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Review Article

A miR-SNP of the *XPO5* gene with the risk and prognosis of cancer: a meta-analysis

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Abstract: Accumulating studies have suggested that a miRNA-SNP of rs11077 may be associated with the risk and outcome of cancer. The aim of this study is to comprehensively investigate the susceptibility and prognostic value of rs11077 in cancer. Pubmed, Elsevier, Web of Science and Google Scholar were searched up to June 2016. Odds ratio and hazard ratio were used to assess the association of rs11077 with the risk and prognosis of cancer, respectively. Significant association between rs11077 and cancer risk were found in allelic model (P = 0.006, OR = 1.22, 95% CI = 1.06-1.40), dominant model (P = 0.05, OR = 1.2, 95% CI = 1.00-1.44), recessive model (P = 0.015, OR = 1.43, 95% CI = 1.07-1.90) and homozygous model (P = 0.01, OR = 1.52, 95% CI = 1.11-2.09). Furthermore, subgroup analysis showed that significant associations were only detected in Caucasians under allelic model (P = 0.001, OR = 1.34, 95% CI = 1.13-1.60), dominant model (P = 0.018, OR = 1.36, 95% CI = 1.05-1.76), recessive model (P = 0.003, OR = 1.56, 95% CI = 1.16-2.10) and homozygous model (P = 0.02, OR = 1.72, 95% CI = 1.23-2.40). Besides, AA genotype was significantly associated with poor prognosis compared with AC (or AC+CC) (P<0.01, RR = 1.69, 95% CI = 1.26-2.28). Our meta-analysis demonstrated that a miR-SNP of rs11077 located in the 3'UTR of *XPO5* increases the risk of cancer, and this association might only exist in Caucasians. Besides, rs11077 of *XPO5* could predict a poor outcome of patients with cancers.

Keywords: XPO5, rs11077, miR-SNPs, cancer, susceptibility, prognosis

Introduction

MicroRNAs (miRNAs) are non-coding RNAs measuring ~22 nucleotides in length, and play a key role in various physiological and developmental processes [1, 3]. It's reported that miRNAs are responsible for regulating up to 30%-60% of all human genes by targeting mRNA [22, 28]. The biogenesis of a functional miRNA involves several proteins [12]. Initially, primary miRNAs (pri-miRNAs), which contain one or more 70-nt hairpin precursor miRNSs, are sequentially cleaved in the nucleus by *DROSHA* and *DGCR8*, converted into pre-miRNAs. Next, the pre-miRNAs are transported by the nuclear transport factor exportin-5 (*XPO5*) and *RAN* from the nucleus into the cytoplasm, where they are further cleaved to produce mature miRNA [21].

Exportin-5 (XPO5), encoded by the XPO5 gene [6, 15, 16], is a member of the karyopherin family that comprise one major class of nucleocytoplasmic transporters. XPO5 binds directly to the free ends of the RNA cargos in a RanGTP-dependent manner, including pre-miRNAs, viral hairpin RNAs, and tRNAs [4, 5, 24]. Numerous recent studies demonstrated that inhibition of XPO5 was associated with down-regulation of *Dicer* and delayed G1/S transition [19, 25], making XPO5 a critical element in miRNA biogenesis.

Dysfunction of XPO5 can also alter the risk and prognosis of many cancers [17, 18]. The XPO5 mutant, microRNA-related single nucleotide polymorphisms (miR-SNPs) of rs11077, located in the 3'UTR of the gene, was demonstrated to be associated with the risks and outcomes of patients with different carcinomas [7, 27, 31]. However, the underlying association remains ambiguous. As new studies about the miR-SNP of rs11077 arising, there has been no meta-analysis conducted to evaluate the risk and prognosis of cancer. Therefore, the aim of this meta-analysis was to assess the prognostic

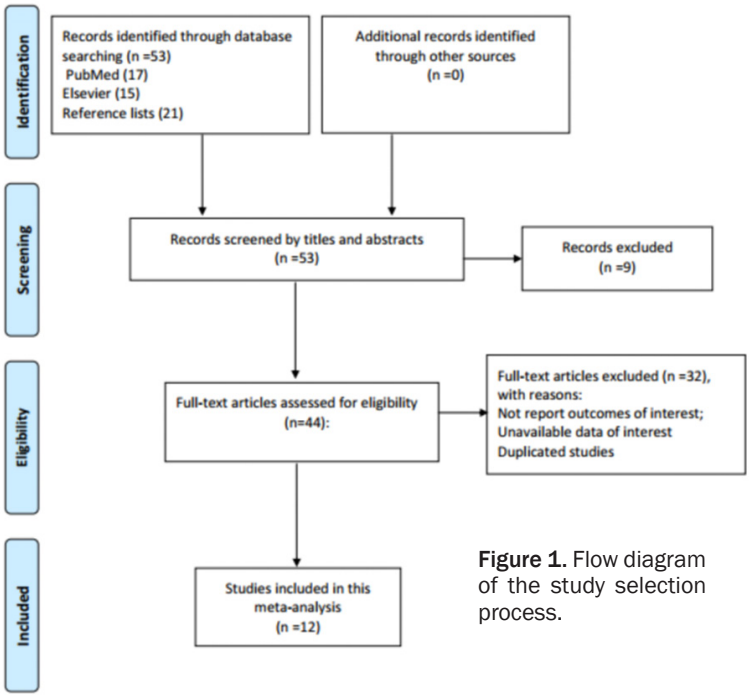

Figure 1. Flow diagram of the study selection process.

value of rs11077 in cancer and to investigate the susceptibility of cancer with the rs11077 mutant.

Methods

Identification of eligible studies

Two researchers independently retrieved and identified eligibility of the studies (F Xu and L Jin). Database of PubMed, Web of Science and Elsevier were searched using the following search terms: "rs11077" or "XPO5", combined with "cancer". Publications from inception up to Mar, 2018 were reviewed for eligibility. Studies were included if they met all of the following criteria: (1) studies were case-control designs; (2) studies assessed the association of rs11077 with cancer risk or survival outcomes; (3) the distribution of genotype were available for cases and controls or the hazard ratio (HR) with 95% confidence interval (CI) could be exacted for prognosis analysis.

Data extraction

Two researchers extracted the data independently using a standard data-collection form, including first author, publication year, country of origin, ethnicity, cancer type, number of cases and controls, the genotype distribution for cases and controls or hazard ratio (HR) with 95% confidential interval (CI) of rs11077 genotype. The ethnic descents were categorized as European or Asian.

Statistical analysis

For susceptibility analysis, the strength of association between rs11077 polymorphism and cancer risk was assessed by odd ratio (OR) with 95% confidence interval (CI) under allelic model (C vs A), dominant model (CC+AC vs AA), recessive model (CC vs AC+AA), homozygous model (CC vs AA) and heterozygous model (AC vs AA). The distribution of frequencies of rs11077 polymorphism under Hardy-Weinberg equilibrium (HWE) was assessed by the goodness-of-fit chi-square test in controls, and $P<0.05$ was considered representative of a departure from HWE. For prognosis analysis, hazard ratio (HR) with 95% confidence interval (CI) was used to evaluate the association of survival outcomes with rs11077 polymorphism.

Heterogeneity was examined by the chi-square-based Q-test, and in the present of heterogeneity ($I^2>50\%$), a random-effect model was used; Otherwise, a fixed-effect model was conducted. Subgroup analyses were performed stratified by ethnicity and cancer type. Publication bias of the included studies was evaluated by funnel plot and Begg's test. And sensitivity analysis was performed to investigate the potential sources of heterogeneity.

Quality evaluation

The Newcastle-Ottawa Scale (NOS) was used to assess the risk of bias and quality of the studies. One star is awarded when they met each item of quality and a study with final score >6 stars was considered as high quality.

Results

After the search of databases, 53 articles were first retrieved. Of those, 9 articles couldn't meet the requirement after scanning the titles and abstracts. Then, the full texts of 44 articles were reviewed for eligibility. Finally, 12 articles were included in this meta-analysis (**Figure 1**).

Table 1. Characteristics of eight eligible studies evaluating the association of rs11077 with the cancer risk (randomized controlled trial)

First author	Year	Country	Cancer	Sample size		Mean age		CC	AC	AA	CC	AC	AA	HWE
				Case	Control	Case (F/M)	Control (F/M)	Case			Control			
Yufei Zhao	2015	China	CRC	163	142	60/60	60/60	1	19	143	1	18	123	0.93
Ying Xie	2015	China	GC	137	142	59/61	58.32/60.87	1	17	119	1	18	123	0.93
Sung Hwan Cho	2015	Korea	CRC	408	400	61.55/61.31	60.37/60.46	1	74	333	2	61	337	0.91
Jong-Sik Kim	2010	Korea	Lung cancer	100	99	61.5/61.5	59.94/59.27	0	12	88	3	9	87	0.002
Yohei Horikawa	2008	America	RCC	276	277	60.29/60.46	60.43/59.68	54	136	86	38	129	110	0.99
Alfons Navarro	2013	Spain	HL	127	104	32/34	33.12/34.63	35	67	25	24	46	34	0.55
Cuimin Ding1	2013	China	NSCLC	112	80	60.13/60.54	58.46/62.39	0	18	94	1	14	65	0.96
Marc Campayo	2011	Spain	NSCLC	181	107	65.36/65.08	64.26/66.93	72	35	74	28	37	42	0.009

F: female; M: male.

Among them, 8 articles [8, 9, 11, 18, 20, 26, 29, 33] contained the information of rs11077 with cancer risk, and 7 articles [8, 10, 11, 13, 14, 23, 26] evaluated the association of rs11077 with the survival outcomes of cancer patients.

Analysis of rs11077 and cancer risk

Characteristics of eight eligible studies: Eight studies, including 1054 cases and 1351 controls, were subjected to examine the association of rs11077 with cancer risk. The characteristics of included studies were summarized in **Table 1**. Among the 8 studies, two studies were conducted for colorectal cancer (CRC), two non-small cell lung cancer (NSCLC), and the other four were renal cell carcinoma (RCC), gastric cancer (GC), lung cancer, Hodgkin Lymphoma (HL). Five of them were conducted in Asia, three in Europe. The genotype distributions of all studies were in agreed with Hardy-Weinberg equilibrium, except for the studies of Marc Campayo [8] and Jong-Sik Kim [20].

Publication bias: Funnel plot and Begg's test were performed to evaluated publication bias of included studies. Publication bias were only found in allelic model (P = 0.019). The result of funnel plot and Begg's test were shown in **Table 2** and Figure S3A-E.

Sensitivity analysis: By omitting one study in each time, sensitivity analysis was performed to evaluate the potential sources of heterogeneity. The results suggested that there was no obviously alteration of overall risk estimates in allelic model (Figure S6A), dominant model (Figure S6B), recessive model (Figure S6C), heterozygous model (Figure S6D) and homozygous model (Figure S6E).

