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ORIGINAL RESEARCH

Association between KIFIB (rs17401966) polymorphism and hepatocellular carcinoma susceptibility: a meta-analysis

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Introduction: The results of the earlier published studies on the association between KIF1B (rs17401966) polymorphism and hepatocellular carcinoma (HCC) risk are inconclusive. Hence, we performed this meta-analysis to evaluate the relationship between KIF1B (rs17401966) polymorphism and HCC risk.

Methods: Databases including PubMed, Web of Science and the Cochrane Library and bibliographies of relevant papers were screened to identify relevant studies published up to March 25, 2018. Pooled ORs and 95% CIs were calculated to evaluate the association. The subgroup analysis was conducted based on ethnicity, age, region and environment. A total of 19 studies from 11 eligible articles published from 2010 to 2016, with 8,741 cases and 10,812 controls, were included.

Results: The pooled results indicated that the association between KIF1B (rs17401966) polymorphism and the decreased HCC risk was significant. Subgroup analysis stratified by ethnicity showed the same association in Chinese, but not in non-Chinese population. When stratified by age, both old and young patients showed a decrease in HCC risk. When stratified by region, we detected the same association in Chinese in southern China. Similarly when stratified by environment, we observed the same association in Chinese in inland areas; however, no statistically significant association was observed in those in coastal areas.

Conclusion: This meta-analysis suggested that KIF1B (rs17401966) polymorphism could decrease HCC risk in Chinese and in overall population, but not in non-Chinese. This association remained significant in Chinese in southern China and inland areas, but not in those in northern and central China and coastal areas. Further large-scale multicenter studies are warranted to confirm these findings.

Keywords: KIF1B, rs17401966, hepatocellular carcinoma, polymorphism

Background

Hepatocellular carcinoma (HCC) is the sixth most common malignant tumor and the second leading cause of cancer-related deaths in the world.¹ The onset of HCC is relatively insidious; in most cases, HCC is diagnosed at advanced stages and is difficult to treat. Presently, surgical resection-based comprehensive treatment is the main treatment for HCC, but with less success rate and high rates of recurrence and metastasis.² Therefore, improving the early diagnosis is particularly important in the prevention and treatment of HCC. Determining the association between KIF1B (rs17401966) polymorphism and HCC risk provides a promising approach to achieve this goal.

KIF1B is a member of the kinesin superfamily and belongs to N-kinesin, encoding two alternatively spliced isoforms, KIF1B α and KIF1B β . Both the isoforms have the

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same 660 amino acid residues in the N terminal domain; the main difference between them is the end of the C binding domain, conferring different axonal cargo specificity.³ KIF1B is located in chromosome region 1p36.22 and is an important molecule for intracellular vesicle trafficking and organelle transporting.^{4,5} In addition to transport function, KIF1B also plays an important role in tumor suppression by promoting apoptosis.⁶ Studies have shown that deficiency of 1p36 region is very common in the individuals with early-onset HCC, but the phenomenon is not observed in individuals with chronic liver disease. It can be speculated that the abnormal chromosomal regions may be associated with the risk of HCC.⁷

Through genome-wide association study (GWAS), Zhang et al⁸ found a significant association between KIF1B rs17401966 polymorphism and HCC, showing that the polymorphism of the site has a protective effect on HCC. However, a consistent conclusion on the correlation between the gene polymorphism and HCC was not reached, which may be caused by differences in race or ethnicity, as well as the difference in sample size.^{8–18} Therefore, we carried out a meta-analysis of the whole included case–control studies to make a more accurate estimate of the association.

Methods

Literature searching strategy

A comprehensive literature searching for all relevant studies published before March 25, 2018 was conducted in PubMed, Web of Science and the Cochrane Library, using the following keywords: KIF1B/Kinesin family member 1B/rs17401966 and locus/mutation/variant*/genotype/polymorphism*/SNP and ([liver/hepatic/hepatocellular/hepato-cellular and carcinom*/ cancer/neoplasm*/malign*/tumor] or HCC or hepatoma*) and the combinations. The relevant bibliographies of identified studies were examined for additional articles. Abstracts and citations were screened by two researchers independently, and any disagreements were resolved by discussing with a third reviewer. The full text of all the eligible articles was reviewed during a second screening. There were no language limitations during the retrieval procedure.

Selection and exclusion criteria

All eligible studies included in this meta-analysis met the following inclusion criteria: 1) independent case–control studies performed on humans; 2) evaluated the association between KIF1B (rs17401966) polymorphism and HCC risk; 3) genotype frequencies in case and control groups were available for risk estimate; 4) the diagnosis of the cases was based on pathology; 5) control subjects had no cancer

and history of radiotherapy or chemotherapy; and 6) genotype frequencies of the subjects in control groups were in accordance with Hardy–Weinberg equilibrium (HWE). We excluded abstracts, case reports, letters, comments, editorials, reviews, meta-analyses and studies lacking sufficient data. Simultaneously, if the researches were duplicated or shared in more than one study, the most recent publications were included.

Data extraction and synthesis

We used endnote bibliographic software (EndNote X6) to construct an electronic library of citations identified in the literature search. Duplicates were found automatically by endnote and deleted manually. All the extracted data were checked and evaluated twice according to the inclusion criteria listed above by two independent investigators. The following data were extracted from each study: first author, year of publication, country, ethnicity, genotyping method, number of cases and controls, genotype distribution of cases and controls and *P*-value of HWE in controls. Meanwhile, multicenter studies were divided into several separate studies according to the origin. A third reviewer participated if some disagreements emerged, and a final decision was not made until a consensus was reached.

Quality assessment

The methodological quality assessment was performed based on the modified scoring system used for studies on genetic epidemiological issues.¹⁹ Points were awarded on the basis of representativeness of cases, source of controls, HWE in controls, genotyping examination and association assessment. Total score ranged from 0 (lowest quality) to 8 (highest quality). A study with a score of ≥ 6 was classified to be of high quality.

Statistical analysis

All statistical analyses were carried out using STATA version 11.0 (StataCorp LP, College Station, TX, USA) and Review Manager version 5.2.0 (The Cochrane Collaboration, 2012). Chi-square test was applied to calculate P-value of HWE in controls, and P>0.05 was considered to be consistent with HWE.²⁰ The association of KIF1B (rs17401966) polymorphism and HCC susceptibility was estimated by pooled ORs with 95% CIs under five different genetic models including allele model, dominant model, recessive model, homozygous genetic model and heterozygous genetic model. *Z* test was used to assess the significance of the ORs. Both *Q*-statistic test and I^2 test were applied to

assess the between-study heterogeneity in this meta-analysis. If there was significant heterogeneity among included studies (*P*-value of *Q*-statistic was < 0.1, or I^2 value was > 75%), ORs with corresponding 95% CIs were calculated using the random effects model; otherwise, the fixed effects model was selected.^{20,21} The subgroup analysis was conducted based on ethnicity and age (>50 years or \leq 50 years). For studies with Chinese population, we also conducted subgroup analysis by region and environment. Sensitivity analyses were performed to assess the stability of the results. Each study involved in this meta-analysis was deleted each time to reflect the influence of the individual data exerted on the pooled OR. We used Begg's funnel plot and Egger's test ($P \le 0.05$ was considered significant) to evaluate the publication bias.^{22,23} All statistical tests were two-sided, and P < 0.05 indicated statistical significance.

Results

Characteristics of the included studies

The selection process of eligible studies is presented in Figure 1. A total of 59 relevant articles were preliminarily

identified based on our selection strategy. We also identified one article through other sources.¹⁸ Thirty-five articles remained after eliminating duplicated literature. Subsequently, 16 obviously irrelevant articles were excluded unquestionably after reviewing their titles and abstracts. Based on the inclusion and exclusion criteria, eight articles were excluded after reviewing the full text. Finally, 11 studies were eventually included in this meta-analysis.⁸⁻¹⁸ The 11 case-control studies were published between 2010 and 2016. Among them, Zhang et al's research consisting of five independent studies was divided into five studies.8 Similarly, Li et al's and Sawai et al's articles were divided into two and four studies, respectively.^{13,15} Thus, a total of 19 studies from 11 articles with 8,741 cases and 10,812 controls were included in this meta-analysis. A summary of the characteristics of the 19 studies, including first author, year of publication, country, ethnicity, genotyping method, age of cases, number of cases and controls, P-value of HWE and quality score, is shown in Table 1. Based on quality assessment, all studies were considered to be of high quality (quality scores of these studies were 6-8).



Figure I Flowchart of studies selection in this meta-analysis.

First author	Year	Country	Ethnicity	Genotyping method	Age	Number (case/control)	HWE	Quality score
Chen et al ⁹	2013	China	Chinese (Beijing)	TaqMan	53.9	503/772	0.646837	6
Chen et al ¹⁰	2016	China	Chinese (Guangdong)	, TaqMan	55.84	306/306	0.05846	7
Hu et al ¹¹	2012	China	Chinese (Jiangsu)	TaqMan	52.9	1,293/2,671	0.05058	6
Jiang et al ¹²	2013	China	Chinese (Jiangsu)	TagMan	51.6	1,161/1,353	0.982272	8
Li et al ¹³	2012	China	Chinese (Guangdong)	iPLEX or TaqMan	49.3	1,058/981	0.975939	6
Li et al ¹³	2012	China	Chinese (Shanghai)	iPLEX or TaqMan	49.3	480/484	0.962279	6
Pan et al ¹⁴	2015	China	Chinese (Fujian)	MassARRAY Typer 4.0	61.7	376/403	0.132385	8
Sawai et al ¹⁵	2012	Japan	Japanese	PCR	62	179/769	0.31108	7
Sawai et al ¹⁵	2012	Japan	Japanese	TagMan	61.3	142/251	0.970885	7
Sawai et al ¹⁵	2012	Japan	Korean	TaqMan	52.2	164/144	0.325085	7
Sawai et al ¹⁵	2012	Japan	Chinese (Hong Kong)	TagMan	58	93/187	0.466716	7
Sopipong et al ¹⁶	2013	Thailand	Thais	PCR	59.8	202/196	0.764716	6
Su et al ¹⁷	2014	China	Chinese (Fujian)	MALDI-TOF-MS	NR	160/160	0.71155	6
Su ¹⁸	2015	China	Chinese (Fujian)	MALDI-TOF	NR	314/346	0.405123	6
Zhang et al ⁸	2010	China	Chinese (Guangxi)	Affymetrix	45.8	348/359	0.98702	7
Zhang et al ⁸	2010	China	Chinese (Beijing)	Affymetrix	55.9	276/266	0.805902	7
Zhang et al ⁸	2010	China	Chinese (Jiangsu)	Affymetrix	52.7	507/215	0.393367	7
Zhang et al ⁸	2010	China	Chinese (Guangdong)	Affymetrix	49.3	751/509	0.906845	7
Zhang et al ⁸	2010	China	Chinese (Shanghai)	Affymetrix	50.6	428/440	0.777482	7

Table I Characteristics of the studies included in the meta-analysis

Abbreviations: HWE, Hardy–Weinberg equilibrium; NR, not reported; PCR, polymerase chain reaction; MALDI-TOF-MS, matrix-associated laser desorption ionizationtime of flight-mass spectrometry.

