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ASSOCIATION BETWEEN *XPO5* rs11077 POLYMORPHISM AND CANCER SUSCEPTIBILITY: A META-ANALYSIS OF 7284 CASES AND 8511 CONTROLS

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Aim: **Several studies evaluated the association between rs11077 polymorphism located in the 3'UTR of the *XPO5* gene and cancer susceptibility. We conducted a meta-analysis to assess the impact of *XPO5* rs11077 polymorphism on cancer risk.** ***Materials and Methods:*** **The online databases were searched for relevant case-control studies published up to July 2018. 15 articles of 16 studies, with totally 7284 cancer cases and 8511 healthy controls, were eligible for inclusion in the meta-analysis. The data were extracted from the eligible studies and were processed using Stata 14.1 and Revman 5.3 software. Pooled estimates of odds ratio with 95% confidence intervals were used to evaluate the strength of association between XPO5 rs11077 and cancer risk.** ***Results*****: Overall, our finding showed no significant association between *XPO5* rs11077 variant and overall cancer risk, either performed subgroup analysis by cancer types and ethnic groups in all genetic model.** ***Conclusion:*** **The findings did not support an association between *rs11077* variant and cancer risk. Due to small sample sizes particularly in stratified analysis, further large-scale well designed studies between this polymorphism and cancer risk are warranted.**

Key Words: **XPO5, meta-analysis, cancer, risk.**

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Cancer is a leading cause of mortality worldwide [1, 2]. There were about 4 292 000 newly-diagnosed cancer cases and 2 814 000 cancer-related deaths in United States in 2017. Although the etiology of cancer is still not clearly disclosed, genetic background and environmental factors are believed to be involved in cancer development [3, 4].

MicroRNAs (miRNAs), as regulators of gene expression, are small single-stranded RNA molecules of about 21–23 nucleotides [5, 6]. The biosynthesis of a functional miRNA involves several miRNA biogenesis genes and occurs in multiple steps [7]. The process of miRNA synthesis begins within the nucleus where RNA polymerase II produces large primary miRNA transcripts (about 500 to 3000 nucleotides) known as pri-miRNA. The pri-miRNA is then processed by multiprotein complex that includes DROSHA into pre-miRNA (about 60 to 100 nucleotides). Next, RAN GTPase and exportin-5 (XPO5) complex transfers pre-miRNA to the cytoplasm, and pre-miRNA is then cut into miRNA duplexes by DICER [6, 8] finally forming 18–24 nucleotide single-stranded, mature miRNA [8, 9].

In general, polymorphisms in miRNA processing genes as well as miRNA genes (pri-miRNAs, pre-miRNAs and mature miRNAs) could influence cancer risk by affecting miRNA function [10].

Preceding studies examining the relationship between *XPO5* rs11077 gene polymorphism and cancer designated inconclusive findings [11–25]. So, this meta-analysis was performed to evaluate the impact of *XPO5* rs11077 polymorphism on cancer risk.

MATERIALS AND METHODS

Literature search. A systemic literature searches in the PubMed, Web of Science, Scopus, and Google Scholar databases was done for all articles focused on association between *XPO5* polymorphism and cancer risk published up to June 2018. The search term was "cancer or carcinoma or tumor or neoplasm" and "*XPO5* or exportin-5 or miRNA biogenesis" and "polymorphism or mutation or variation or rs11077".

Inclusion and exclusion criteria*. Studies* were comprised in the *meta-analysis* by *meeting the following criteria*: 1) original case-control studies of the association between the *XPO5* rs11077 polymorphism and cancer; 2) studies providing sufficient data of the genotype frequencies of *XPO5* rs11077 polymorphism in both cases and controls; 3) the studies have not repeated reports in the same population. The following studies were excluded: 1) conference abstracts, letters, case reports, reviews, overlapped data, animal or mechanism studies for *XPO5* rs11077 polymorphism and cancer; 2) studies with insufficient information on genotype frequency. Finally, 15 articles were considered for meta-analysis.

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Abbreviation used: miRNAs — microRNAs; SNP – single nucleotide polymorphisms; XPO5 – exportin-5.

Data extraction. The authors independently extracted data that met the inclusion and exclusion criteria. The following information was collected from each study including the name of first author, year of publication, country, ethnicity, number of cases and controls, and the genotype and allele frequencies of cases and controls.