Overall analysis: Overall, significant association that rs11077 of *XPO5* increases the risk of cancer was found in allelic model (C vs A, P = 0.006, OR = 1.22, 95% CI = 1.06-1.40, **Figure 2**), dominant model (CC+AC vs AA, P = 0.05, OR = 1.2, 95% CI = 1.00-1.44, **Figure 3**), recessive model (CC vs AC+AA, P = 0.015, OR = 1.43, 95% CI = 1.07-1.90, **Figure 4**) and homozygous model (CC vs AA, P = 0.01, OR = 1.52, 95% CI = 1.11-2.09, **Figure 5**), except heterozygous model (AC vs AA, P = 0.138, OR = 1.14, 95% CI = 0.94-1.38, **Figure 6**) (**Table 2**).

Subgroup analysis: Stratified by ethnicity, the phenomenon that rs11077 of *XPO5* increases the risk of cancer was only detected in Caucasians under allelic model (C vs A, P = 0.001, OR = 1.34, 95% CI = 1.13-1.60, Figure S1A), dominant model (CC+AC vs AA, P = 0.018, OR = 1.36, 95% CI = 1.05-1.76, Figure S1B), recessive model (CC vs AC+AA, P = 0.003, OR = 1.56, 95% CI = 1.16-2.10, Figure S1C) and homozygous model (CC vs AA, P = 0.02, OR = 1.72, 95% CI = 1.23-2.40, Figure S1D).

Furthermore, in our subgroup analysis by cancer types (mainly divided into gastrointestinal cancer and lung cancer), only gastrointestinal cancer (GC) showed that rs11077 of *XPO5* increased the risk of GC under allelic model (C vs A, P = 0.029, OR = 1.22, 95% CI = 1.02-1.4, Figure S2A) and homozygous model (CC vs AA, P = 0.037, OR = 1.65, 95% CI = 1.03-2.65, Figure S2B).

Analysis of rs11077 and survival time of cancer patients

Characteristics of seven eligible studies: Seven studies enrolling 824 cases were included in

Table 2. Meta-analysis of the association between rs11077 and cancer risk under five genotype models

Allelic model (Cohorts)	I^2	*P*	OR (95% CI)	*P* (bias)	Dominant model (Cohorts)	I^2	*P*	OR (95% CI)	*P* (bias)
Overall (8)	0	0.006	1.22 (1.06-1.40)	0.019	Overall (8)	0	0.05	1.2 (1.00-1.44)	0.536
Asian (5)	0	0.966	1.01 (0.79-1.28)		Asian (5)	0	0.692	1.05 (0.81-1.37)	
European (3)	0	0.001	1.34 (1.13-1.60)		European (3)	49.1	0.018	1.36 (1.05-1.76)	
Gastrointestinal cancer (1)	0	0.029	1.22 (1.02-1.47)		Gastrointestinal cancer (1)	0	0.066	1.23 (0.99-1.54)	
Lung cancer (3)	13.6	0.5	1.10 (0.83-1.47)		Lung cancer (3)	0	0.65	0.92 (0.63-1.33)	
HL (1)		0.062	1.42 (0.98-2.05)		HL (1)		0.025	1.98 (1.09-3.61)	
Recessive model	I^2	*P*	OR (95% CI)	*P* (bias)	Homozygous model	I^2	*P*	OR (95% CI)	*P* (bias)
Overall (8)	0	0.015	1.43 (1.07-1.90)	0.108	Overall (8)	0	0.01	1.52 (1.11-2.09)	0.063
Asian (5)	0	0.139	0.41 (0.13-1.34)		Asian (5)	0	0.144	0.41 (0.13-1.35)	
European (3)	0	0.003	1.56 (1.16-2.10)		European (3)	0	0.02	1.72 (1.23-2.40)	
Gastrointestinal cancer (1)	0	0.101	1.22 (1.02-1.47)		Gastrointestinal cancer (1)	0	0.037	1.65 (1.03-2.65)	
Lung cancer (3)	54.3	0.089	1.10 (0.83-1.47)		Lung cancer (3)	42.1	0.536	1.19 (0.69-2.03)	
HL (1)		0.438	1.4 (0.98-2.05)		HL (1)		0.067	1.98 (0.95-4.13)	
Heterozygous model	I^2	*P*	OR (95% CI)	*P* (bias)					
Overall (8)	36.5	0.187	1.14 (0.94-1.38)	0.711					
Asian (5)	0	0.475	1.1 (0.85-1.43)						
European (3)	79.4	0.243	1.18 (0.89-1.56)						
Gastrointestinal cancer (1)	0	0.121	1.2 (0.95-1.51)						
Lung cancer (3)	29.9	0.186	0.76 (0.50-1.14)						

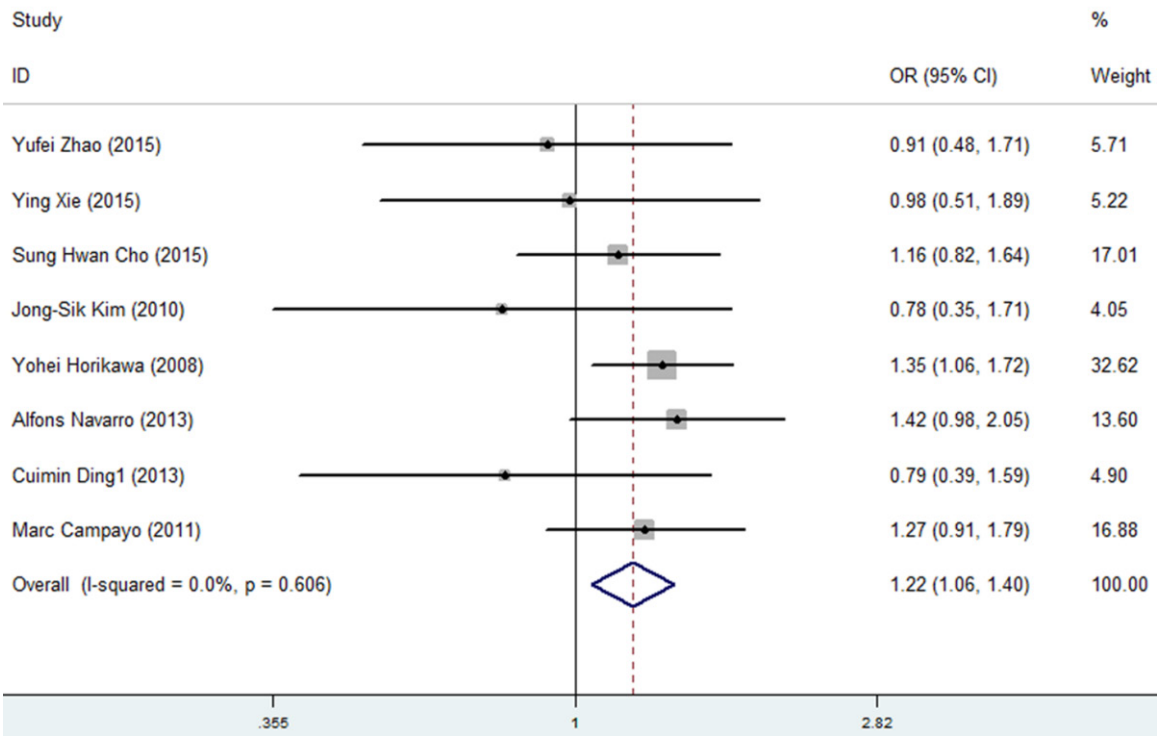

Figure 2. Association between rs11077 and cancer risk in allelic model (C vs A).

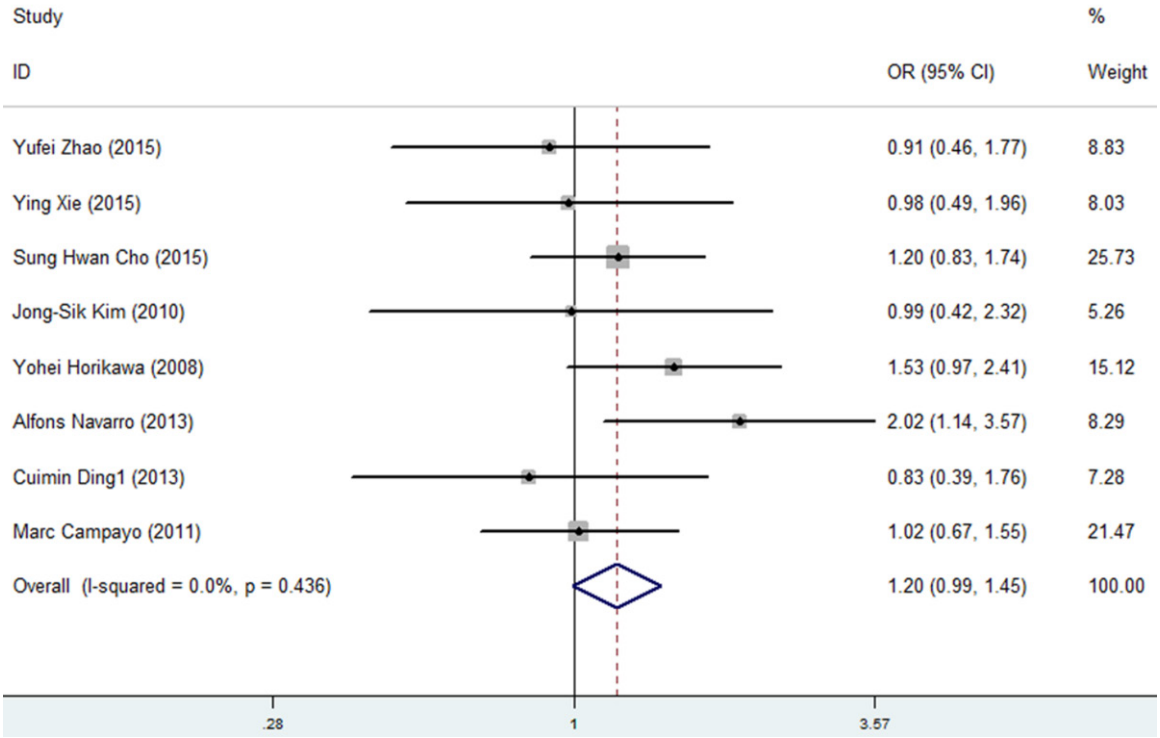

Figure 3. Association between rs11077 and cancer risk in dominant model (CC+AC vs AA).

the prognosis analysis. Of them, the subjects in three studies were Spain or European, and the other four were Chinese or Asian. Non-small cell lung cancer (NSCLC) was analyzed in three