Meta-analysis results

The genotype distribution and allele frequencies of KIF1B (rs17401966) polymorphism in cases and controls are listed in Table 2. The main results of our study are shown in Tables 3 and 4.

As shown in Table 3 and Figure 2, the pooled results indicated that the association between KIF1B (rs17401966) polymorphism and the decreased occurrence of HCC was

significant in overall population in three genetic models: allele model (OR=0.87, 95% CI=0.78-0.97, P=0.01), dominant model (OR=0.84, 95% CI=0.74-0.94, P=0.003) and heterozygote comparison (OR=0.84, 95% CI=0.76-0.93, P=0.0009). The subgroup analysis stratified by ethnicity showed the same association in Chinese population (allele model: OR=0.84, 95% CI=0.74-0.96, P=0.009; dominant model: OR=0.81, 95% CI=0.71-0.93, P=0.003; homozygous

Table 2 KIFIB (rs17401966) polymorphisms genotype distribution and allele frequency in cases and controls

First author	Year	Genoty	Genotype (N)									Allele frequency (N)			
		Case				Contro	I			Case		Contro	bl		
		Total	AA	AG	GG	Total	AA	AG	GG	Α	G	A	G		
Chen et al ⁹	2013	503	63	194	246	772	65	309	398	320	686	439	1,105		
Chen et al ¹⁰	2016	306	21	126	159	306	18	138	150	168	444	174	438		
Hu et al''	2012	1,293	107	480	706	2,671	231	1,038	1,402	694	1,892	1,500	3,842		
Jiang et al ¹²	2013	1,161	84	458	619	1,353	106	546	701	626	1,696	758	1,948		
Li et al ¹³	2012	1,058	77	417	564	981	77	395	509	571	1,545	549	1,413		
Li et al ¹³	2012	480	35	189	256	484	41	199	244	259	701	281	687		
Pan et al ¹⁴	2015	376	34	138	204	403	53	167	183	206	546	273	533		
Sawai et al ¹⁵	2012	179	13	61	105	769	45	261	463	87	271	351	1,187		
Sawai et al ¹⁵	2012	142	5	46	91	251	14	91	146	56	228	119	383		
Sawai et al ¹⁵	2012	164	17	59	88	144	15	55	74	93	235	85	203		
Sawai et al ¹⁵	2012	93	10	39	44	187	13	80	94	59	127	106	268		
Sopipong et al ¹⁶	2013	202	21	81	100	196	16	83	97	123	281	115	277		
Su et al ¹⁷	2014	160	24	60	76	160	16	66	78	108	212	98	222		
Su ¹⁸	2015	314	32	153	129	346	26	149	171	217	411	201	491		
Zhang et al ⁸	2010	348	8	100	240	359	26	141	192	116	580	193	525		
Zhang et al ⁸	2010	276	5	86	185	266	24	109	133	96	456	157	375		
Zhang et al ⁸	2010	507	26	181	300	215	21	101	93	233	781	143	287		
Zhang et al ⁸	2010	751	26	228	497	509	35	195	279	280	1,222	265	753		
Zhang et al ⁸	2010	428	12	141	275	440	32	169	239	165	691	233	647		

Outcome or	Studies	Participants	Statistical method	Effect	P-value	Heterogeneity		
subgroup				estimate		1 ²	P-value	
Allele model								
Overall	19	39,106	OR (M–H, random, 95% CI)	0.87 (0.78, 0.97)	0.01	80%	< 0.00001	
Chinese	15	35,012	OR (M–H, random, 95% CI)	0.84 (0.74, 0.96)	0.009	84%	< 0.00001	
Non-Chinese	4	4,094	OR (M–H, fixed, 95% CI)	0.98 (0.84, 1.15)	0.84	0%	0.53	
>50 years	13	27,206	OR (M–H, random, 95% CI)	0.86 (0.76, 0.98)	0.02	77%	< 0.00001	
\leq 50 years	4	9,940	OR (M–H, random, 95% CI)	0.75 (0.59, 0.97)	0.03	85%	0.0001	
Dominant model								
Overall	19	19,553	OR (M–H, random, 95% Cl)	0.84 (0.74, 0.94)	0.003	72%	< 0.00001	
Chinese	15	17,506	OR (M–H, random, 95% Cl)	0.81 (0.71, 0.93)	0.003	78%	< 0.00001	
Non-Chinese	4	2,047	OR (M–H, fixed, 95% CI)	0.95 (0.78, 1.16)	0.63	0%	0.71	
>50 years	13	13,603	OR (M–H, random, 95% Cl)	0.83 (0.73, 0.95)	0.006	66%	0.0004	
\leq 50 years	4	4,970	OR (M–H, random, 95% Cl)	0.73 (0.56, 0.96)	0.03	82%	0.001	
Recessive model								
Overall	19	19,553	OR (M–H, random, 95% Cl)	0.85 (0.69, 1.04)	0.12	67%	<0.0001	
Chinese	15	17,506	OR (M–H, random, 95% Cl)	0.80 (0.63, 1.02)	0.08	73%	< 0.00001	
Non-Chinese	4	2,047	OR (M–H, fixed, 95% CI)	1.09 (0.75, 1.57)	0.66	0%	0.64	
>50 years	13	13,603	OR (M–H, random, 95% Cl)	0.85 (0.66, 1.11)	0.23	67%	0.0003	
\leq 50 years	4	4,970	OR (M–H, random, 95% Cl)	0.64 (0.41, 0.99)	0.04	68%	0.03	
Homozygous gener	tic model							
Overall	19	12,024	OR (M–H, random, 95% Cl)	0.79 (0.62, 1.00)	0.05	74%	< 0.00001	
Chinese	15	10,714	OR (M–H, random, 95% Cl)	0.74 (0.56, 0.98)	0.03	79%	< 0.00001	
Non-Chinese	4	1,310	OR (M–H, fixed, 95% CI)	1.06 (0.72, 1.54)	0.77	0%	0.58	
>50 years	13	8,366	OR (M–H, random, 95% Cl)	0.79 (0.59, 1.06)	0.11	73%	<0.0001	
\leq 50 years	4	3,106	OR (M–H, random, 95% Cl)	0.57 (0.34, 0.95)	0.03	76%	0.006	
Heterozygote com	parison							
Overall	. 19	18,059	OR (M–H, random, 95% CI)	0.84 (0.76, 0.93)	0.0009	56%	0.002	
Chinese	15	16,158	OR (M–H, random, 95% CI)	0.83 (0.74, 0.93)	0.001	64%	0.0003	
Non-Chinese	4	1,901	OR (M–H, fixed, 95% CI)	0.93 (0.76, 1.15)	0.52	0%	0.87	
>50 years	13	12,532	OR (M–H, random, 95% CI)	0.85 (0.76, 0.94)	0.002	39%	0.07	
\leq 50 years	4	4,645	OR (M–H, random, 95% CI)	0.77 (0.60, 0.97)	0.03	74%	0.01	

Table 3 Overall meta-anal	vsis results	with subgroup	conducted by	ethnicity and age
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Abbreviation: M–H, Mantel–Haenszel.

genetic model: OR=0.74, 95% CI=0.56-0.98, P=0.03; heterozygote comparison: OR=0.83, 95% CI=0.74-0.93, P=0.001) (Figure 3), while no genetic model showed significant association in non-Chinese. When stratified by age, we found that both old (allele model: OR=0.86, 95% CI=0.76-0.98, P=0.02; dominant model: OR=0.83, 95% CI=0.73-0.95, P=0.006; heterozygote comparison: OR=0.85, 95% CI=0.76-0.94, P=0.002) and young patients (allele model: OR=0.75, 95% CI=0.59-0.97, P=0.03; dominant model: OR=0.73, 95% CI=0.56-0.96, P=0.03; recessive model: OR=0.64, 95% CI=0.41-0.99, P=0.04; homozygous genetic model: OR=0.57, 95% CI=0.34-0.95, P=0.03; heterozygote comparison: OR=0.77, 95% CI=0.60-0.97, P=0.03) showed a significant association between KIF1B (rs17401966) polymorphism and decreased HCC risk (Figure 4).

For studies with Chinese population, we also conducted subgroup analysis by region and environment. As shown in Table 4, when stratified by region (northern China, central China, southern China), we detected an association of the KIF1B (rs17401966) polymorphism with decreased HCC risk in Chinese in southern China based on heterozygote comparison (OR=0.78, 95% CI=0.63–0.98, P=0.03) (Figure 5). When stratified by environment (inland areas, coastal areas), we observed an association between decreased HCC risk and KIF1B (rs17401966) polymorphism in Chinese in inland areas (allele model: OR=0.76, 95% CI=0.61–0.96, P=0.02; dominant model: OR=0.73, 95% CI=0.58–0.94, P=0.01; homozygous genetic model: OR=0.60, 95% CI=0.36–0.98, P=0.04; heterozygote comparison: OR=0.77, 95% CI=0.63–0.94, P=0.01) (Figure 6); however, no statistically significant association was observed in those in coastal areas.