Statistical analysis. Hardy-Weinberg equilibrium (HWE) for the controls of each study was determined by the chi-square test. We used Revman 5.3 software (Version 5.3. Copenhagen: The Nordic Cochrane Centre, the Cochrane Collaboration, 2014) and STATA 14.1 software (Stata Corporation, College Station, TX, USA) for all statistical analyses and to produce the plots. The strength of the association between *XPO5* rs11077 polymorphism and cancer risk was evaluated through calculating pooled odds ratios (ORs) with the corresponding 95% confidence intervals (95% CIs) using following genetic models: codominant, dominant, recessive, overdominant and allele model. The significance of the pooled OR was determined with the Z-test, and *p*-values less than 0.05 were considered statistically significant.

Heterogeneity between selected studies was inspected using the I^2 statistic and the χ^2-based Q test. A $p < 0.10$ representing the presence of significant heterogeneity. When significant heterogeneity values were returned, the random-effects model was used to estimate pooled ORs. Otherwise, the fixed-effects model was employed.

Publication bias across enrolled studies was estimated by Begg's funnel plot. The degree of asymmetry was assessed using Egger's linear regression test and $p < 0.05$ was considered significant publication bias.

Sensitivity analysis was conducted through sequential deleting each of included studies so as to verify the stability of overall estimates.

RESULTS

Fifteen articles [11–25] of 16 studies, with totally 7284 cancer cases and 8511 controls, were eligible for meta-analysis. The main detailed characteristics of the eligible studies are listed in Table 1.

Quantitative synthesis. All eligible studies were pooled into the analysis and the results showed that *XPO5* rs11077 polymorphism was not associated with the overall cancer risk in codominant, dominant, recessive, overdominant, and allele genetics models (Fig. 1 and Table 2).

We also performed stratified analysis by cancer type and ethnicity (see Table 2). The findings proposed that *XPO5* rs11077 was not associated with gastrointestinal cancer, breast cancer and lung cancer. Besides, the variant was not associated with cancer risk in Asian as well as Caucasian population.

Table 1. Characteristics of the studies eligible for meta-analysis

Author	Year	Country	Ethnicity	Cancer type	Source of control	Genotyping method	Case/ control	Cases					Controls					HWE
								AA	AC	CC	A	C	AA	AC	CC	A	C	
Buas	2015	Europe	Caucasian	Esophageal cancer	HB	TaqMan	2495/3206	–	–	–	2879	2111	–	–	–	3751	2661	–
Cho	2015	Korea	Asian	Colorectal cancer	HB	PCR-RFLP	408/400	333	74	1	740	76	337	61	2	735	65	0.667
Ding	2013	China	Asian	Non-small cell lung cancer		PCR-LDR	112/80	94	18	0	206	18	65	14	1	144	16	0.803
Horikawa	2008	USA	Caucasians	Renal cell carcinoma	HB	SNPlex	276/277	88	134	54	310	242	89	150	38	328	226	0.044
Kim	2010	Korea	Asian	Lung cancer	HB	Sequencing	100/99	88	12	0	188	12	87	9	3	183	15	< 0.001
Kim	2016	China	Asian	Hepatocellular carcinoma	HB	PCR-RFLP	147/209	128	19	0	275	19	170	38	1	378	40	0.465
Osuch-Wojcikiewicz	2015	Poland	European	Larynx cancer	HB	TaqMan	124/160	36	62	26	134	114	34	44	82	112	208	< 0.001
Sung	2011	Korea	Asian	Breast cancer	HB	TaqMan	559/567	473	82	4	1028	90	501	64	2	1066	68	0.977
Thakkar	2018	India	Asian	Hodgkin Lymphoma	PB	TaqMan	101/200	39	41	21	119	83	76	92	32	244	156	0.638
Wen	2017	China	Asian	Thyroid cancer	HB	TaqMan	1134/1228	907	210	17	2024	244	1023	194	11	2240	216	0.593
Xie	2015	China	Asian	Gastric cancer	HB	PCR-LDR	137/142	119	17	1	255	19	123	18	1	264	20	0.705
Yang	2008	American	Caucasian	Bladder cancer	HB	SNPlex	746/746	248	356	114	852	584	241	363	122	845	607	0.456
Yao	2013	USA	African American	Breast cancer	PB	Illumina GoldenGate	242/411	39	203		–	–	45	214	152	304	518	0.018
Yao	2013	USA	European American	Breast cancer	PB	Illumina GoldenGate	200/310	76	124		–	–	127	130	53	384	236	0.052
Ye	2008	American	Caucasian	Esophageal cancer	HB	SNPlex	340/334	129	150	61	408	272	113	175	46	401	267	0.093
Zhao	2015	China	Asian	Colorectal cancer	HB	PCR-LDR	163/142	143	19	1	305	21	123	18	1	264	20	0.705

Heterogeneity. Heterogeneity among the studies included in the meta-analysis is shown in Table 2. The results showed that heterogeneity exists between the studies in homozygous codominant, recessive, over-dominant and allele genetic models. So, random-effects model was used to determine pooled ORs.