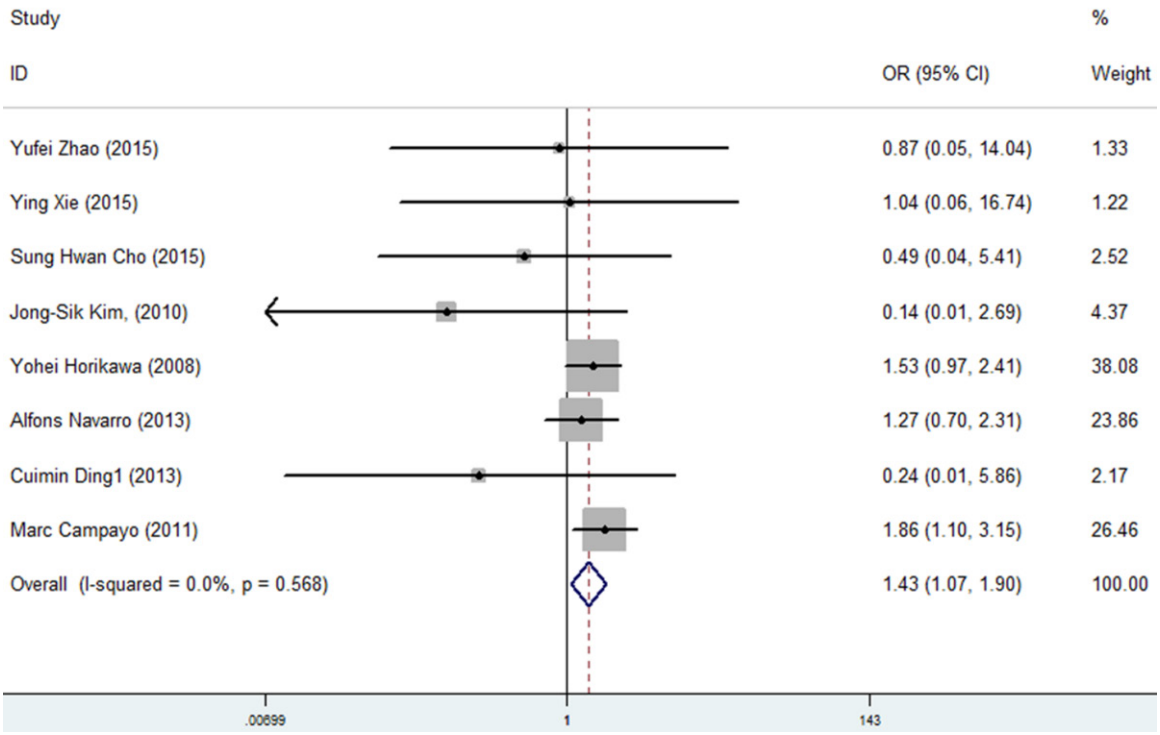

Figure 4. Association between rs11077 and cancer risk in recessive model (CC vs AC+AA).

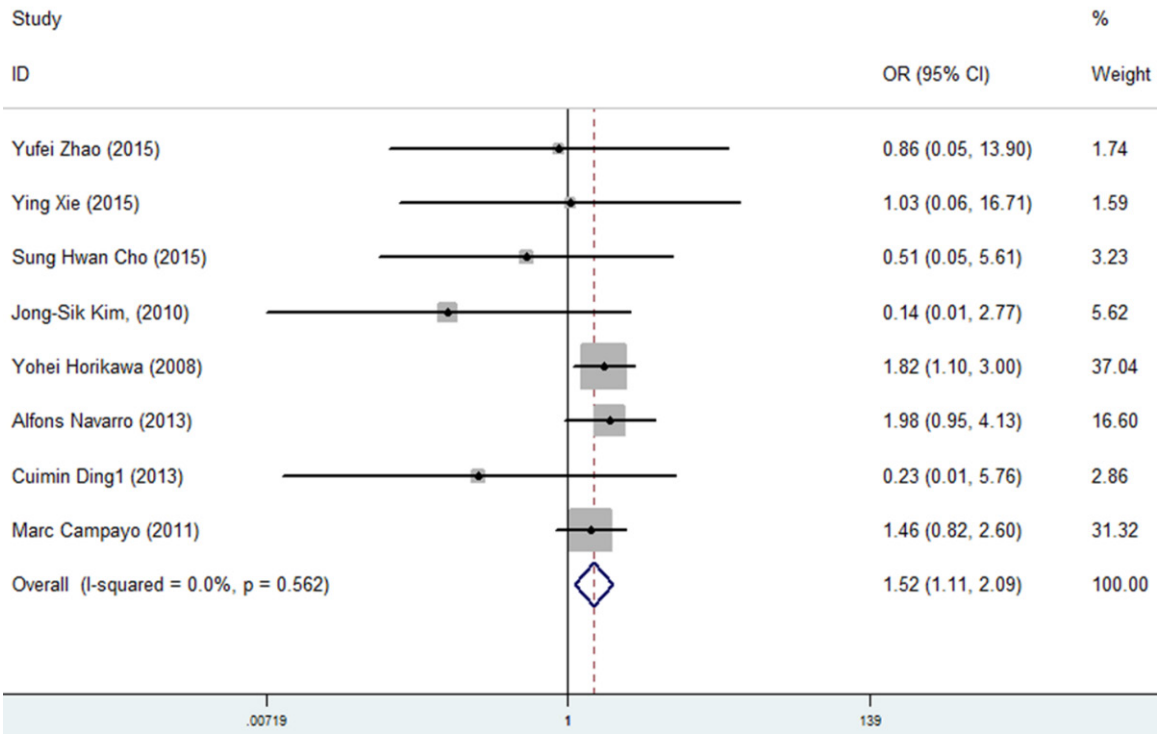

Figure 5. Association between rs11077 and cancer risk in homozygous model (CC vs AA).

studies, small cell lung cancer (SCLC), Hodgkin lymphoma (HL) and multiple myeloma in other studies respectively. Most of the studies compared the survival outcome between AA geno-

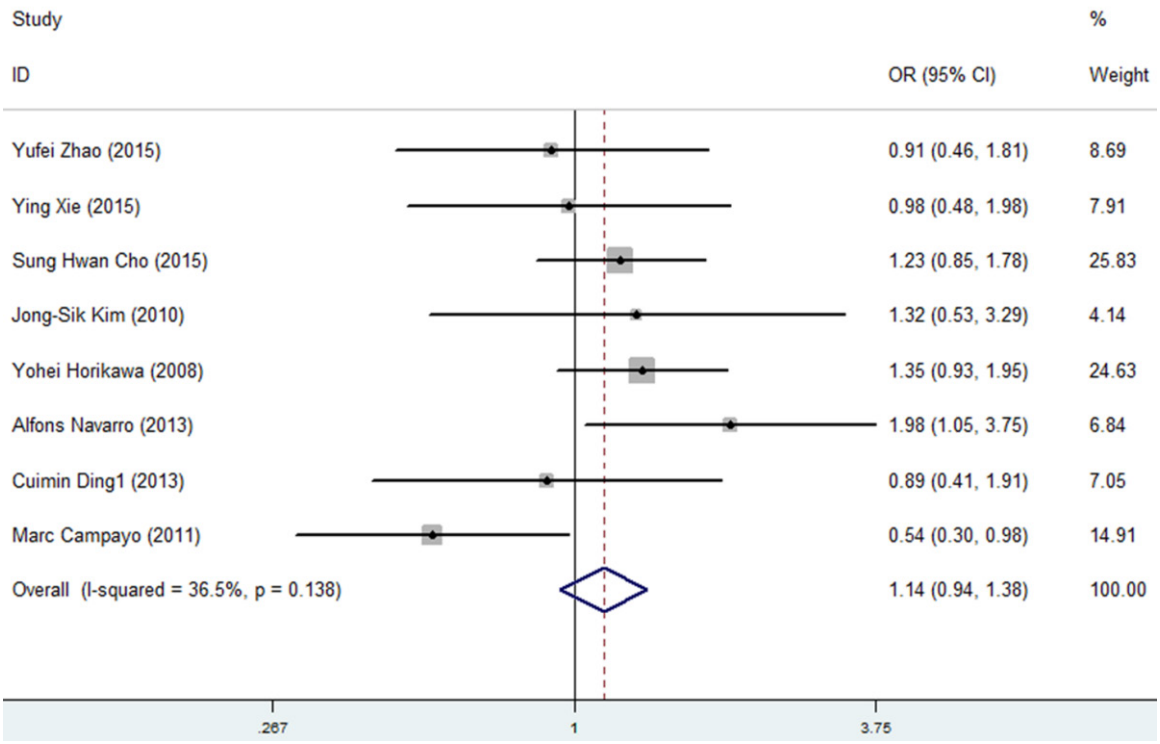

Figure 6. Association between rs11077 and cancer risk in heterozygous model (CA vs AA).

Table 3. Characteristics of seven eligible studies evaluating the association of rs11077 with the survival time of cancer patients

First author	Year	Country	Cancer	Sample size	F/M	Age	Outcome	RR (95% CI)
Alfons Navarro	2013	Spain	HL	127	80/47	32	AA+CC/AC	5.01 (0.9-28.7)
Zhanjun Guo	2013	China	SCLC	42	12/30	60	AA/AC+CC	0.28 (0.07-1.17)
Ji-Qun Geng	2015	China	NSCLC	131	47/84	60	AA/AC	2.11 (1.1-4.04)
Shuang Liu	2014	China	HCC	108	26/82	55	AA/AC+CC	1.01 (0.36-2.87)
Cuimin Ding1	2013	China	NSCLC	112	35/77	60	AA/CC	1.2 (0.49-2.92)
Marc Campayo	2011	Spain	NSCLC	167	74/93	65	AA/AC+CC	1.77 (1.07-2.91)
de Larrea	2012	Spain	Multiple Myeloma	137	62/75	55	AA/AC+CC	2.5 (1.2-5.0)

F: female; M: male.

type and AC (or AC/CC) genotype carries. The characteristics of the seven studies were summarized in **Table 3**.

Publication bias: No obvious asymmetry was found in funnel plot (Figure S4) and no publication bias was detected according to the results of Begg's test (**Table 4**).

Sensitivity analysis: No obvious changes of overall risk estimate was found by omitting one study each time (Figure S7).

Overall and subgroup analysis: People with AA genotype was associated with shorter survival time compared with AC (or AC+CC) (P<0.01, RR = 1.69, 95% CI = 1.26-2.28, **Figure 7**). We then evaluated this effect in subgroup analysis by ethnicity, similar result was detect in Caucasians (P<0.001, RR = 2.08, 95% CI = 1.40-3.10, Figure S5A), rather than in Asian. When stratified by cancer type, the association was especially significant in lung cancer (P = 0.001, RR = 1.56, 95% CI = 1.10-2.22, Figure S5B).