Sensitivity analyses

As shown in Table 1, all the studies were in line with the balance of HWE in control groups. To evaluate the stability of our results, we performed sensitivity analysis to assess

 Table 4 Subgroup meta-analysis results of Chinese conducted by region and environment

Outcome or	Studies	Participants	Statistical method	Effect	P-value	Heterogeneity		
subgroup				estimate		1 ²	P-value	
Allele model								
Overall	15	35,012	OR (M–H, random, 95% CI)	0.84 (0.74, 0.96)	0.009	84%	< 0.0000	
Northern China	2	3,634	OR (M–H, random, 95% CI)	0.77 (0.34, 1.78)	0.55	96%	< 0.0000	
Central China	8	21,582	OR (M–H, random, 95% CI)	0.88 (0.76, 1.01)	0.07	79%	< 0.000 I	
Southern China	5	9,796	OR (M–H, random, 95% Cl)	0.81 (0.63, 1.04)	0.1	84%	<0.0001	
Inland areas	6	19,448	OR (M–H, random, 95% Cl)	0.76 (0.61, 0.96)	0.02	90%	< 0.0000	
Coastal areas	9	15,564	OR (M–H, random, 95% CI)	0.90 (0.77, 1.05)	0.18	77%	< 0.0001	
Dominant model				х <i>У</i>				
Overall	15	17,506	OR (M–H, random, 95% Cl)	0.81 (0.71, 0.93)	0.003	78%	< 0.0000	
Northern China	2	1,817	OR (M–H, random, 95% CI)	0.75 (0.34, 1.66)	0.48	93%	0.0001	
Central China	8	10,791	OR (M–H, random, 95% Cl)	0.85 (0.72, 1.01)	0.06	74%	0.0003	
Southern China	5	4,898	OR (M–H, random, 95% CI)	0.77 (0.59, 1.01)	0.05	78%	0.001	
Inland areas	6	9,724	OR (M–H, random, 95% CI)	0.73 (0.58, 0.94)	0.01	86%	< 0.0000	
Coastal areas	9	7,782	OR (M–H, random, 95% CI)	0.87 (0.73, 1.03)	0.11	69%	0.001	
Recessive model								
Overall	15	17,506	OR (M–H, random, 95% CI)	0.80 (0.63, 1.02)	0.08	73%	< 0.0000	
Northern China	2	1,817	OR (M–H, random, 95% CI)	0.57 (0.07, 4.64)	0.6	9 4%	<0.0001	
Central China	8	10,791	OR (M–H, random, 95% CI)	0.84 (0.65, 1.08)	0.17	60%	0.01	
Southern China	5	4,898	OR (M–H, random, 95% CI)	0.76 (0.47, 1.24)	0.27	71%	0.008	
Inland areas	6	9,724	OR (M–H, random, 95% CI)	0.68 (0.44, 1.06)	0.09	83%	<0.0001	
Coastal areas	9	7,782	OR (M–H, random, 95% CI)	0.87 (0.65, 1.17)	0.37	63%	0.006	
Homozygous genetic	model							
Overall	15	10,714	OR (M–H, random, 95% CI)	0.74 (0.56, 0.98)	0.03	79%	< 0.0000	
Northern China	2	1,119	OR (M–H, random, 95% CI)	0.51 (0.05, 5.19)	0.57	95%	<0.0001	
Central China	8	6,556	OR (M–H, random, 95% CI)	0.78 (0.58, 1.06)	0.12	72%	0.0009	
Southern China	5	3,039	OR (M–H, random, 95% CI)	0.70 (0.40, 1.22)	0.2	77%	0.002	
Inland areas	6	5,981	OR (M–H, random, 95% CI)	0.60 (0.36, 0.98)	0.04	87%	< 0.0000	
Coastal areas	9	4,733	OR (M–H, random, 95% CI)	0.84 (0.59, 1.18)	0.31	71%	0.0006	
Heterozygote compa	rison							
Overall	15	16,158	OR (M–H, random, 95% CI)	0.83 (0.74, 0.93)	0.001	64%	0.0003	
Northern China	2	1,660	OR (M–H, random, 95% CI)	0.77 (0.44, 1.36)	0.37	86%	0.008	
Central China	8	9,911	OR (M–H, random, 95% Cl)	0.87 (0.75, 1.00)	0.06	62%	0.01	
Southern China	5	4,587	OR (M–H, random, 95% Cl)	0.78 (0.63, 0.98)	0.03	66%	0.02	
Inland areas	6	8,958	OR (M–H, random, 95% Cl)	0.77 (0.63, 0.94)	0.01	77%	0.0005	
Coastal areas	9	7,200	OR (M–H, random, 95% CI)	0.87 (0.75, 1.01)	0.06	53%	0.03	

Abbreviation: M–H, Mantel–Haenszel.

the effect of each individual study on the pooled ORs. After excluding each study sequentially, the corresponding ORs were not substantially changed, suggesting that the results of our meta-analysis were stable and reliable.

Heterogeneity analysis

Heterogeneity among studies was assessed by *Q*-statistic. Random effects models were applied if *P*-value of heterogeneity tests was ≤ 0.1 or I^2 was $\geq 75\%$ ($P \leq 0.1$ or $I^2 \geq 75\%$), otherwise, fixed effects models were selected (Tables 3 and 4).

Publication bias

Begg's test, Egger's test and funnel plot were all used to evaluate the publication bias of the included studies.

No significant publication bias was found in Begg's and Egger's test (P>0.05). Funnel plot also indicated that publication bias did not exist with no obvious asymmetry that could be observed (Figure 7).

Discussion

GWASs have been shown to be unbiased and effective in exploring disease phenotype-associated single-nucleotide polymorphism (SNP). Currently, a large number of GWASs have been reported, most of which are about cancer.²⁴ Epidemiological and experimental studies have shown that HCC is a complex disease that occurs due to multiple factors, including viral, environmental and genetic factors. With the same environmental background, a small number of people suffer from HCC, whereas others do not, which also

Study or	Case		Control		Weight	OR M–H,		OR M–H,		
subgroup	events	Total	events	Total	(%)	random, 95% Cl		random, 95%	CI	
Chen et al ⁹	194	440	309	707	6.6	1.02 (0.80–1.29)		+		
Chen et al ¹⁰	126	285	138	288	4.9	0.86 (0.62-1.20)				
Hu et al ¹¹	480	1,186	1,038	2,440	8.8	0.92 (0.80-1.06)				
Jiang et al ¹²	458	1,077	546	1,247	8.2	0.95 (0.81-1.12)		-		
Li et al13	417	981	395	904	7.8	0.95 (0.79–1.14)		+		
Li et al13	189	445	199	443	6.1	0.91 (0.69–1.18)				
Pan et al14	138	342	167	350	5.4	0.74 (0.55–1.00)				
Sawai et al ¹⁵	61	166	261	724	4.6	1.03 (0.73–1.46)		_ _		
Sawai et al15	46	137	91	237	3.4	0.81 (0.52-1.26)				
Sawai et al ¹⁵	59	147	55	129	3.1	0.90 (0.56-1.46)				
Sawai et al ¹⁵	39	83	80	174	2.7	1.04 (0.62-1.76)				
Sopipong et al16	81	181	83	180	3.7	0.95 (0.63-1.43)				
Su et al17	60	136	66	144	3.1	0.93 (0.58–1.49)				
Su ¹⁸	153	282	149	320	5.0	1.36 (0.99–1.88)		 		
Zhang et al ⁸	100	340	141	333	5.1	0.57 (0.41-0.78)				
Zhang et al ⁸	86	271	109	242	4.4	0.57 (0.40-0.81)				
Zhang et al ⁸	181	481	101	194	4.8	0.56 (0.40-0.78)				
Zhang et al ⁸	228	725	195	474	6.5	0.66 (0.52-0.84)				
Zhang et al ⁸	141	416	169	408	5.7	0.73 (0.55–0.96)				
Total (95% CI)		8,121		9,938	100	0.84 (0.76–0.93)		•		
Total events	3,237	•	4,292			. ,				
Heterogeneity: τ^{2}	=0.02; χ^2 =4	0.53, <i>df</i> =18	3 (P=0.002);	l²=56%						
Test for overall eff						(0.01 0.1	1	10	100
							Favors (experi	mental) I	avors (contro	n

Figure 2 Forest plots of the KIFIB (rs17401966) polymorphism and hepatocellular carcinoma risk in overall population (heterozygous genetic model, AG vs GG). Abbreviations: *df*, degrees of freedom; M–H, Mantel–Haenszel.

shows the importance of genotype. GWASs have found a number of HCC-associated SNPs, such as K1F1B, MICA, HLA-DQA/DQB, SL47W and so on.^{12,13,25,26} The existence of genetic etiology of HCC is further confirmed. Identification of HCC susceptibility genes and gene-related molecular mechanisms will provide a theoretical basis for the prevention and clinical diagnosis of HCC and treatment of population at high HCC risk. It is expected to achieve early prevention

and individualized treatment of HCC and to improve the therapeutic effect of HCC.

Through GWAS, Zhang et al⁸ found a significant association between KIF1B rs17401966 polymorphism and HCC, showing that the polymorphism of the site has a protective effect on HCC. However, a consistent conclusion on the correlation between the gene polymorphism and HCC was not reached.^{8–18} Hence, we performed this meta-analysis aiming

Study or subgroup	Case events	Total	Control events	Total	Weight (%)	OR M–H, random, 95% Cl		OR M–H, random, s	95% CI	
Chen et al ⁹	194	440	309	707	7.6	1.02 (0.80–1.29)		+		
Chen et al ¹⁰	126	285	138	288	5.9	0.86 (0.62-1.20)		-+-		
Hu et al ¹¹	480	1,186	1,038	2,440	9.8	0.92 (0.80-1.06)		-		
Jiang et al ¹²	458	1,077	546	1,247	9.3	0.95 (0.81-1.12)		+		
Li et al13	417	981	395	904	8.9	0.95 (0.79–1.14)		+		
Li et al ¹³	189	445	199	443	7.1	0.91 (0.69–1.18)		-+-		
Pan et al14	138	342	167	350	6.4	0.74 (0.55–1.00)				
Sawai et al15	39	83	80	174	3.4	1.04 (0.62-1.76)		-+	_	
Su et al ¹⁷	60	136	66	144	3.9	0.93 (0.58-1.49)			_	
Su ¹⁸	153	282	149	320	6.1	1.36 (0.99–1.88)		+		
Zhang et al ⁸	100	340	141	333	6.1	0.57 (0.41-0.78)				
Zhang et al ⁸	86	271	109	242	5.4	0.57 (0.40-0.81)				
Zhang et al ⁸	181	481	101	194	5.8	0.56 (0.40-0.78)				
Zhang et al ⁸	228	725	195	474	7.6	0.66 (0.52-0.84)				
Zhang et al ⁸	141	416	169	408	6.8	0.73 (0.55–0.96)				
Total (95% CI)		7,490		8,668	100	0.83 (0.74–0.93)		•		
Total events	2,990		3,802			. ,				
Heterogeneity:	$\tau^2 = 0.03; \chi^2 =$	=39.22, df=	14 (<i>P</i> =0.000); /²=64%)		L			
Test for overall	effect: Z=3.	18 (P=0.00	1)				0.01	0.1 1	10	100
							Favors	(experimental)	Favors (control))

Figure 3 Forest plots of the KIFIB (rs17401966) polymorphism and hepatocellular carcinoma risk in Chinese subgroup (heterozygous genetic model, AG vs GG). Abbreviations: df, degrees of freedom; M–H, Mantel–Haenszel.