Publication bias. A funnel plot was created as a visual aid to detect risk of publication bias (Fig. 2). Egger's linear regression test and Begg's test proposed no publication bias in all genetic model tested (see Table 2).

Sensitivity analysis. Sensitivity analysis was done and the findings revealed that our data are stable and reliable in all inheritance genetic models tested (Fig. 3).

DISCUSSION

The etiology of cancer is multifactorial in which both host genetic factors and environmental factors play a role [26, 27]. Accumulating evidence proposed that genetic variation is associated with cancer susceptibility [4, 28]. In this study, we conducted a meta-analysis to evaluate the association between

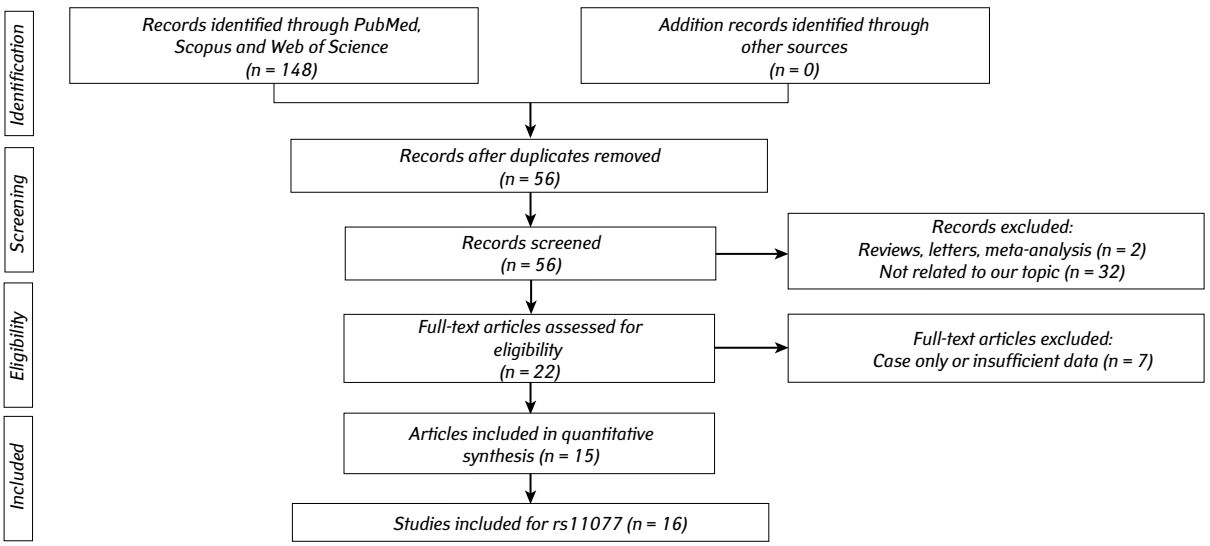

Fig. 1. Flow chart of articles selection for this meta-analysis

Table 2. The pooled ORs and 95% CIs for the association between *XPO5* polymorphism and cancer susceptibility