Quality judgment of studies: Based on the Newcastle-Ottawa scale, the quality of included studies was assessed. A study scored six or more could be regarded as high-quality. In our

Table 4. Meta-analysis of the association between rs11077 and the survival time of cancer patients

Group	Cohorts	I^2	*P*	HR (95% CI)	*P* (bias)
Overall	7	45.1	0.001	1.69 (1.26-2.28)	0.764
Spain	3	0	0	2.08 (1.40-3.10)	
China	4	56.9	0.235	1.31 (0.84-2.04)	
Lung cancer	4	57.9	0.001	1.56 (1.10-2.22)	
Other	3	35.6	0.012	2.07 (1.19-3.61)	

meta-analysis, the scores of 8 studies ranged from 7 to 9, which declared that all studies included in our meta-analysis were in compliance with high quality (**Table 5**).

Discussion

XPO5 is responsible for nuclear export and stabilization to form mature miRNA to produce physiological effects, for instance, embryonic development, proliferation and insulin secretion [1, 2]. A growing body of evidence showed that a miR-SNP of XPO5 (rs11077) may be associated with the risk and prognosis of cancer. The present study might be the first meta-analysis concerning rs11077 in cancer susceptibility and prognostic value.

On the basis of 8 studies enrolling 1054 cases and 1351 controls about *XPO5* polymorphism (rs11077) and the risk of cancer, significant association between rs11077 and cancer risk were found in allelic model (C vs A, P = 0.006, OR = 1.22, 95% CI = 1.06-1.40), dominant model (CC+AC vs AA, P = 0.05, OR = 1.2, 95% CI = 1.00-1.44), recessive model (CC vs AC+AA, P = 0.015, OR = 1.43, 95% CI = 1.07-1.90) and homozygous model (CC vs AA, P = 0.01, OR = 1.52, 95% CI = 1.11-2.09). We subsequently conducted a subgroup analysis stratified by ethnicity. The results illustrated a significant association between rs11077 and cancer risk in European under allelic model (C vs A, P = 0.001, OR = 1.34, 95% CI = 1.13-1.60), dominant model (CC+AC vs AA, P = 0.018, OR = 1.36, 95% CI = 1.05-1.76), recessive model (CC vs AC+AA, P = 0.003, OR = 1.56, 95% CI = 1.16-2.10) and homozygous model (CC vs AA, P = 0.02, OR = 1.72, 95% CI = 1.23-2.40). The fact that risks of cancer in Caucasians and Asians were different indicated that ethnic background and genetic structure played an important part in the susceptibility of cancer. The analysis results based on the cancer types exhibited that only gastrointestinal cancer showed significant association with rs11077 under allelic model (C vs A, P = 0.029, OR = 1.22, 95% CI = 1.02-1.4) and homozygous model (CC vs AA, P = 0.037, OR = 1.65, 95% CI = 1.03-2.65). However, the subgroup analysis stratified by ethnicity need more studies to confirm.

Besides, seven studies enrolling 824 cases were included to evaluate the prognostic value of rs11077 in cancers, and results suggested that, compared with AC (or AC+CC), people with AA genotype was associated with poor outcome (P<0.01, RR = 1.69, 95% CI = 1.26-2.28).

The identification of rs11077 for the risk and prognostic value in cancer may be the novel marker to measure the susceptibility and outcome of patients. Campayo M et al [8] demonstrated the relationship between rs11077 and the recurrence in post-operative NSCLC patients. Ye Y et al [30] found that *XPO5* polymorphism was novel susceptibility loci for esophageal cancer risk, which is consistent with our findings. The alteration of risk and outcome for rs11077 in cancer may be attributed to the fact that domains of XPO5 binding directly to RNA substrates have changed. Mutant genotypes (CC and CA) generated XPO5 may differ from the wild genotype (AA) for the recognizing of export structure [4, 15, 32].

Despite the elaborative investigation, there are still some limitations in our meta-analysis. Firstly, in the overall analysis of rs11077 and survival time of cancer patients, we only investigated the limited genotypes for the lack of sufficient data. It was difficult for us to explore all the genotypes. Secondly, software Engauge Digitizer 4.1 was used to estimate the prognostic data of the patients, which made the calculation error unavoidable. Finally, the studies included in our meta-analysis are not quite enough. More studies are needed to validate our findings.

Conclusion

Our meta-analysis demonstrated that a miR-SNP of rs11077 located in the 3'UTR of *XPO5* increases the risk of cancer, and this association might only exist in Caucasians.

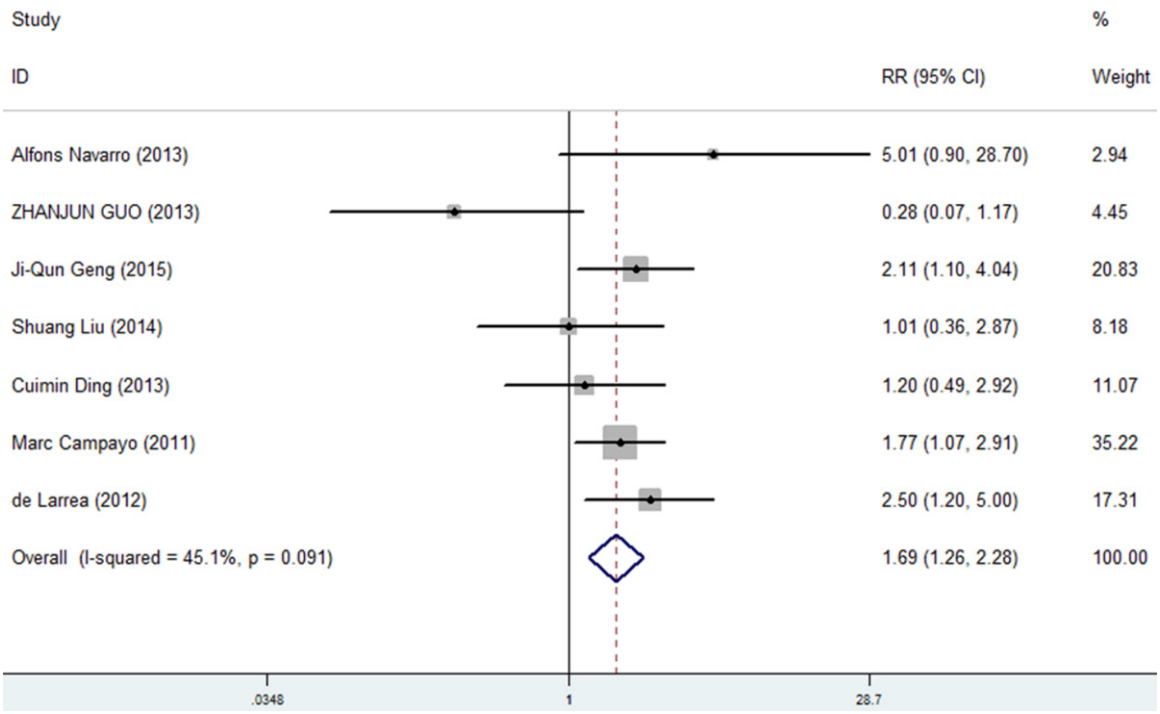

Figure 7. Forest plot of rs11077 and cancer prognosis.

Table 5. Quality assessment of studies enrolled using the Newcastle-Ottawa quality assessment scale

Study (author, year)	Selection				Comparability	Outcome			Scores
	1	2	3	4		1	2	3	
Yufei Zhao (2015)	★	★	★	★	★★	-	★	★	8
Ying Xie (2015)	★	★	★	★	★	★	★	★	8
Sung Hwan Cho (2015)	-	★	★	★	★★	-	★	★	7
Jong-Sik Kim (2010)	★	★	★	-	★★	★	-	★	7
Yohei Horikawa (2008)	★	★	★	★	★	★	-	★	8
Alfons Navarro (2013)	-	★	★	★	★★	★	★	★	8
Cuimin Ding1 (2013)	★	★	★	★	★★	★	★	★	9
MASAHIROTAKADA (2004)	★	★	★	-	★	★	★	★	7
Marc Campayo (2011)	★	★	★	★	★★	★	★	★	9

Besides, rs11077 of *XPO5* could predict a poor outcome of patients with cancers. These findings may provide new approach for the treatment and assess the susceptibility and prognostic value of cancer.

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Disclosure of conflict of interest

None.