$\begin{array}{c} \mathbf{S0} \mathbf{years} \\ \text{Chen et al}^{(0)} & 194 & 440 & 309 & 707 & 6.6 \\ \text{Chen et al}^{(0)} & 126 & 285 & 138 & 288 & 4.9 & 0.66 (0.62-1.20) \\ \text{Hu et al}^{(1)} & 480 & 1.186 & 1.038 & 2.440 & 8.8 & 0.92 (0.80-1.06) \\ \text{Jiang et al}^{(2)} & 458 & 1.077 & 546 & 1.247 & 8.2 & 0.95 (0.81-1.12) \\ \text{Pan et al}^{(1)} & 138 & 342 & 167 & 350 & 5.4 & 0.74 (0.55-1.00) \\ \text{Sawai et al}^{(0)} & 61 & 166 & 261 & 724 & 4.6 & 1.03 (0.72-1.46) \\ \text{Sawai et al}^{(0)} & 59 & 147 & 55 & 129 & 3.1 & 0.90 (0.56-1.46) \\ \text{Sawai et al}^{(0)} & 59 & 147 & 55 & 129 & 3.1 & 0.90 (0.56-1.46) \\ \text{Sawai et al}^{(0)} & 59 & 147 & 55 & 129 & 3.1 & 0.90 (0.56-1.46) \\ \text{Sawai et al}^{(0)} & 86 & 271 & 109 & 242 & 4.4 & 0.57 (0.40-0.81) \\ \text{Zhang et al}^{(0)} & 181 & 181 & 83 & 180 & 3.7 & 0.95 (0.63-1.43) \\ \text{Zhang et al}^{(0)} & 181 & 481 & 101 & 194 & 4.8 & 0.56 (0.40-0.78) \\ \text{Take events} & 2.090 & 3.147 \\ \text{Heterogeneity: } r^{(2)} 0.01; r^{(1)} 1.98 & 1.47 & 114 & 4.8 & 0.56 (0.40-0.78) \\ \text{Test for overall effect: $Z=3.13 ($P=0.002$)$ \\ \hline \text{Solutotal ($5\% Cl$)} & 2.491 & 2.154 & 25.5 & 0.66 (0.52-0.94) \\ \hline \text{Subtotal ($5\% Cl$)} & 2.491 & 2.154 & 25.5 & 0.66 (0.52-0.84) \\ \hline \text{Total events} & 2.090 & 3.147 \\ \text{Heterogeneity: } r^{(2)} 0.01; r^{(2)} 1.81, d^{(-1)} (P=0.017); r^{(2)} 39\% \\ \hline \text{Test for overall effect: $Z=2.18 ($P=0.03$)$ \\ \hline \textbf{Nr} \\ \text{Subtotal ($5\% Cl$)} & 2.491 & 2.154 & 25.5 & 0.66 (0.52-0.84) \\ \hline \textbf{Nr} \\ \hline \text{Total events} & 2.13 & 2.15 \\ \text{Heterogeneity: } r^{(2)} 0.03; r^{(2)} 1.89, d^{(-1)} (P=0.010); r^{(2)} r^{(2)} r^{(2)} \\ \hline \textbf{Total events} & 2.327 & 4.292 \\ \text{Heterogeneity: } r^{(2)} 0.03; r^{(2)} -1.69, (T=14) (P=0.002); r^{(2)} r^{(2)} \\ \hline \textbf{Total events} & 3.237 & 4.292 \\ \text{Heterogeneity: } r^{(2)} 0.03; r^{(2)} -1.69, (T=0.19); r^{(2)} r^{(2)} \\ \hline \textbf{Total events} & 3.237 & 4.292 \\ \text{Heterogeneity: } r^{(2)} 0.03; r^{(2)} -1.61 (P=0.002); r^{(2)} =56\% \\ \hline \textbf{Total events} & 3.237 & 4.292 \\ \text{Heterogeneity: } r^{(2)} 0.03; r^{(2)} =0.030 \\ \hline \textbf{Dotal events} & 3.237 & 4.292 \\ \text{Heterogeneity: } r^{(2)} 0.02; $	Study or subgroup	Case events	Total	Control events	Total	Weight	OR M–H, random, 95% Cl	OR M–H	
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	• •	events	TOLAI	events	TOLAI	(%)		ranuom	95% CI
Then et al ¹⁰ 126 285 138 288 4.9 0.86 (0.62-1.20) tu et al ¹¹ 480 1.186 1.038 2.440 8.8 0.92 (0.80-1.06) tu et al ¹¹ 480 1.186 1.075 546 1.247 8.2 0.95 (0.81-1.12) The et al ¹⁴ 138 342 167 350 5.4 0.74 (0.55-1.00) The et al ¹⁵ 46 137 91 237 3.4 0.81 (0.52-1.26) Sawai et al ¹⁵ 59 147 55 129 3.1 0.90 (0.56-1.46) Sawai et al ¹⁵ 59 147 155 129 3.1 0.90 (0.56-1.46) Sawai et al ¹⁶ 88 271 109 242 4.4 0.57 (0.40-0.81) Thang et al ⁸ 181 481 101 194 4.8 0.56 (0.40-0.78) Thang et al ⁸ 181 481 101 194 4.8 0.56 (0.40-0.78) Thang et al ⁸ 141 416 169 408 5.7 0.73 (0.55-0.96) Subtotal (95% CI) 5.212 7,320 66.3 0.85 (0.76-0.94) The eterogeneity: r^2 =0.01; r^2 =19.81, df =12 (P =0.07); P =39% feat for overall effect: Z =3.13 (P =0.002) 50 years Li et al ¹⁶ 417 981 395 904 7.8 0.95 (0.79-1.14) Li et al ¹⁶ 417 981 395 904 7.8 0.95 (0.79-1.14) Li et al ¹⁶ 417 981 395 904 7.8 0.95 (0.79-1.14) Li et al ¹⁶ 417 981 395 904 7.8 0.95 (0.79-1.14) Li et al ¹⁶ 417 981 395 904 7.8 0.95 (0.79-1.14) Li et al ¹⁶ 417 981 305 004 7.8 0.95 (0.79-1.14) Li et al ¹⁶ 417 981 305 0.904 7.8 0.95 (0.79-1.14) Li et al ¹⁶ 417 981 305 0.904 7.8 0.95 (0.79-1.14) Li et al ¹⁶ 417 981 305 0.904 7.8 0.95 (0.79-1.14) Li et al ¹⁶ 417 981 305 0.904 7.8 0.95 (0.79-1.14) Li et al ¹⁶ 417 981 305 0.904 7.8 0.95 (0.79-1.14) Li et al ¹⁶ 417 981 305 0.904 7.8 0.95 (0.79-1.14) Li et al ¹⁶ 417 981 305 0.904 7.8 0.95 (0.79-1.14) Li et al ¹⁷ 60 136 66 144 3.1 0.91 (0.69-1.18) The eterogeneity: r^2 =0.02; r^2 =10.9, f =10, P =0.19; P =21% Eve ta al ¹⁷ 60 136 66 144 3.1 0.93 (0.58-1.49) Su ¹⁶ 153 282 149 320 5.0 1.36 (0.99-1.88) Subtotal (95% CI) 8,121 9.938 100 0.84 (0.76-0.93) Fotal events 2.13 2.15 teterogeneity: r^2 =0.03; r^2 =1.69, f =1 (P =0.002); P =24% feat rowerall effect: Z =2.07 (P =0.005) Lot al (95% CI) 8,121 9.938 100 0.84 (0.76-0.93) Fotal events 3.237 4.292 teterogeneity: r^2 =0.02; r^2 =0.05, d =10 (P =0.002); P =26% teterogeneity: r^2 =0.02; P^2 =0.05; D =0.000	•								
Huel al ¹¹ 400 1,186 1.038 2,440 8.8 0.92 (0.80-1.06) Hang et al ¹² 458 1,077 546 1,247 8.2 0.92 (0.80-1.02) Sawai et al ¹⁸ 138 342 167 350 5.4 0.74 (0.55-1.00) Sawai et al ¹⁸ 61 166 261 724 4.6 1.03 (0.73-1.46) Sawai et al ¹⁸ 46 137 91 237 3.4 0.80 (0.56-1.46) Sawai et al ¹⁸ 59 147 55 129 3.1 0.90 (0.56-1.43) Schopeng et al ¹⁸ 86 271 109 242 4.4 0.57 (0.40-0.81) Zhang et al ¹⁸ 86 271 109 242 4.4 0.57 (0.40-0.78) Chang et al ¹⁸ 86 271 109 242 4.4 0.57 (0.40-0.78) Subtotal (95% CI) 5,212 7,320 66.3 0.85 (0.76-0.94)							· · · ·	-	-
liang et al ¹² 488 1,077 546 1,247 8.2 0.55 (0.81-1.12) Pan et al ¹⁴ 138 342 167 350 5.4 0.74 (0.55-1.00) Sawai et al ¹⁵ 61 166 261 724 4.6 1.33 (0.75-1.46) Sawai et al ¹⁵ 46 137 91 237 3.4 0.81 (0.52-1.26) Sawai et al ¹⁵ 39 83 80 174 2.7 1.04 (0.62-1.76) Sawai et al ¹⁶ 81 181 83 180 3.7 0.95 (0.63-1.43) Zhang et al ⁸ 81 181 83 180 3.7 0.95 (0.63-1.43) Zhang et al ⁸ 181 481 101 194 4.8 0.56 (0.40-0.81) That et al ¹⁶ 82 271 109 242 4.4 0.57 (0.40-0.81) That et al ¹⁶ 82 271 109 242 4.4 0.57 (0.40-0.81) That et al ¹⁶ 81 181 481 101 194 4.8 0.56 (0.40-0.78) That et al ¹⁶ 81 181 481 101 194 4.8 0.56 (0.40-0.78) That et al ¹⁶ 181 481 101 194 4.8 0.56 (0.40-0.78) That et al ¹⁶ 181 481 101 194 4.8 0.56 (0.40-0.78) That et al ¹⁷ 181 395 904 7.8 0.95 (0.79-1.14) Li et al ¹⁹ 141 416 169 408 5.7 0.73 (0.55-0.96) Total events 2,090 3.147 Heterogeneity: $r^2=0.01$; $r^2=10.81$, $d^{r=12}$ ($P=0.07$); $r^2=39\%$ Test for overall effect: Z=3.13 ($P=0.002$) Solutotal (95% CI) 2,491 2,154 25.5 0.77 (0.60-0.97) Total events 934 930 Heterogeneity: $r^2=0.04$; $r^2=1.141$, $d^{r=3}$ ($P=0.010$); $r=74\%$ Test for overall effect: Z=2.18 ($P=0.03$) NR Subtotal (95% CI) 2,491 2,154 25.5 0.77 (0.60-0.97) Total events 934 930 Heterogeneity: $r^2=0.03$; $r^2=1.63$, $d^{r=11}$ ($P=0.019$); $r=74\%$ Test for overall effect: Z=2.18 ($P=0.03$) NR Subtotal (95% CI) 8,121 9,938 100 0.84 (0.76-0.93) Total events 213 215 Heterogeneity: $r^2=0.02$; $r^2=40.53$, $d^{r=11}$ ($P=0.002$); $P=56\%$ Total (95% CI) 8,121 9,938 100 0.84 (0.76-0.93) Total events 213 225 Heterogeneity: $r^2=0.02$; $r^2=0.03$; $d^{r=16}$ ($P=0.002$); $P=56\%$ Total (95% CI) 8,121 9,938 100 0.84 (0.76-0.93) Total events 2,32 ($P=0.009$) 0.01 0.1 100							. ,	-	-