Polymorphism	No	Association test			Heterogeneity			Egger's test *p*-value	Begg's test *p*-value
		OR (95% CI)	Z	*p*	χ^2	I^2 (%)	*p*		
Overall cancer									
AC *vs* AA	13	1.04 (0.93–1.15)	0.64	0.52	13.72	13	0.32	0.515	1.00
CC *vs* AA	13	0.96 (0.68–1.36)	0.23	0.82	22.49	47	0.03	0.916	0.929
AC+CC *vs* AA	13	1.02 (0.92–1.12)	0.33	0.75	18.82	26	0.17	0.101	0.347
CC *vs* AC+AA	13	0.95 (0.62–1.46)	0.24	0.81	38.13	69	0.0001	0.940	0.531
AC *vs* CC+AA	13	1.04 (0.87–1.25)	0.45	0.65	30.80	61	0.002	0.983	0.542
C *vs* A	14	0.99 (0.88–1.12)	0.14	0.89	34.61	62	0.001	0.423	0.208
GI cancer									
AC *vs* AA	5	0.90 (0.73–1.10)	1.03	0.30	4.87	18	0.30	–	–
CC *vs* AA	5	1.10 (0.71–1.70)	0.43	0.67	0.80	0	0.94	–	–
AC+CC *vs* AA	5	9.92 (0.76–1.13)	0.77	0.44	3.80	0	0.43	–	–
CC *vs* AC+AA	5	1.29 (0.87–1.92)	1.25	0.21	1.18	0	0.88	–	–
AC *vs* CC+AA	5	0.88 (0.68–1.14)	0.98	0.33	5.79	31	0.22	–	–
C *vs* A	6	1.03 (0.96–1.10)	0.74	0.46	3.11	0	0.68	–	–
Breast cancer									
C *vs* A	3	1.05 (0.87–1.25)	0.49	0.63	3.96	50	0.14	–	–
Lung cancer									
AC *vs* AA	2	1.05 (0.58–1.88)	0.16	0.88	0.42	0	0.52	–	–
CC *vs* AA	2	0.18 (0.02–1.58)	1.55	0.12	0.05	0	0.82	–	–
AC+CC *vs* AA	2	0.90 (0.51–1.58)	0.38	0.70	0.09	0	0.76	–	–
CC *vs* AC+AA	2	0.18 (0.02–1.56)	1.56	0.12	0.06	0	0.81	–	–
AC *vs* CC+AA	2	0.75 (0.47–1.20)	1.21	0.23	0.37	0	0.54	–	–
C *vs* A	2	0.78 (0.46–1.32)	0.91	0.36	0.00	0	0.99	–	–
Asian									
AC *vs* AA	9	1.14 (0.99–1.31)	1.80	0.07	6.75	0	0.56	–	–
CC *vs* AA	9	1.21 (0.78–1.86)	0.86	0.39	5.29	0	0.73	–	–
AC+CC *vs* AA	9	1.14 (1.0–1.31)	1.93	0.05	7.30	0	0.50	–	–
CC *vs* AC+AA	9	1.24 (0.82–1.87)	1.01	0.31	5.20	0	0.74	–	–
AC *vs* CC+AA	9	1.12 (0.98–1.29)	1.63	0.10	7.55	0	0.48	–	–
C *vs* A	9	1.06 (1.00–1.13)	1.87	0.06	9.55	16	0.30	–	–
Caucasian									
AC *vs* AA	3	0.89 (0.75–1.05)	1.39	0.16	1.34	0	0.51	–	–
CC *vs* AA	3	1.08 (0.83–1.40)	0.57	0.57	2.48	19	0.29	–	–
AC+CC *vs* AA	3	0.93 (0.79–1.09)	0.93	0.35	0.66	0	0.72	–	–
CC *vs* AC+AA	3	1.20 (0.87–1.65)	1.13	0.26	4.31	0.54	0.12	–	–
AC *vs* CC+AA	3	0.85 (0.70–1.04)	1.59	0.11	3.16	37	0.21	–	–
C *vs* A	4	1.02 (0.96–1.09)	0.72	0.47	1.66	0	0.65	–	–