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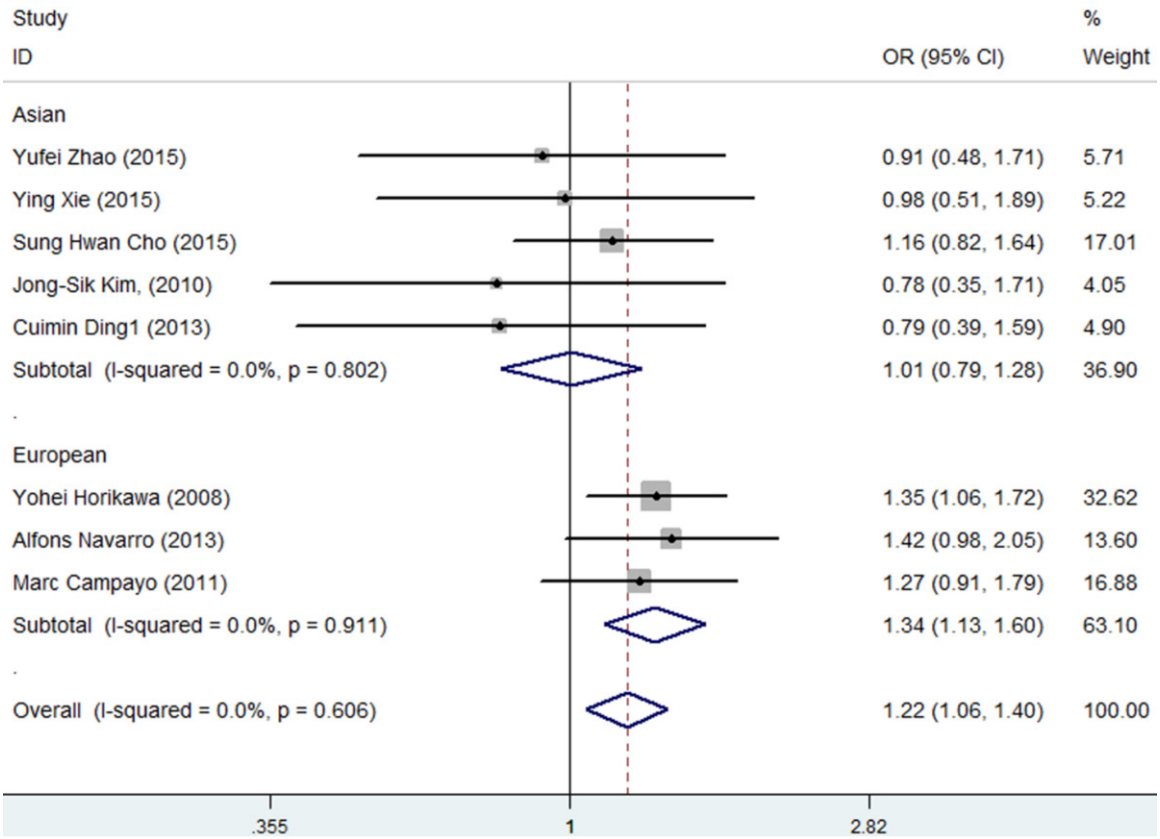
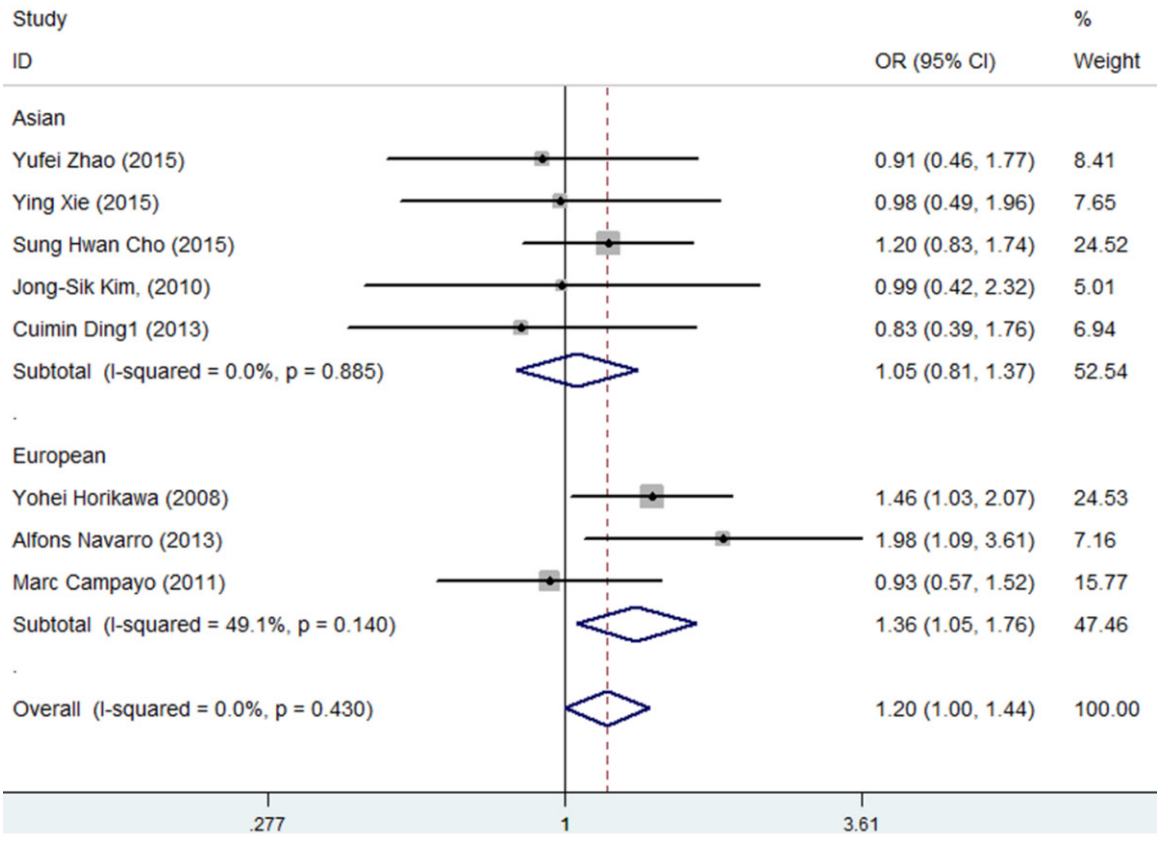
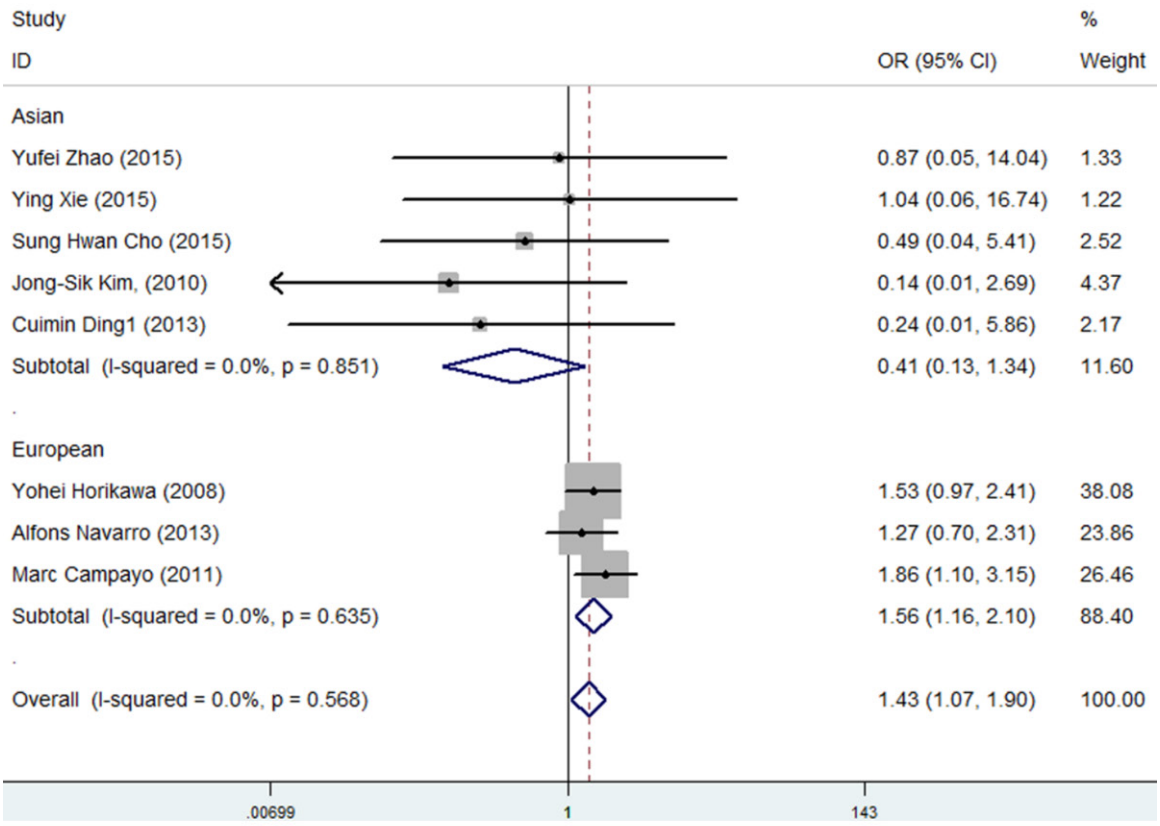
A


Study
ID
OR (95% CI)
%
Weight
Asian
Yufei Zhao (2015)
0.91 (0.48, 1.71)
5.71
Ying Xie (2015)
0.98 (0.51, 1.89)
5.22
Sung Hwan Cho (2015)
1.16 (0.82, 1.64)
17.01
Jong-Sik Kim, (2010)
0.78 (0.35, 1.71)
4.05
Cuimin Ding1 (2013)
0.79 (0.39, 1.59)
4.90
Subtotal (I-squared = 0.0%, p = 0.802)
1.01 (0.79, 1.28)
36.90
European
Yohei Horikawa (2008)
1.35 (1.06, 1.72)
32.62
Alfons Navarro (2013)
1.42 (0.98, 2.05)
13.60
Marc Campayo (2011)
1.27 (0.91, 1.79)
16.88
Subtotal (I-squared = 0.0%, p = 0.911)
1.34 (1.13, 1.60)
63.10
Overall (I-squared = 0.0%, p = 0.606)
1.22 (1.06, 1.40)
100.00
.355
1
2.82

B


Study
ID
OR (95% CI)
%
Weight
Asian
Yufei Zhao (2015)
0.91 (0.46, 1.77)
8.41
Ying Xie (2015)
0.98 (0.49, 1.96)
7.65
Sung Hwan Cho (2015)
1.20 (0.83, 1.74)
24.52
Jong-Sik Kim, (2010)
0.99 (0.42, 2.32)
5.01
Cuimin Ding1 (2013)
0.83 (0.39, 1.76)
6.94
Subtotal (I-squared = 0.0%, p = 0.885)
1.05 (0.81, 1.37)
52.54
European
Yohei Horikawa (2008)
1.46 (1.03, 2.07)
24.53
Alfons Navarro (2013)
1.98 (1.09, 3.61)
7.16
Marc Campayo (2011)
0.93 (0.57, 1.52)
15.77
Subtotal (I-squared = 49.1%, p = 0.140)
1.36 (1.05, 1.76)
47.46
Overall (I-squared = 0.0%, p = 0.430)
1.20 (1.00, 1.44)
100.00
.277
1
3.61

C


Study
ID
OR (95% CI)
%
Weight
Asian
Yufei Zhao (2015) 0.87 (0.05, 14.04) 1.33
Ying Xie (2015) 1.04 (0.06, 16.74) 1.22
Sung Hwan Cho (2015) 0.49 (0.04, 5.41) 2.52
Jong-Sik Kim, (2010) 0.14 (0.01, 2.69) 4.37
Cuimin Ding1 (2013) 0.24 (0.01, 5.86) 2.17
Subtotal (I-squared = 0.0%, p = 0.851) 0.41 (0.13, 1.34) 11.60
European
Yohei Horikawa (2008) 1.53 (0.97, 2.41) 38.08
Alfons Navarro (2013) 1.27 (0.70, 2.31) 23.86
Marc Campayo (2011) 1.86 (1.10, 3.15) 26.46
Subtotal (I-squared = 0.0%, p = 0.635) 1.56 (1.16, 2.10) 88.40
Overall (I-squared = 0.0%, p = 0.568) 1.43 (1.07, 1.90) 100.00
.00699
1
143