Pan et al ¹⁴ 138 342 167 350 5.4 0.74 (0.55-1.00) awai et al ¹⁶ 61 166 261 724 4.6 1.03 (0.73-1.46) Sawai et al ¹⁶ 91 167 257 3.4 0.81 (0.52-1.26) Sawai et al ¹⁶ 9 147 55 129 3.1 0.90 (0.56-1.46) Sawai et al ¹⁶ 9 147 55 129 3.1 0.90 (0.56-1.46) Sawai et al ¹⁶ 81 181 83 180 3.7 0.95 (0.63-1.43) Thang et al ¹⁸ 86 271 109 242 4.4 0.57 (0.40-0.78) Thang et al ¹⁸ 86 271 109 242 4.4 0.57 (0.40-0.78) Thang et al ¹⁸ 86 271 109 242 4.4 0.57 (0.40-0.78) Thang et al ¹⁹ 181 481 101 194 4.8 0.56 (0.40-0.78) Thang et al ¹⁹ 141 416 169 408 5.7 0.73 (0.55-0.96) Subtotal (95% CI) 5.212 7,320 66.3 0.85 (0.76-0.94) Total events 2.090 3.147 Heterogeneity: $r^2=0.01; r^2=19.81, df=12 (P=0.07); P=39\%$ Total events 2.090 3.147 Heterogeneity: $r^2=0.04; r^2=11.41, df=3 (P=0.010); P=39\%$ Total events 934 2725 195 474 6.5 0.66 (0.52-0.84) Subtotal (95% CI) 2.491 2.154 25.5 0.77 (0.60-0.97) Total events 934 293 Subtotal (95% CI) 2.491 9.215 Subtotal effect: Z=2.18 (P=0.010); P=74\% Test for overall effect: Z=2.18 (P=0.010); P=74\% Test for overall effect: Z=2.18 (P=0.010); P=74\% Total events 213 215 Heterogeneity: $r^2=0.03; r^2=16.9, df=1 (P=0.19); P=41\%$ Test for overall effect: Z=0.87 (P=0.38) Total events 2.13 215 Heterogeneity: $r^2=0.02; r^2=10.83, df=1 (P=0.19); P=41\%$ Test for overall effect: Z=0.87 (P=0.38) Total events 3.237 4.292 Heterogeneity: $r^2=0.02; r^2=10.83, df=1 (P=0.02); P=56\%$ Heterogeneity: $r^2=0.02; r^2=10.83, df=1 (P=0.002); P=56\%$ Total (95% CI) 8.121 9.938 100 0.84 (0.76-0.93) Total events 3.237 4.292 Heterogeneity: $r^2=0.02; r^2=40.53, df=1 (P=0.002); P=56\%$ Heterogeneity: $r^2=0.02; r^2=40.53, df=1 (P=0.002); P=56\%$ Heterogeneity: $r^2=0.02; r^2=40.53, df=1 (P=0.002); P=56\%$							· · · ·	-	
Sawai et al ¹⁶ 61 166 261 724 4.6 1.03 (0.73-1.46) Sawai et al ¹⁶ 46 137 91 237 3.4 0.81 (0.52-1.26) Sawai et al ¹⁶ 59 147 55 129 3.1 0.90 (0.56-1.46) Sawai et al ¹⁶ 39 83 80 174 2.7 1.04 (0.62-1.76) Shipping et al ¹⁶ 81 181 83 180 3.7 0.95 (0.63-1.43) Chang et al ¹⁶ 86 271 109 242 4.4 0.57 (0.40-0.81) Chang et al ¹⁶ 181 481 101 194 4.8 0.56 (0.40-0.78) Chang et al ¹⁸ 181 481 101 194 4.8 0.56 (0.40-0.78) Chang et al ¹⁹ 181 441 101 194 4.8 0.56 (0.40-0.78) Chang et al ¹⁹ 181 441 101 194 4.8 0.56 (0.76-0.94) Subtotal (95% CI) 5.212 7.320 66.3 0.85 (0.76-0.94) Total events 2.090 3.147 Teterogeneity: r^2 -0.01; r^2 =19.81, d =12 (P =0.07); P =39% Test for overall effect: Z=3.13 (P =0.002) Solution (95% CI) 2.491 2.154 25.5 0.77 (0.41-0.78) Chang et al ¹⁹ 100 340 141 333 5.1 0.57 (0.41-0.78) Chang et al ¹⁹ 228 725 195 474 0.5 0.66 (0.52-0.84) Subtotal (95% CI) 2.491 2.154 25.5 0.77 (0.60-0.97) Fotal events 934 930 Teterogeneity: r^2 =0.04; r^2 =11.41, d =3 (P =0.010); P =74% Test for overall effect: Z=2.18 (P =0.03) NR Subtotal (95% CI) 8.121 9.938 100 0.84 (0.76-0.93) Fotal events 213 225 15 Total events 213 2215 Teterogeneity: r^2 =0.03; r^2 =16.89, d =11 (P =0.19); P =41% Test for overall effect: Z=0.87 (P =0.38) Fotal (95% CI) 8.121 9.938 100 0.84 (0.76-0.93) Fotal events 2.3207 4.292 Teterogeneity: r^2 =0.03; r^2 =0.032; P =56% Test for overall effect: Z=0.32 (P =0.0002); P =56% Test for overall effect: Z=0.32 (P =0.0009) 0.01 0.1 1 10	Jiang et al ¹²	458	1,077	546	1,247	8.2	0.95 (0.81–1.12)	-	-
Sawai et al ¹⁶ 46 137 91 237 3.4 0.81 (0.52–1.26) Sawai et al ¹⁶ 59 147 55 129 3.1 0.90 (0.56–1.46) Sawai et al ¹⁸ 39 83 80 174 2.7 1.04 (0.62–1.76) Soppong et al ¹⁸ 81 181 83 180 3.7 0.95 (0.63–1.43) Chang et al ⁸ 181 481 101 194 4.8 0.56 (0.40–0.78) Chang et al ⁸ 181 414 416 169 408 5.7 0.73 (0.55–0.96) Subtotal (95% CI) 5.212 7,320 66.3 0.85 (0.76–0.94) Total events 2.090 3.147 Teletrogeneity: $r^2=0.01; r^2=19.81, dr=12$ ($P=0.07$); $r^2=39\%$ Test for overall effect: Z=3.13 ($P=0.002$) Stop years Liet al ¹⁹ 189 445 199 443 6.1 0.91 (0.69–1.18) Chang et al ⁸ 100 340 141 333 5.1 0.57 (0.41–0.78) Thang et al ⁸ 122 725 195 474 6.5 0.66 (0.52–0.84) Subtotal (95% CI) 2.491 2.154 25.5 0.77 (0.60–0.97) Fotal events 934 930 Total events 934 ($P=0.010$); $r^2=74\%$ Test for overall effect: Z=2.18 ($P=0.03$) NR Subtotal (95% CI) 418 464 8.2 1.17 (0.82–1.69) Subtotal (95% CI) 8,121 9,938 100 0.84 (0.76–0.93) Fotal events 213 215 Heterogeneity: $r^2=0.03; x^2=1.69, dr=1 (P=0.002); r^2=56\%$ Test for overall effect: Z=0.87 ($P=0.002$); $r^2=56\%$ Test for overall effect: Z=3.32 ($P=0.002$); $r^2=56\%$ Test for overall effect: Z=3.32 ($P=0.002$); $r^2=56\%$	Pan et al ¹⁴	138	342	167	350	5.4	0.74 (0.55–1.00)		
Sawai et al ¹⁶ 59 147 55 129 3.1 0.90 (0.56-1.46) Sawai et al ¹⁶ 39 83 80 174 2.7 1.04 (0.62-1.76) Sopioporg tal ¹⁶ 81 181 83 180 3.7 0.55 (0.63-1.43) Zhang et al ⁶ 86 271 109 242 4.4 0.57 (0.40-0.81) Zhang et al ⁸ 181 481 101 194 4.8 0.56 (0.40-0.78) Zhang et al ⁸ 181 481 101 194 4.8 0.56 (0.40-0.78) Subtotal (95% CI) 5.212 7,320 66.3 0.85 (0.76-0.94) Total events 2.090 3,147 teterogeneity: $r^2=10.01$; $r^2=13.81$, $df=12$ ($P=0.07$); $P=39\%$ Test for overall effect: Z=3.13 ($P=0.002$) S50 years i. et al ¹³ 189 445 199 443 6.1 0.91 (0.69-1.18) Zhang et al ⁸ 100 340 141 333 5.1 0.57 (0.41-0.78) Total events 934 930 teterogeneity: $r^2=0.04$; $r^2=11.41$, $df=3$ ($P=0.010$); $P=74\%$ Test for overall effect: Z=2.18 ($P=0.010$); $P=74\%$ Test for overall effect: Z=2.18 ($P=0.03$) NR Su et al ¹⁷ 60 136 66 144 3.1 0.93 (0.58-1.49) Su ¹⁶ 153 282 149 320 5.0 1.36 (0.99-1.88) Subtotal (95% CI) 418 464 8.2 1.17 (0.82-1.69) Total events 213 215 teterogeneity: $r^2=0.02$; $r^2=16.9$, $df=1$ ($P=0.19$); $P=74\%$ Test for overall effect: Z=0.87 ($P=0.38$) Total events 3.237 4.292 teterogeneity: $r^2=0.02$; $r^2=16.9$, $df=1$ ($P=0.02$); $P=76\%$ Test for overall effect: Z=0.87 ($P=0.38$) Total events 3.237 4.292 teterogeneity: $r^2=0.02$; $r^2=16.9$, $df=1$ ($P=0.02$); $P=76\%$ Test for overall effect: Z=0.87 ($P=0.38$) Total events 3.247 4.292 teterogeneity: $r^2=0.02$; $r^2=16.9$, $df=1$ ($P=0.02$); $P=76\%$ Test for overall effect: Z=0.87 ($P=0.38$) Total events 3.247 4.292 teterogeneity: $r^2=0.02$; $r^2=16.9$, $df=18$ ($P=0.002$); $P=56\%$ Total events 3.247 4.292 teterogeneity: $r^2=0.02$; $r^2=0.03$, $r^2=16.9$, $df=18$ ($P=0.002$); $P=56\%$ Test for overall effect: Z=0.37 ($P=0.009$) 0.01 0.1 100	Sawai et al ¹⁵	61	166	261	724	4.6	1.03 (0.73–1.46)	_	—