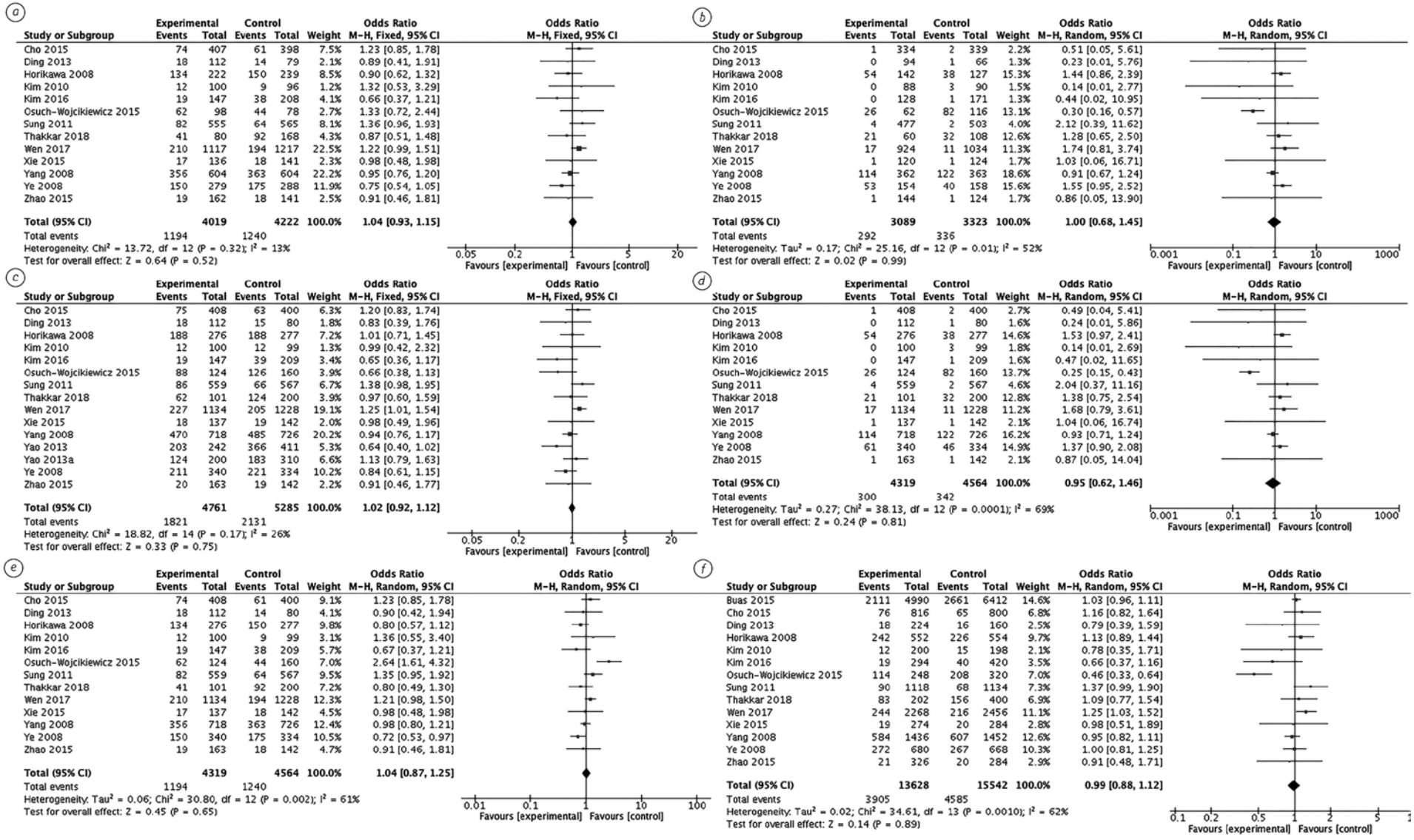

Fig. 2. Forest plots of the association between *XPO5* rs11077 A>C polymorphism and cancer risk in the overall study population under the following models: *a* — AC *vs* AA, *b* — CC *vs* AA, *c* — AC+CC *vs* AA, *d* — CC *vs* AC+AA, *e* — AC *vs* AA+CC, and *f* — C *vs* A

XPO5 rs11077 gene polymorphism and cancer risk based on 16 eligible case-control studies with a total of 7284 cancer cases and 8511 healthy controls. Overall, pooled risk estimates proposed that this polymorphism is not associated with cancer risk. Stratified analyses by cancer types and ethnicities did not support an association between rs11077 polymorphism and cancer susceptibility.

Preceding studies examining the association between *XPO5* rs11077 gene polymorphism and cancer indicated inconclusive results [11–25]. A genome-wide association study conducted by Buas *et al*. [11] on miRNA biogenesis genes (157 single nucleotide polymorphisms (SNPs), 21 genes); miRNA gene loci (234 SNPs, 210 genes); and miRNA-targeted mRNAs (177 SNPs, 158 genes) showed no significant association between *XPO5* rs11077 A>C polymorphism and risk of esophageal adenocarcinoma. Cho *et al.* [12] revealed no significant association between *XPO5* rs11077 and colorectal cancer risk in Korean population. Horikawa *et al.* [14] have found no significant correlation between rs11077 variant and risk of renal cell carcinoma. No significant association between rs11077 variant and risk of lung cancer, hepatocellular carcinoma, non-small cell lung cancer were found [13–16]. Osuch-Wojcikiewicz *et al.* [17] have found that rs11077 variant is associated with the risk of laryngeal cancer in Polish population. Sung *et al.* [18] have found no significant association between rs11077 variant and risk of breast cancer in Korean population. The rs11077 variant was found to be associated with increased risk of thyroid cancer [19]. No significant

