 1.29)/0/0.517	1.01(0.75, 1.36)/0/0.753	0.98(0.86, 1.13)/0/0.558
Other methods	2	0.99(0.77, 1.27)/57/0.128	1.32(0.96, 1.69)/0/0.395	1.26(0.96, 1.65)/0/0.864	1.35(0.94, 1.76)/42/0.189	1.06(0.94, 1.19)/0/0.443
High quality (> 9)	4	0.96(0.84, 1.09)/1/0.387	1.15(0.94, 1.40)/40/0.173	1.10(0.89, 1.36)/27/0.251	1.21(0.98, 1.50)/38/0.186	1.01(0.92, 1.11)/0/0.558
Low quality (≤ 9)	2	1.13(0.85, 1.51)/0/0.861	1.12(0.95, 1.38)/0/0.995	1.18(0.71, 1.95)/0/0.963	1.04(0.62, 1.75)/0/0.986	1.10(0.88, 1.38)/0/0.907

Abbreviation: OR: Odds ratio; CI: Confidence interval; P_Q: P value of the Q-test for heterogeneity test.

Supplementary Figures

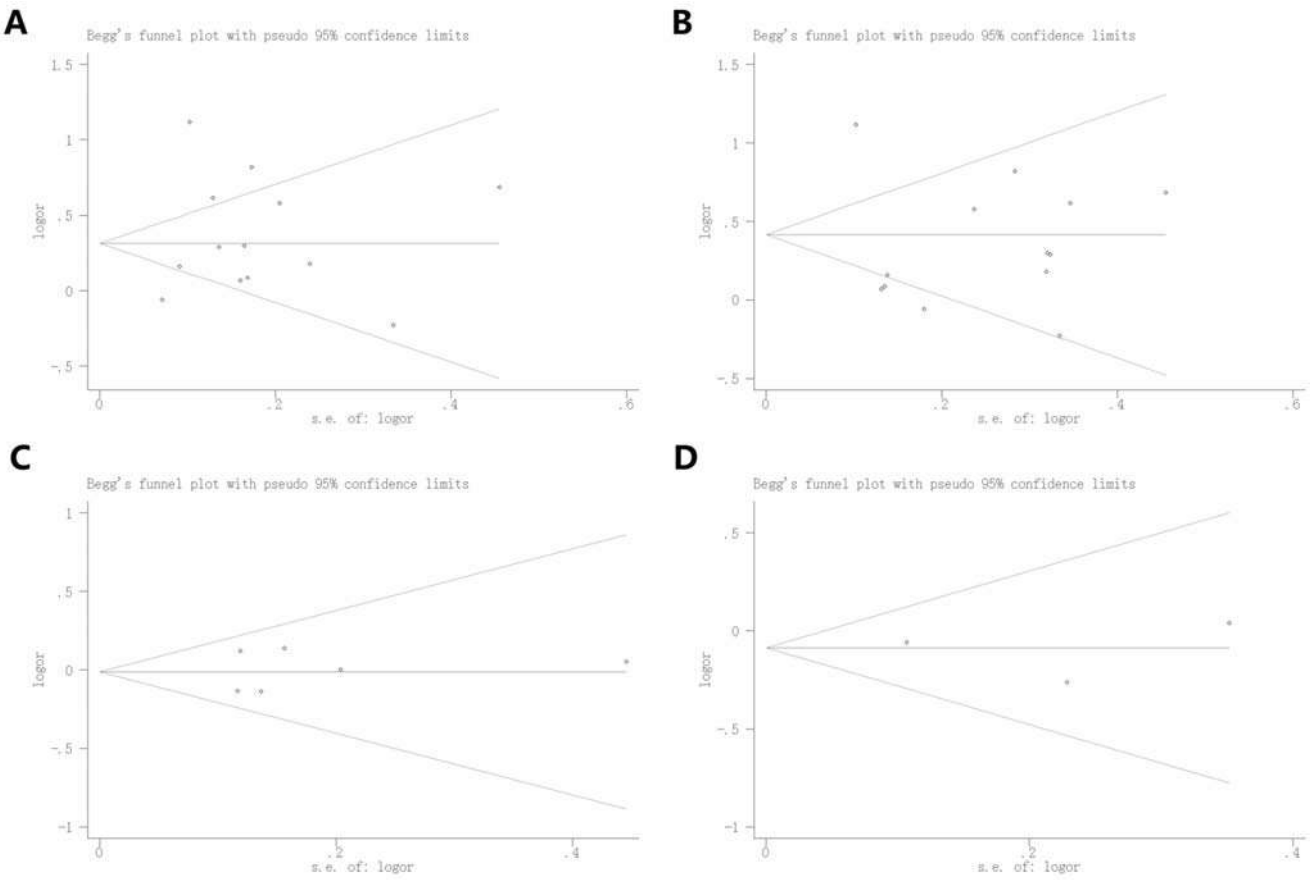


Figure S1. Begg's test for publication bias (dominant model). A rs4588; **B** rs7041; **C** rs3782130; **D** rs4646537