Savai et al ¹¹⁵ 39 83 80 174 2.7 1.04 $(0.62-1.76)$ Sopipong et al ¹⁶ 81 181 83 180 3.7 0.95 $(0.63-1.43)$ Zhang et al ⁸ 81 481 101 194 4.8 0.56 $(0.40-0.81)$ Zhang et al ⁸ 141 416 169 408 5.7 0.73 $(0.55-0.96)$ Subtotal (95% CI) 5.212 7.320 66.3 0.85 $(0.76-0.94)$ Total events 2.090 3.147 Heterogeneity: $r^2=0.01$; $r^2=19.81$, $dr=12$ ($P=0.07$); $P=39\%$ Test for overall effect: Z=3.13 ($P=0.02$) S50 years Li et al ¹³ 417 981 395 904 7.8 0.95 $(0.79-1.14)$ Li et al ¹³ 189 445 199 443 6.1 0.91 $(0.69-1.18)$ Zhang et al ⁸ 100 340 141 333 5.1 0.57 $(0.41-0.78)$ Zhang et al ⁸ 228 725 195 474 6.5 0.66 (0.52-0.84) Subtotal (95% CI) 2.491 2.154 25.5 0.77 $(0.60-0.97)$ Total events 934 930 Heterogeneity: $r^2=0.04$; $r^2=11.41$, $dr=3$ ($P=0.010$); $P=74\%$ Test for overall effect: Z=2.18 ($P=0.03$) NR Subtotal (95% CI) 418 464 8.2 1.17 $(0.82-1.69)$ Stottotal (95% CI) 8.121 9.938 100 0.84 $(0.76-0.93)$ Total events 3.237 4.292 Heterogeneity: $r^2=0.03$; $r^2=0.05$; $r^2=0.05$; $r^2=66\%$ Test for overall effect: Z=0.37 ($P=0.38$) Total events 3.237 4.292 Heterogeneity: $r^2=0.02$; $r^2=0.05$; $r^2=66\%$ Test for overall effect: Z=0.87 ($P=0.38$) Total events 3.247 4.292 Heterogeneity: $r^2=0.02$; $r^2=0.02$; $r^2=66\%$ Total events 3.247 4.292 Heterogeneity: $r^2=0.02$; $r^2=16.97$ ($P=0.38$) Total events 3.247 4.292 Heterogeneity: $r^2=0.02$; $r^2=0.02$; $r^2=60\%$ Total events 3.247 4.292 Heterogeneity: $r^2=0.02$; $r^2=0.03$; $r^2=16.97$ Heterogeneity: $r^2=0.02$; $r^2=0.03$; $r^2=16.97$ Total events 3.247 4.292 Heterogeneity: $r^2=0.02$; $r^2=0.03$; $r^2=16.97$ Total events 3.247 4.292 Heterogeneity: $r^2=0.02$; $r^2=0.03$; $r^2=16.97$ $r^2=0.02$; $r^2=0.03$; $r^2=16.97$ ($P=0.38$) Total events 3.247 4.292 Heterogeneity: $r^2=0.02$; $r^2=0.03$; $r^2=16.97$ $r^2=0.02$; $r^2=0.03$; $r^2=16.97$ $r^2=0.02$; $r^2=0.03$; $r^2=0.03$; $r^2=0.03$ $r^2=0.03$; $r^2=0.03$; $r^2=0.03$; $r^2=0.03$ $r^2=0.03$; $r^2=0.03$; $r^2=0.03$; $r^2=0.03$ $r^2=0.03$; $r^2=0.03$; $r^2=0.03$	Sawai et al ¹⁵	46	137	91	237	3.4	0.81 (0.52–1.26)		-
Sopipong et al ¹⁶ 81 181 83 180 3.7 0.95 (0.63–1.43) Chang et al ¹⁶ 86 271 109 242 4.4 0.57 (0.40–0.81) Chang et al ¹⁸ 141 416 169 408 5.7 0.73 (0.55–0.96) Subtotal (95% CI) 5,212 7,320 66.3 0.85 (0.76–0.94) Total events 2.090 3.147 Heterogeneity: $r^2=0.01; r^2=19.81, df=12$ ($P=0.07$); $P=39\%$ Test for overall effect: Z=3.13 ($P=0.002$) S50 years Li et al ¹³ 189 445 199 443 6.1 0.91 (0.69–1.14) Li et al ¹³ 189 445 199 443 6.1 0.91 (0.69–1.18) Chang et al ⁸ 100 340 141 333 5.1 0.57 (0.41–0.78) Chang et al ⁸ 228 725 195 474 6.5 0.66 (0.52–0.84) Subtotal (95% CI) 2,491 2,154 25.5 0.77 (0.60–0.97) Total events 934 930 Subtotal (95% CI) 418 464 8.2 1.17 (0.82–1.69) Subtotal (95% CI) 418 464 8.2 1.17 (0.82–1.69) Total events 2.13 ($P=0.03$) NR Sub et al ¹⁷ 60 136 66 144 3.1 0.93 (0.58–1.49) Su ¹⁸ 153 282 149 320 5.0 1.36 (0.99–1.88) Subtotal (95% CI) 418 464 8.2 1.17 (0.82–1.69) Total events 2.13 215 Heterogeneity: $r^2=0.03$; $r^2=1.69, df=1$ ($P=0.19$); $P=41\%$ Test for overall effect: Z=0.37 ($P=0.38$) Total events 3.237 4.292 Heterogeneity: $r^2=0.03$; $r^2=1.69, df=1$ ($P=0.002$); $P=56\%$ Total events 3.237 4.292 Heterogeneity: $r^2=0.03$; $r^2=4.053, df=8$ ($P=0.002$); $P=56\%$ Total events 3.237 4.292 Heterogeneity: $r^2=0.02$; $r^2=40.53, df=18$ ($P=0.002$); $P=56\%$	Sawai et al15	59	147	55	129	3.1	0.90 (0.56–1.46)		<u> </u>
Zhang et al ⁸ 86 271 109 242 4.4 0.57 (0.40-0.81) Zhang et al ⁸ 181 481 101 194 4.8 0.56 (0.40-0.78) Zhang et al ⁸ 181 481 101 194 4.8 0.56 (0.40-0.78) Total events 2.090 3.147 Heterogeneity: z^{2} =0.01; z^{2} =19.81, df=12 (<i>P</i> =0.07); <i>P</i> =39% Test for overall effect: Z^{2} .13 (<i>P</i> =0.002) S50 years Li et al ¹³ 189 445 199 443 6.1 0.91 (0.69-1.18) Zhang et al ⁸ 100 340 141 333 5.1 0.57 (0.41-0.78) Total events 934 930 Heterogeneity: z^{2} =0.04; z^{2} =11.41, df=3 (<i>P</i> =0.101); <i>P</i> =74% Test for overall effect: Z^{2} .18 (<i>P</i> =0.003) NR Subtotal (95% CI) 2.491 2.154 25.5 0.77 (0.60-0.97) Total events 934 930 Heterogeneity: z^{2} =0.04; z^{2} =11.41, df=3 (<i>P</i> =0.010); <i>P</i> =74% Test for overall effect: Z^{2} .18 (<i>P</i> =0.03) NR Subtotal (95% CI) 418 464 8.2 1.17 (0.82-1.69) Total events 213 215 Heterogeneity: z^{2} =0.03; z^{2} =1.69, df=1 (<i>P</i> =0.19); <i>P</i> =41% Test for overall effect: Z^{2} .32 (<i>P</i> =0.009) Total events 3.237 4.292 Heterogeneity: z^{2} =0.03; z^{2} =40.53, df=18 (<i>P</i> =0.002); <i>P</i> =56% Test for overall effect: Z^{2} .32 (<i>P</i> =0.009) 0.01 0.1 1 10	Sawai et al15	39	83	80	174	2.7	1.04 (0.62–1.76)		<u> </u>
Zhang et al ⁸ 181 481 101 194 4.8 0.56 $(0.40-0.78)$ Zhang et al ⁸ 141 416 169 408 5.7 0.73 $(0.55-0.96)$ Total events 2,090 3,147 Heterogeneity: $t^{2}=0.01$; $t^{2}=19.81$, $df=12$ ($P=0.07$); $P=39\%$ Test for overall effect: Z=3.13 ($P=0.002$) S50 years Li et al ¹³ 417 981 395 904 7.8 0.95 $(0.79-1.14)$ Li et al ¹³ 189 445 199 443 6.1 0.91 $(0.69-1.18)$ Zhang et al ⁸ 100 340 141 333 5.1 0.57 $(0.41-0.78)$ Zhang et al ⁸ 228 725 195 474 6.5 0.66 $(0.52-0.84)$ Subtotal (95% CI) 2,491 2,154 25.5 0.77 $(0.60-0.97)$ Total events 934 930 Heterogeneity: $t^{2}=0.04; t^{2}=11.41, df=3$ ($P=0.010$); $P=74\%$ Test for overall effect: Z=2.18 ($P=0.010$); $P=74\%$ Total events 213 215 Heterogeneity: $t^{2}=0.03; t^{2}=1.59, df=1$ ($P=0.19$); $P=41\%$ Total events 213 215 Heterogeneity: $t^{2}=0.03; t^{2}=40.53, df=18$ ($P=0.002$); $P=5\%$ Total events 3,237 4,292 Heterogeneity: $t^{2}=0.03; t^{2}=40.53, df=18$ ($P=0.002$); $P=5\%$ Total events 3,237 4,292 Heterogeneity: $t^{2}=0.02; t^{2}=40.53, df=18$ ($P=0.002$); $P=5\%$ Total events 3,237 4,292 Heterogeneity: $t^{2}=0.02; t^{2}=40.53, df=18$ ($P=0.002$); $P=5\%$ Total events 3,237 4,292 Heterogeneity: $t^{2}=0.02; t^{2}=40.53, df=18$ ($P=0.002$); $P=5\%$ Total events 3,237 4,292 Heterogeneity: $t^{2}=0.02; t^{2}=40.53, df=18$ ($P=0.002$); $P=5\%$ Total events 3,237 4,292 Heterogeneity: $t^{2}=0.02; t^{2}=40.53, df=18$ ($P=0.002$); $P=5\%$ Total events 3,237 4,292 Heterogeneity: $t^{2}=0.02; t^{2}=40.53, df=18$ ($P=0.002$); $P=5\%$ Total events 3,237 4,292 Heterogeneity: $t^{2}=0.02; t^{2}=40.53, df=18$ ($P=0.002$); $P=5\%$ Total events 3,237 4,292 Heterogeneity: $t^{2}=0.02; t^{2}=40.53, df=18$ ($P=0.002$); $t^{2}=5\%$ Total events 3,237 4,292 Heterogeneity: $t^{2}=0.02; t^{2}=40.53, df=18$ ($P=0.002$); $t^{2}=5\%$ Total events 3,237 4,292 Heterogeneity: $t^{2}=0.02; t^{2}=40.53, df=18$ ($P=0.002$); $t^{2}=5\%$ Total events 3,237 4,292 Heterogeneity: $t^{2}=0.02; t^{2}=40.53, df=18$ ($P=0.002$); $t^{2}=5\%$ Total events 4,292 Hetero	Sopipong et al ¹⁶	81	181	83	180	3.7	0.95 (0.63–1.43)		_