D

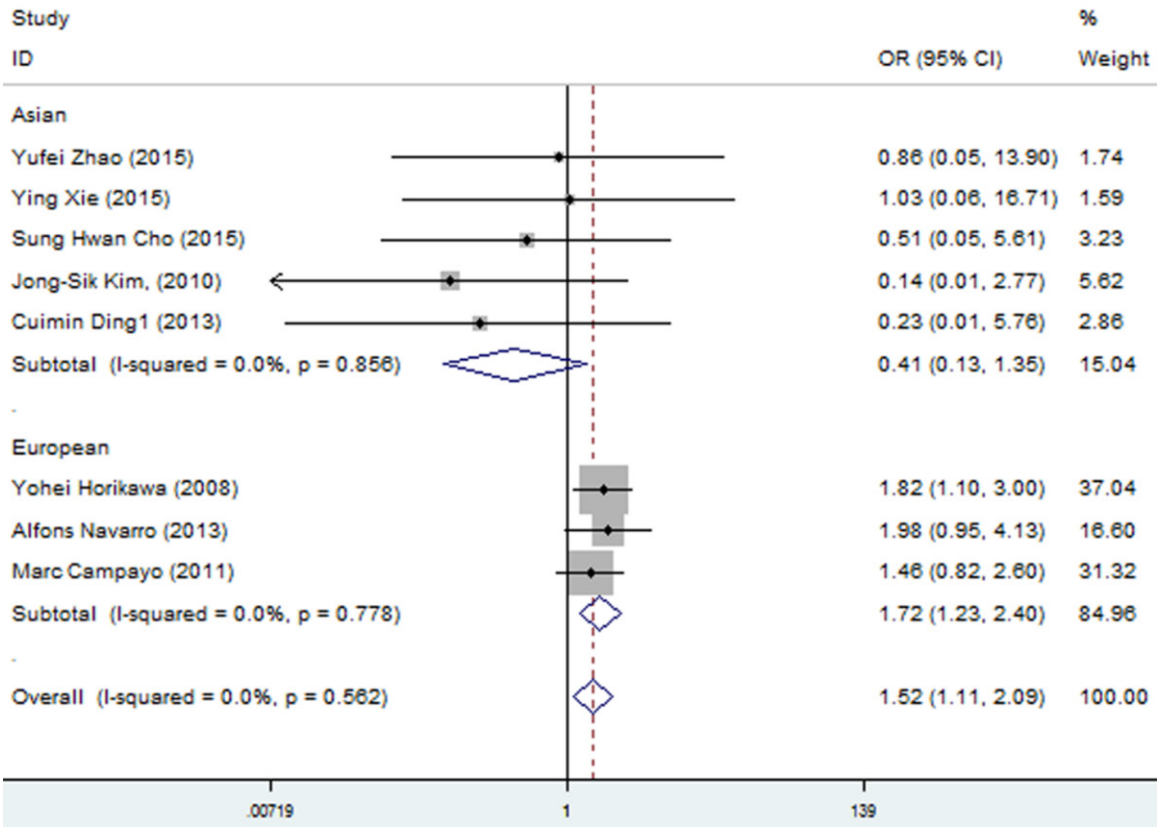
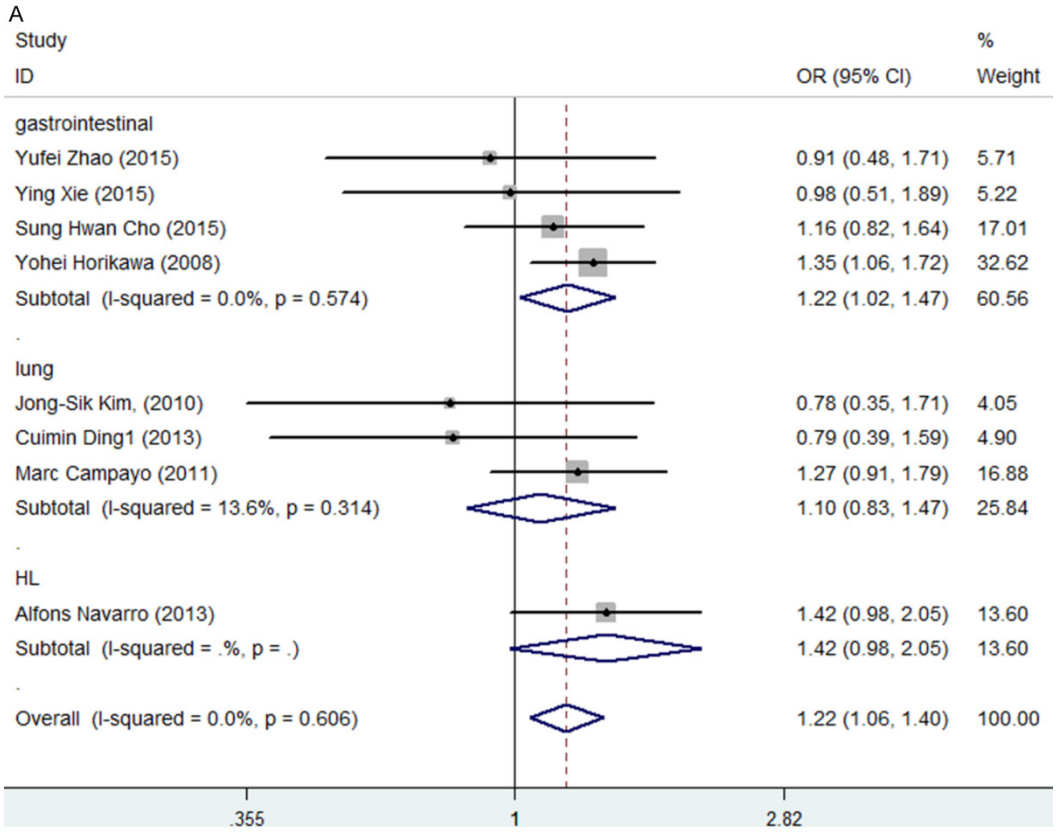

Study
ID
OR (95% CI)
%
Weight
Asian
Yufei Zhao (2015) 0.86 (0.05, 13.90) 1.74
Ying Xie (2015) 1.03 (0.06, 16.71) 1.59
Sung Hwan Cho (2015) 0.51 (0.05, 5.61) 3.23
Jong-Sik Kim, (2010) 0.14 (0.01, 2.77) 5.62
Cuimin Ding1 (2013) 0.23 (0.01, 5.76) 2.86
Subtotal (I-squared = 0.0%, p = 0.856) 0.41 (0.13, 1.35) 15.04
European
Yohei Horikawa (2008) 1.82 (1.10, 3.00) 37.04
Alfons Navarro (2013) 1.98 (0.95, 4.13) 16.60
Marc Campayo (2011) 1.46 (0.82, 2.60) 31.32
Subtotal (I-squared = 0.0%, p = 0.778) 1.72 (1.23, 2.40) 84.96
Overall (I-squared = 0.0%, p = 0.562) 1.52 (1.11, 2.09) 100.00
.00719
1
139

Figure S1. Subgroup analysis of associations between rs11077 and cancer risk in four models, stratified by ethnicity. A. Allelic model (C vs A); B. Dominant model (CC+AC vs AA); C. Recessive model (CC vs AC+AA); D. Homozygous model (CC vs AA).



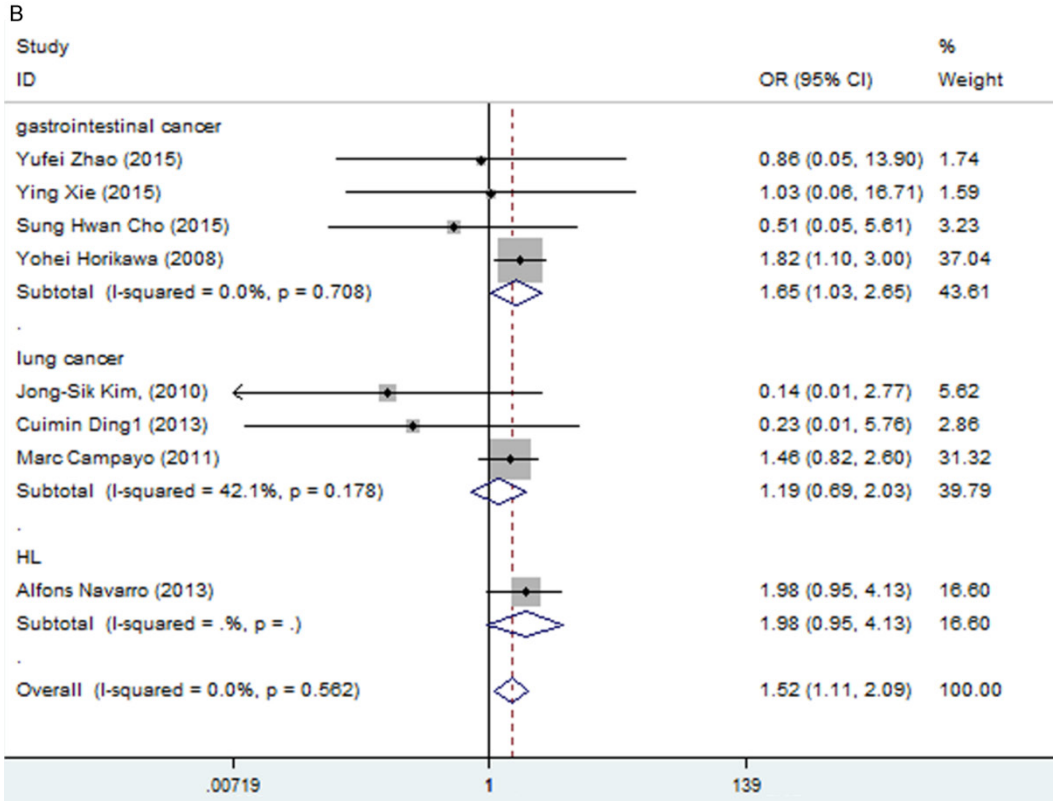
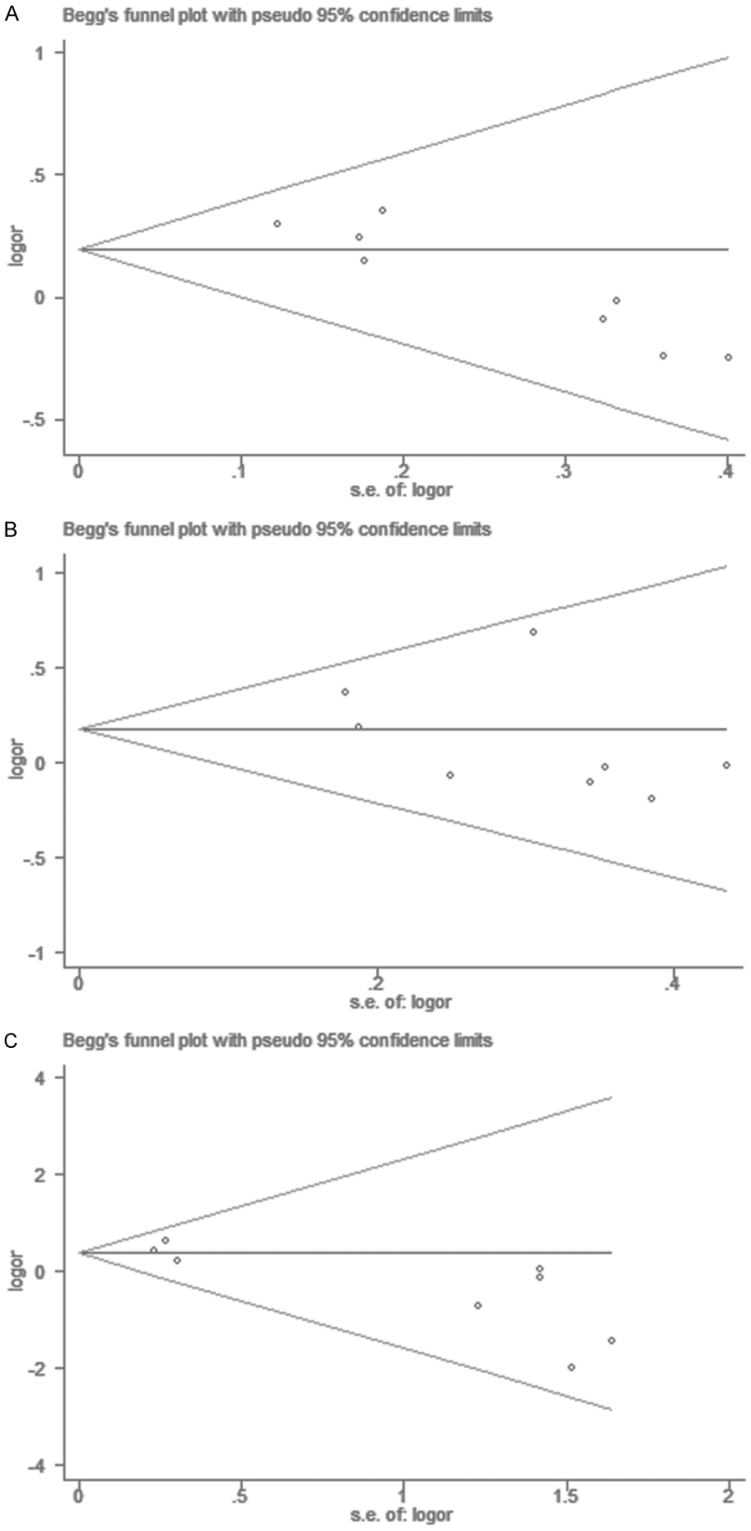