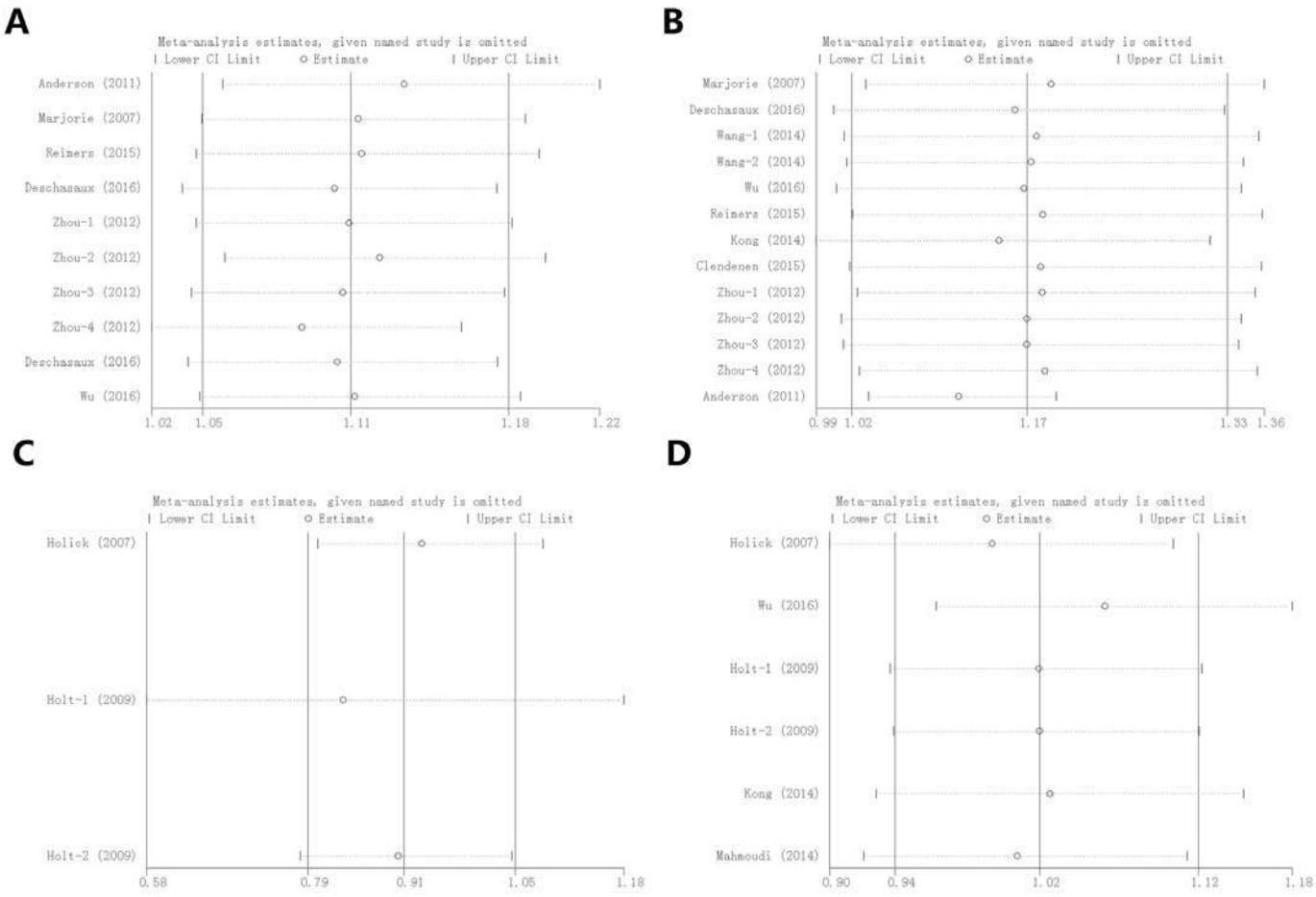


Figure S2. Sensitivity analyses of the studies (allele model). A rs4588; **B** rs7041; **C** rs4646537; **D** rs3782130