Zhang et al ⁸ 141 416 169 408 5.7 0.73 ($0.55-0.96$) Subtotal (95% CI) 5.212 7,320 66.3 0.85 ($0.76-0.94$) Total events 2.090 3.147 Heterogeneity: $r^2=0.01$; $r^2=19.81$, $df=12$ ($P=0.07$); $l^2=39\%$ Test for overall effect: Z=3.13 ($P=0.002$) S50 years Li et al ¹³ 417 981 395 904 7.8 0.95 ($0.79-1.14$) Li et al ¹³ 189 445 199 443 6.1 0.91 ($0.69-1.18$) Zhang et al ⁸ 100 340 141 333 5.1 0.57 ($0.41-0.78$) Zhang et al ⁸ 228 725 195 474 6.5 0.66 ($0.52-0.64$) Subtotal (95% CI) 2,491 2,154 25.5 0.77 ($0.60-0.97$) Total events 934 930 Heterogeneity: $r^2=0.04$; $r^2=11.41$, $df=3$ ($P=0.010$); $l^2=74\%$ Test for overall effect: Z=2.18 ($P=0.03$) NR Su et al ¹⁷ 60 136 66 144 3.1 0.93 ($0.58-1.49$) Su ¹⁸ 153 282 149 320 5.0 1.36 ($0.99-1.88$) Subtotal (95% CI) 418 464 8.2 1.17 ($0.82-1.69$) Total events 213 215 Heterogeneity: $r^2=0.03$; $r^2=1.69$, $df=1$ ($P=0.19$); $l^2=41\%$ Test for overall effect: Z=0.37 ($P=0.38$) Total events 3.237 4.292 Heterogeneity: $r^2=0.02$; $r^2=40.53$, $df=18$ ($P=0.002$); $l^2=56\%$ Test for overall effect: Z=0.32 ($P=0.002$) 0.01 0.1 100	Zhang et al ⁸	86	271	109	242	4.4	0.57 (0.40-0.81)		
Zhang et al ⁸ 141 416 169 408 5.7 0.73 (0.55–0.96) Subtotal (95% CI) 5.212 7,320 66.3 0.85 (0.76–0.94) Total events 2.090 3.147 Test for overall effect: Z=3.13 (P =0.002) S50 years Li et al ¹³ 417 981 395 904 7.8 0.95 (0.79–1.14) Li et al ¹³ 189 445 199 443 6.1 0.91 (0.69–1.18) Zhang et al ⁸ 100 340 141 333 5.1 0.57 (0.41–0.78) Zhang et al ⁸ 228 725 195 474 6.5 0.66 (0.52–0.84) Subtotal (95% CI) 2.491 2.154 25.5 0.77 (0.60–0.97) Total events 934 930 Heterogeneity: $r^2=0.04$; $r^2=11.41$, $dr=3$ ($P=0.010$); $P=74\%$ Test for overall effect: Z=2.18 ($P=0.03$) NR Su et al ¹⁷ 60 136 66 144 3.1 0.93 (0.58–1.49) Subtotal (95% CI) 418 464 8.2 1.17 (0.82–1.69) Total events 213 215 Heterogeneity: $r^2=0.03$; $r^2=1.69$, $dr=1$ ($P=0.19$); $P=41\%$ Test for overall effect: Z=0.37 ($P=0.38$) Total events 3.237 4.292 Heterogeneity: $r^2=0.02$; $r^2=40.53$, $dr=18$ ($P=0.002$); $P=56\%$ Test for overall effect: Z=3.32 ($P=0.003$)	•	181	481		194		· · · ·	—	
Subtotal (95% CI) 5,212 7,320 66.3 0.85 (0.76–0.94) Total events 2,090 3,147 Heterogeneity: $r^2=0.01$; $r^2=19.81$, $df=12$ ($P=0.07$); $l^2=39\%$ Test for overall effect: Z=3.13 ($P=0.002$) SSO years Li et al ¹³ 189 445 199 443 6.1 0.91 (0.69–1.18) Zhang et al ⁸ 100 340 141 333 5.1 0.57 (0.41–0.78) Zhang et al ⁸ 228 725 195 474 6.5 0.66 (0.52–0.84) Subtotal (95% CI) 2,491 2,154 25.5 0.77 (0.60–0.97) Total events 934 930 Heterogeneity: $r^2=0.04$; $r^2=11.41$, $df=3$ ($P=0.010$); $l^2=74\%$ Test for overall effect: Z=2.18 ($P=0.03$) NR Su et al ¹⁷ 60 136 66 144 3.1 0.93 (0.58–1.49) Su ¹⁸ 153 282 149 320 5.0 1.36 (0.99–1.88) Subtotal (95% CI) 418 464 8.2 1.17 (0.82–1.69) Total events 213 215 Heterogeneity: $r^2=0.03$; $r^2=1.69$, $df=1$ ($P=0.19$); $l^2=41\%$ Test for overall effect: Z=0.87 ($P=0.38$) Total events 3.237 4.292 Heterogeneity: $r^2=0.03$; $r^2=1.69$, $df=1$ ($P=0.19$); $l^2=56\%$ Test for overall effect: Z=3.32 ($P=0.002$): $l^2=56\%$ Test for overall effect: Z=3.32 ($P=0.002$): $l^2=56\%$	Zhang et al [®]	141	416	169	408	5.7	0.73 (0.55–0.96)	_+_	
Total events 2,090 3,147 Heterogeneity: $r^2=0.01$; $r^2=19.81$, $df=12$ ($P=0.07$); $l^2=39\%$ Test for overall effect: Z=3.13 ($P=0.002$) S50 years Li et al ¹³ 189 445 199 443 6.1 0.91 (0.69–1.14) Li et al ¹³ 189 445 199 443 6.1 0.91 (0.69–1.18) Zhang et al ⁸ 100 340 141 333 5.1 0.57 (0.41–0.78) Zhang et al ⁸ 228 725 195 474 6.5 0.66 (0.52–0.84) Subtotal (95% CI) 2,491 2,154 25.5 0.77 (0.60–0.97) Total events 934 930 Heterogeneity: $r^2=0.04$; $r^2=11.41$, $df=3$ ($P=0.010$); $l^2=74\%$ Test for overall effect: Z=2.18 ($P=0.03$) NR Su et al ¹⁷ 60 136 66 144 3.1 0.93 (0.58–1.49) Su ¹⁸ 153 282 149 320 5.0 1.36 (0.99–1.88) Subtotal (95% CI) 418 464 8.2 1.17 (0.82–1.69) Total events 213 215 Heterogeneity: $r^2=0.03$; $r^2=1.69$, $df=1$ ($P=0.19$); $l^2=41\%$ Test for overall effect: Z=0.87 ($P=0.38$) Total events 3.237 4.292 Heterogeneity: $r^2=0.02$; $r^2=40.53$, $df=18$ ($P=0.002$); $l^2=56\%$ Test for overall effect: Z=3.32 ($P=0.0009$) 0.01 0.1 1 10	•		5,212		7,320		· · · ·	•	
Heterogeneity: $r^2=0.01$; $r^2=19.81$, $df=12$ ($P=0.07$); $l^2=39\%$ Test for overall effect: $Z=3.13$ ($P=0.002$) S50 years Li et al ¹³ 417 981 395 904 7.8 0.95 (0.79–1.14) Li et al ¹³ 189 445 199 443 6.1 0.91 (0.69–1.18) Zhang et al ⁸ 100 340 141 333 5.1 0.57 (0.41–0.78) Zhang et al ⁸ 228 725 195 474 6.5 0.66 (0.52–0.84) Subtotal (95% CI) 2,491 2,154 25.5 0.77 (0.60–0.97) Total events 934 930 Heterogeneity: $r^2=0.04$; $r^2=11.41$, $df=3$ ($P=0.010$); $l^2=74\%$ Test for overall effect: $Z=2.18$ ($P=0.03$) NR Su et al ¹⁷ 60 136 66 144 3.1 0.93 (0.58–1.49) Subtotal (95% CI) 418 464 8.2 1.17 (0.82–1.69) Total events 213 215 Heterogeneity: $r^2=0.03$; $r^2=1.69$, $df=1$ ($P=0.19$); $l^2=41\%$ Test for overall effect: $Z=0.87$ ($P=0.38$) Total (95% CI) 8,121 9,938 100 0.84 (0.76–0.93) Total events 3,237 4.292 Heterogeneity: $r^2=0.002$; $r^2=40.53$, $df=18$ ($P=0.002$); $l^2=56\%$ Test for overall effect: $Z=3.32$ ($P=0.0009$) 0.01 0.1 1 10	· · ·	2.090	-,	3.147	,		· · · · ·		
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Total events 3,237 4,292 Heterogeneity: r²=0.02; χ²=40.53, df=18 (P=0.002); l²=56%			0 4 9 4		0.020	400	0.94 (0.76, 0.02)		
Heterogeneity: r²=0.02; χ²=40.53, df=18 (P=0.002); l²=56% Image: heterogeneity = r²=0.02 Image: heterogeneity = r²=		2 2 2 7	ð,1∠1	4 000	9,938	100	0.04 (0.76–0.93)	•	
Test for overall effect: Z=3.32 (P=0.0009) 0.01 0.1 1 10		,	0 50 46 4	,	12-500/				
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First for subgroup differences: χ^2 =3.81, df=2 (P=0.15); l ² =47.5% Favors (experimental) Favors (control)			•	,					