Figure S2. Subgroup analysis of associations between rs11077 and cancer risk, stratified by cancer types. A. Allelic model (C vs A); B. Homozygous model (CC vs AA).



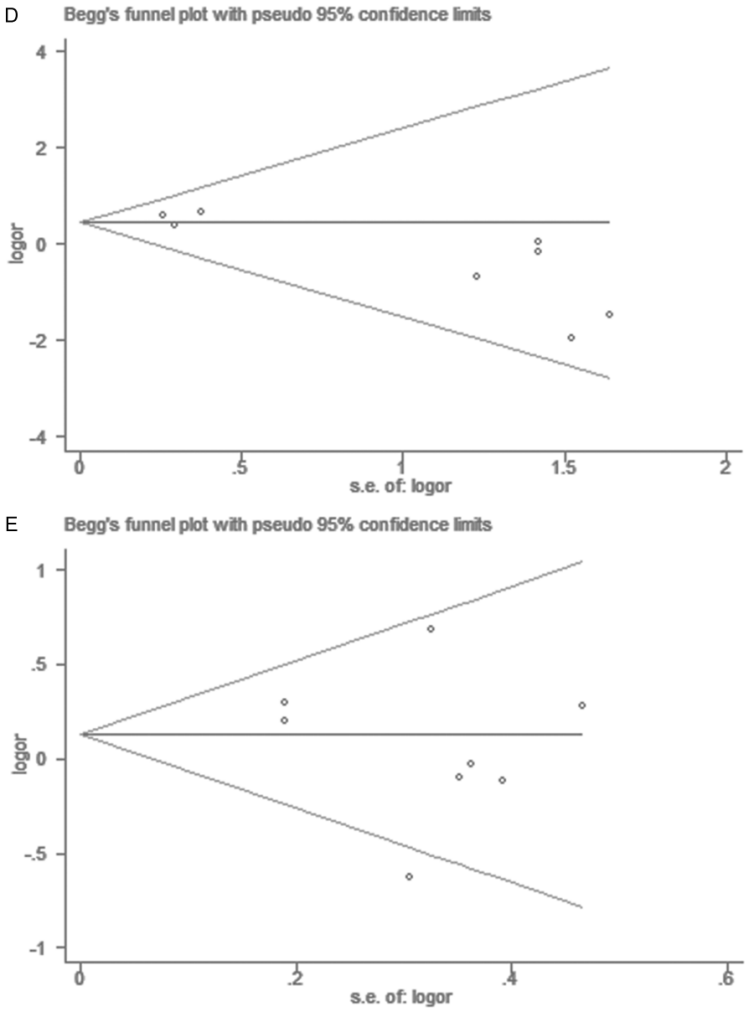


Figure S3. Funnel plot analysis investigating the publication bias between rs11077 and cancer risk. A. Allelic model (C vs A); B. Dominant model (CC+AC vs AA); C. Recessive model (CC vs AC+AA); D. Homozygous model (CC vs AA); E. Heterozygous model (CA vs AA).

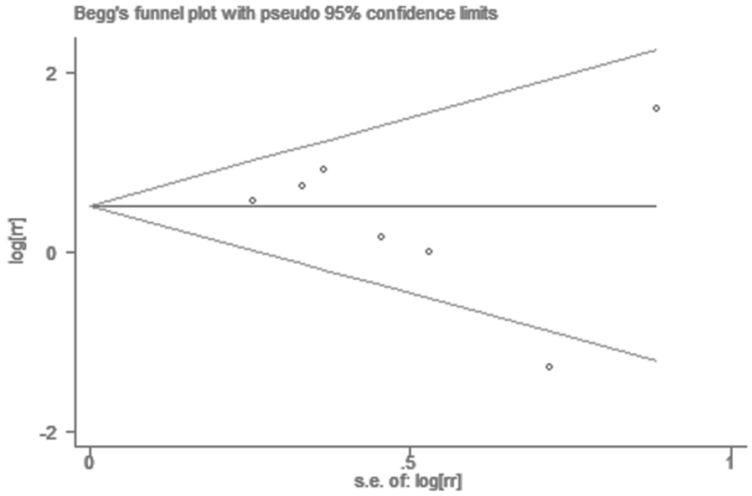
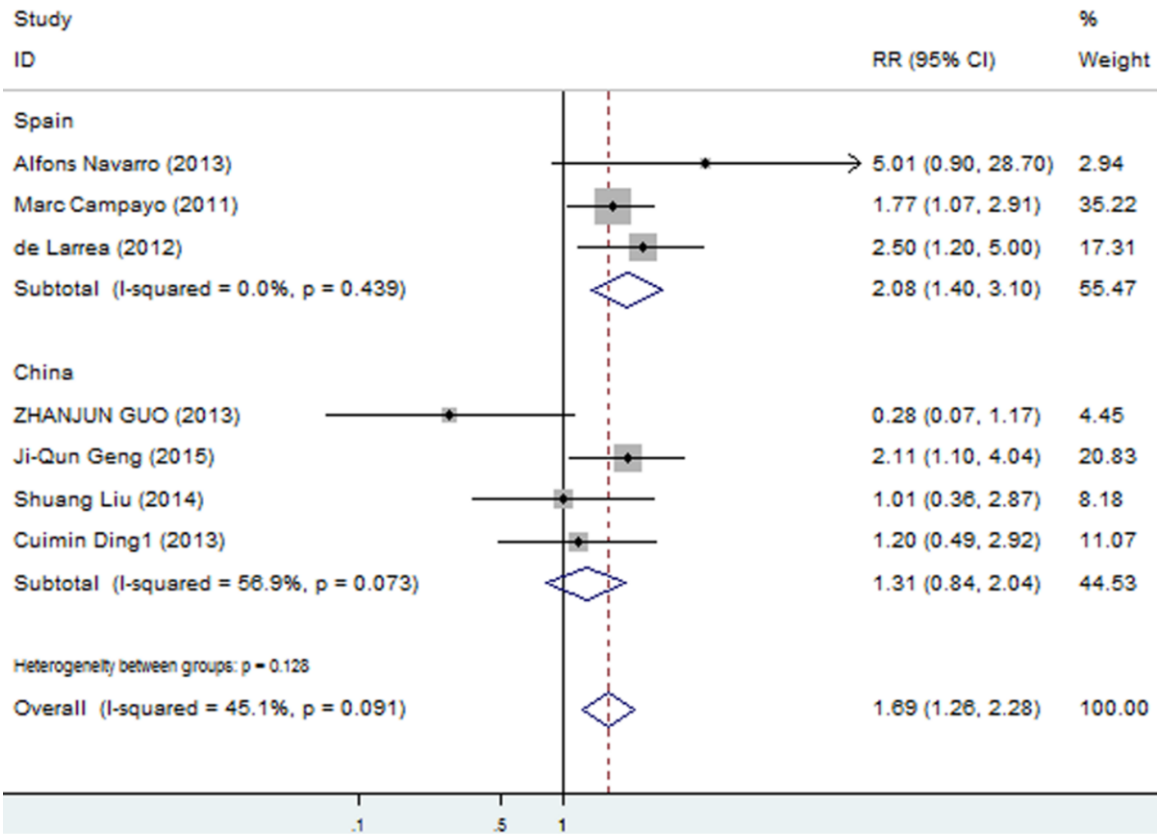


Figure S4. Funnel plot analysis investigating the publication bias between rs11077 and cancer prognosis.

A


Study
ID
RR (95% CI)
%
Weight
Spain
Alfons Navarro (2013)
5.01 (0.90, 28.70)
2.94
Marc Campayo (2011)
1.77 (1.07, 2.91)
35.22
de Larrea (2012)
2.50 (1.20, 5.00)
17.31
Subtotal (I-squared = 0.0%, p = 0.439)
2.08 (1.40, 3.10)
55.47
China
ZHANJUN GUO (2013)
0.28 (0.07, 1.17)
4.45
Ji-Qun Geng (2015)
2.11 (1.10, 4.04)
20.83
Shuang Liu (2014)
1.01 (0.36, 2.87)
8.18
Cuimin Ding1 (2013)
1.20 (0.49, 2.92)
11.07
Subtotal (I-squared = 56.9%, p = 0.073)
1.31 (0.84, 2.04)
44.53
Heterogeneity between groups: p = 0.128
Overall (I-squared = 45.1%, p = 0.091)
1.69 (1.26, 2.28)
100.00
.1
.5
1

B

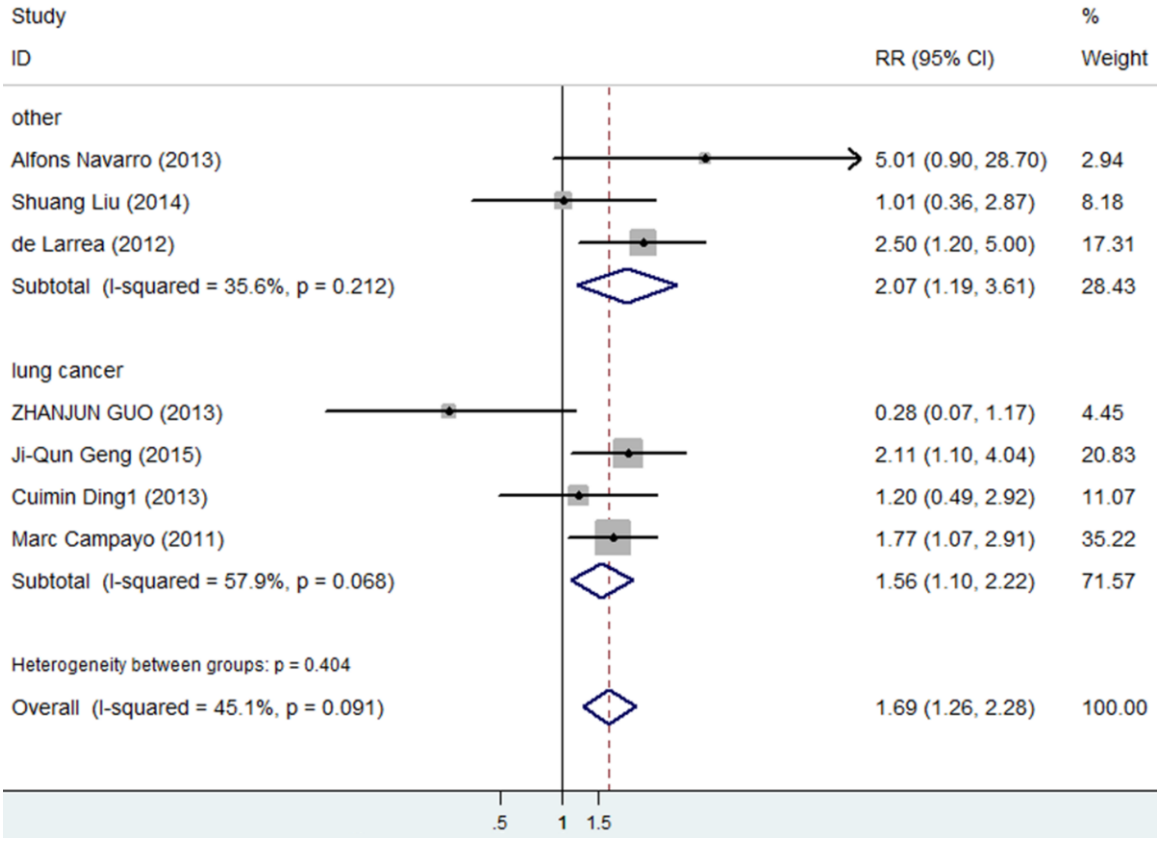
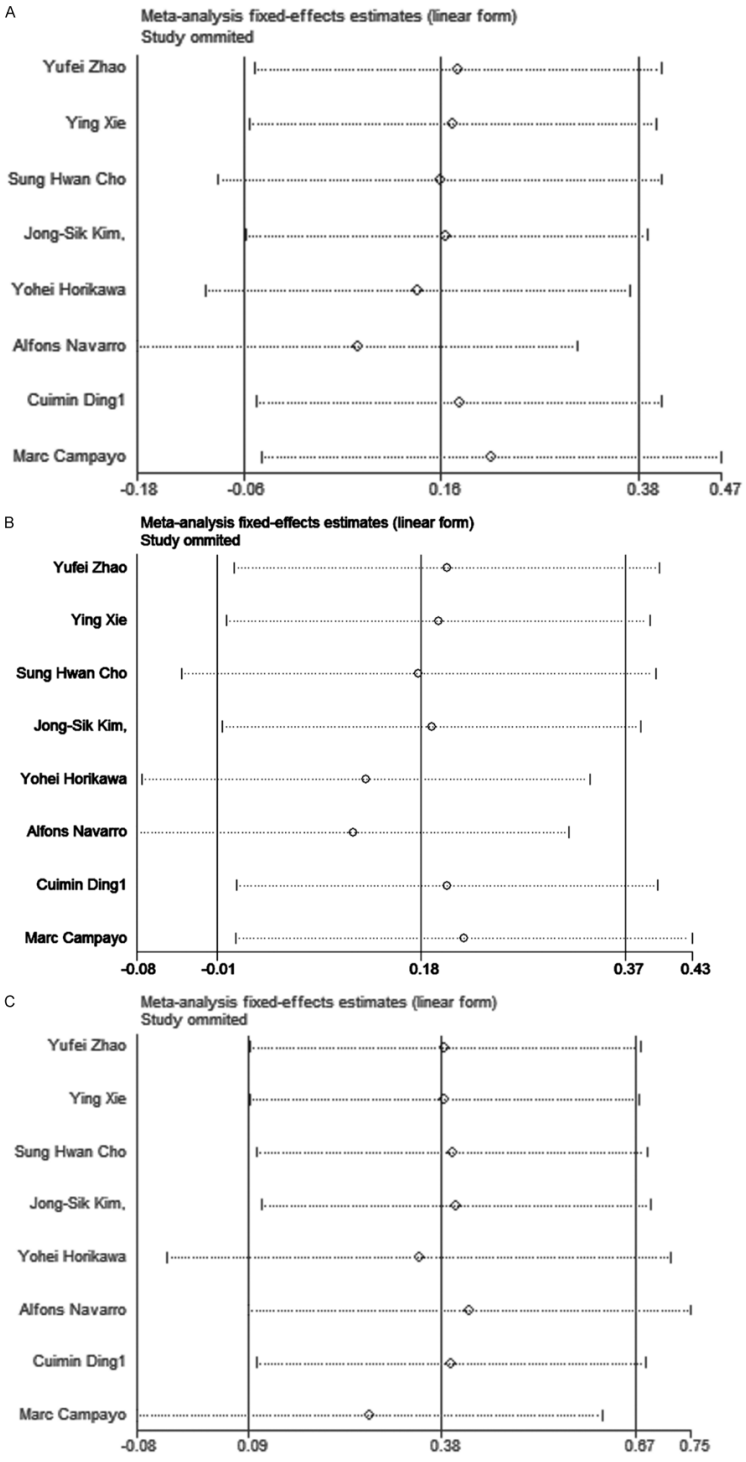

Study
ID
RR (95% CI)
%
Weight
other
Alfons Navarro (2013)
5.01 (0.90, 28.70)
2.94
Shuang Liu (2014)
1.01 (0.36, 2.87)
8.18
de Larrea (2012)
2.50 (1.20, 5.00)
17.31
Subtotal (I-squared = 35.6%, p = 0.212)
2.07 (1.19, 3.61)
28.43
lung cancer
ZHANJUN GUO (2013)
0.28 (0.07, 1.17)
4.45
Ji-Qun Geng (2015)
2.11 (1.10, 4.04)
20.83
Cuimin Ding1 (2013)
1.20 (0.49, 2.92)
11.07
Marc Campayo (2011)
1.77 (1.07, 2.91)
35.22
Subtotal (I-squared = 57.9%, p = 0.068)
1.56 (1.10, 2.22)
71.57
Heterogeneity between groups: p = 0.404
Overall (I-squared = 45.1%, p = 0.091)
1.69 (1.26, 2.28)
100.00
.5
1
1.5

Figure S5. Subgroup analysis of the associations between rs11077 and cancer prognosis. A. Stratified by ethnicity; B. Stratified by cancer type.



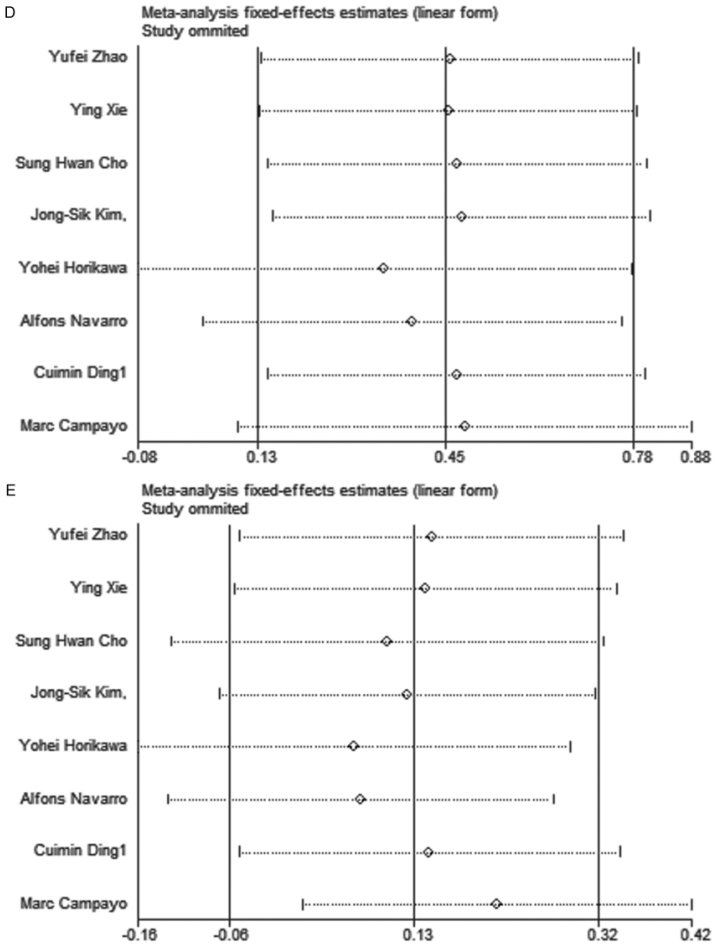


Figure S6. Sensitivity test of the association between rs11077 and cancer risk. A. Allelic model (C vs A); B. Dominant model (CC+AC vs AA); C. Recessive model (CC vs AC+AA); D. Homozygous model (CC vs AA); E. Heterozygous model (CA vs AA).

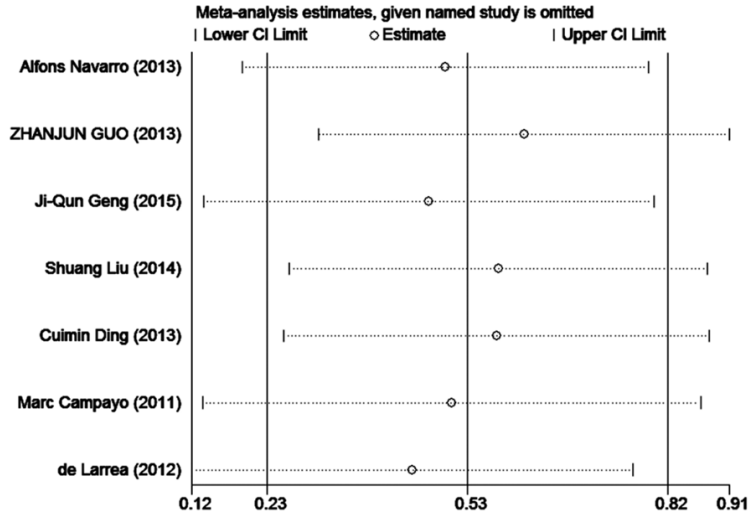


Figure S7. Sensitivity test of the association between rs11077 and cancer prognosis.