Figure 4 Forest plots of the KIFIB (rs17401966) polymorphism and hepatocellular carcinoma risk in subgroup stratified by age (heterozygous genetic model, AG vs GG). Abbreviations: df, degrees of freedom; M–H, Mantel–Haenszel; NR, not reported.

to illuminate the association between KIF1B (rs17401966) polymorphism and HCC. The pooled results of our study indicated that the association was significant. Subgroup analysis stratified by ethnicity showed the same association in Chinese population, but not in non-Chinese. All the above results were consistent with the results of the meta-analysis of Zhang et al²⁷ and Wang et al.²⁸ However, the number of included papers in their analysis was less than that in our study. When stratified by age, both old and young patients showed decreased HCC risk, which was consistent with the results of Zhang et al's²⁷ study. When stratified by region (northern China, central China, southern China), we detected an association between KIF1B (rs17401966) polymorphism and decreased HCC risk in Chinese in southern China.

When stratified by environment (inland areas, coastal areas), we observed the same association in Chinese in Inland areas; however, no statistically significant association was observed in those in coastal areas. It was the first subgroup analysis on Chinese population stratified by region and environment.

Zhang et al²⁷ also performed subgroup analysis by gender and found that KIF1B rs17401966 polymorphism was significantly associated with HCC in men but not in women. However, the number of papers from which gender data were extracted for their study was only five, and the sample size of women was extremely small. Therefore, we should interpret the results of their study with caution. Zhang et al²⁷ also performed subgroup analysis based on sample sizes and quality scores and found that rs17401966 polymorphism was

Study or subgroup	Case events	Total	Control events	Total	Weight (%)	OR M–H, random, 95% C	OR M–H, I random, 95% CI
Northern China							
Chen et al9	194	440	309	707	7.6	1.02 (0.80–1.29)	• +
Zhang et al ⁸	86	271	109	242	5.4	0.57 (0.40-0.81)	·
Subtotal (95% CI)		711		949	13	0.77 (0.44–1.36)	
Total events	280		418				
Heterogeneity: $\tau^2=0$			P=0.008); I ² :	=86%			
Test for overall effe	ct: Z=0.89	(P=0.37)					
Central China							
Hu et al ¹¹	480	1,186	1,038	2,440	9.8	0.92 (0.80–1.06)	• -
Jiang et al ¹²	458	1,077	546	1,247	9.3	0.95 (0.81–1.12)	• •
Li et al13	189	445	199	443	7.1	0.91 (0.69–1.18)) -
Pan et al ¹⁴	138	342	167	350	6.4	0.74 (0.55–1.00)	·
Su et al ¹⁷	60	136	66	144	3.9	0.93 (0.58–1.49))
Su ¹⁸	153	282	149	320	6.1	1.36 (0.99–1.88)) -
Zhang et al ⁸	181	481	101	194	5.8	0.56 (0.40-0.78)	·
Zhang et al ⁸	141	416	169	408	6.8	0.73 (0.55–0.96)	·
Subtotal (95% CI)		4,365		5,546	55.1	0.87 (0.75-1.00)	•
Total events	1,800		2,435				
Heterogeneity: $\tau^2=0$ Test for overall effe			(P=0.010); I	² =62%			
Southern China							
Chen et al ¹⁰	126	285	138	288	5.9	0.86 (0.62-1.20)	·
Li et al13	417	981	395	904	8.9	0.95 (0.79-1.14)	
Sawai et al15	39	83	80	174	3.4	1.04 (0.62-1.76)	
Zhang et al8	100	340	141	333	6.1	0.57 (0.41-0.78)	
Zhang et al ⁸	228	725	195	474	7.6	0.66 (0.52–0.84)	
Subtotal (95% CI)		2,414		2,173	31.9	0.78 (0.63-0.98)	\bullet
Total events	910	•	949			. ,	•
Heterogeneity: $\tau^2=0$).04; χ²=11	.74, df=4 (P=0.02); I ² =	=66%			
Test for overall effe	ct: Z=2.15	(P=0.03)					
Total (95% CI)		7,490		8,668	100	0.83 (0.74–0.93)	•
Total events	2.990	.,	3.802	2,223			*
Heterogeneity: $\tau^2=0$,).22. df=14	-,): /²=64%			
Test for overall effe				,,. 0.70			0.01 0.1 1 10 10
Test for subgroup d				2): /²=0%			
		λ 0.00, (_,,. 070			Favors (experimental) Favors (control)

Figure 5 Forest plots of the KIFIB (rs17401966) polymorphism and hepatocellular carcinoma risk in subgroup stratified by region (heterozygous genetic model, AG vs GG). Abbreviations: df, degrees of freedom; M–H, Mantel–Haenszel.

significantly associated with reduced HCC risk in studies with large sample size and of high quality; however, no significant associations were found in studies with small sample size and of low quality. However, we should realize that small sample sizes and low-quality scores were sources for this heterogeneity, so subgroup analyses stratified by sample sizes and quality scores may not be appropriate.

Nevertheless, some limitations of our meta-analysis should be addressed. First, we could not obtain all the raw data of the patients and hence could not conduct subgroup analysis by sex, hepatitis, liver function and other variables. We also failed to clarify gene–gene and gene–environment interactions in the occurrence and development of HCC. Second, only published studies were included in this metaanalysis; however, some unpublished papers may exist and conform to our inclusion criteria. Therefore, publication bias may have appeared, although no statistical evidence was found. Third, our research is only a comprehensive analysis of existing data. We did not verify the association through basic experiments. Moreover, the included papers were mostly based on Chinese population; only four papers were about non-Chinese. Therefore, data from large-scale multicenter studies based on non-Chinese population are still needed to confirm the association between KIF1B (rs17401966) polymorphism and HCC.

Conclusion

Our meta-analysis indicates that KIF1B (rs17401966) polymorphism could decrease HCC risk in Chinese and in overall population, but not in non-Chinese. This association remained significant in Chinese in southern China and inland areas, but not in those in northern or central China and in coastal areas. Further large-scale multicenter studies are warranted to confirm our findings.

Study or subgroup	Case events	Total	Control events	Total	Weight (%)	OR M–H, random, 95% Cl	OR M–H, random, 95% Cl
Inland areas							
Chen et al ⁹	194	440	309	707	7.6	1.02 (0.80-1.29)	+
Hu et al ¹¹	480	1,186	1,038	2,440	9.8	0.92 (0.80-1.06)	-
Jiang et al ¹²	458	1,077	546	1,247	9.3	0.95 (0.81-1.12)	-
Zhang et al ⁸	100	340	141	333	6.1	0.57 (0.41-0.78)	
Zhang et al ⁸	86	271	109	242	5.4	0.57 (0.40-0.81)	_ _ _
Zhang et al ⁸	181	481	101	194	5.8	0.56 (0.40-0.78)	_ —
Subtotal (95%	CI)	3,795		5,163	43.9	0.77 (0.63-0.94)	◆
Total events	1,499		2,244				
Heterogeneity:	$\tau^2 = 0.05; \chi^2$	=22.18, <i>df</i>	=5 (P=0.000	5); /²=77%			
Test for overall	effect: Z=2.	58 (<i>P</i> =0.0	10)				
Coastal areas							
Chen et al ¹⁰	126	285	138	288	5.9	0.86 (0.62-1.20)	
Li et al ¹³	417	981	395	904	8.9	0.95 (0.79–1.14)	-
Li et al ¹³	189	445	199	443	7.1	0.91 (0.69–1.18)	
Pan et al ¹⁴	138	342	167	350	6.4	0.74 (0.55–1.00)	
Sawai et al ¹⁵	39	83	80	174	3.4	1.04 (0.62–1.76)	
Su et al ¹⁷	60	136	66	144	3.9	0.93 (0.58–1.49)	
Su ¹⁸	153	282	149	320	6.1	1.36 (0.99–1.88)	
Zhang et al ⁸	228	725	195	474	7.6	0.66 (0.52-0.84)	
Zhang et al ⁸	141	416	169	408	6.8	0.73 (0.55–0.96)	
Subtotal (95%	S CI)	3,695		3,505	56.1	0.87 (0.75–1.01)	•
Total events	1,491		1,558				
Heterogeneity:	τ ² =0.02; χ ²	=16.97, <i>df</i>	=8 (P=0.03);	l²=53%			
Test for overall	effect: Z=1.	85 (<i>P</i> =0.0	6)				
Total (95% CI))	7,490		8,668	100	0.83 (0.74–0.93)	•
Total events	2,990		3,802				
Heterogeneity:	τ ² =0.03; χ ²	=39.22, df	=14 (P=0.00	03); /²=64%	6		⊢
Test for overall			,				0.01 0.1 1 10
Test for subgro	oup difference	es: χ ² =1.0)4, <i>df</i> =1 (<i>P</i> =0	.31); /2=3.0	5%		Favors (experimental) Favors (control)

Figure 6 Forest plots of the KIFIB (rs17401966) polymorphism and hepatocellular carcinoma risk in subgroup stratified by environment (heterozygous genetic model, AG vs GG).

Abbreviations: df, degrees of freedom; M-H, Mantel-Haenszel.



Figure 7 Funnel plot assessing evidence of publication bias from 19 studies (heterozygous genetic model, AG vs GG). Abbreviation: SE, standard error.

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Disclosure

The authors report no conflicts of interest in this work.

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