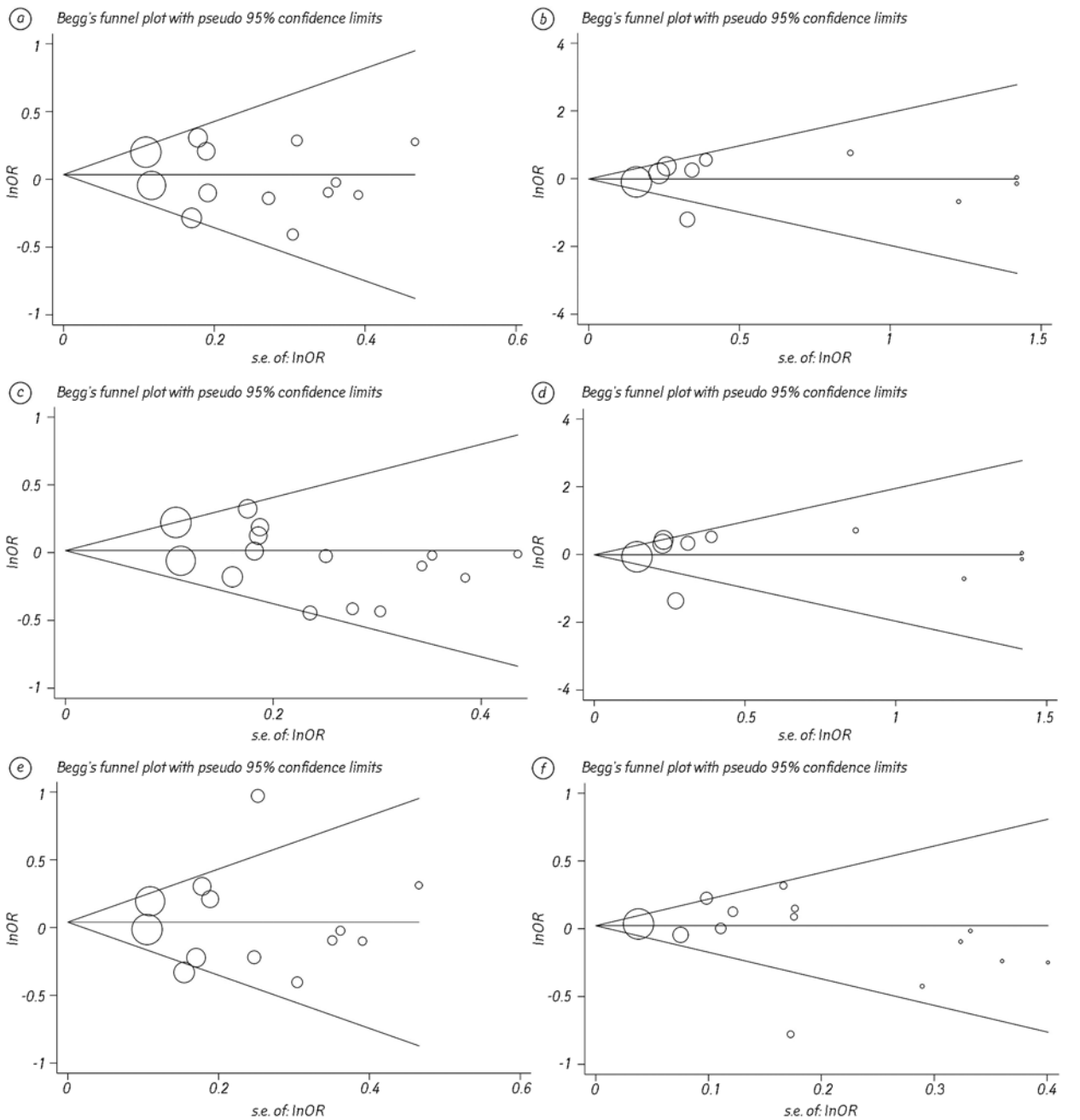

Fig. 3. Funnel plots of the association between cancer risk and *XPO5* rs11077 A>C polymorphism in the overall study population under the following models: *a* — AC *vs* AA, *b* — CC *vs* AA, *c* — AC+CC *vs* AA, *d* — CC *vs* AC+AA, *e* — AC *vs* AA+CC, and *f* — C *vs* A

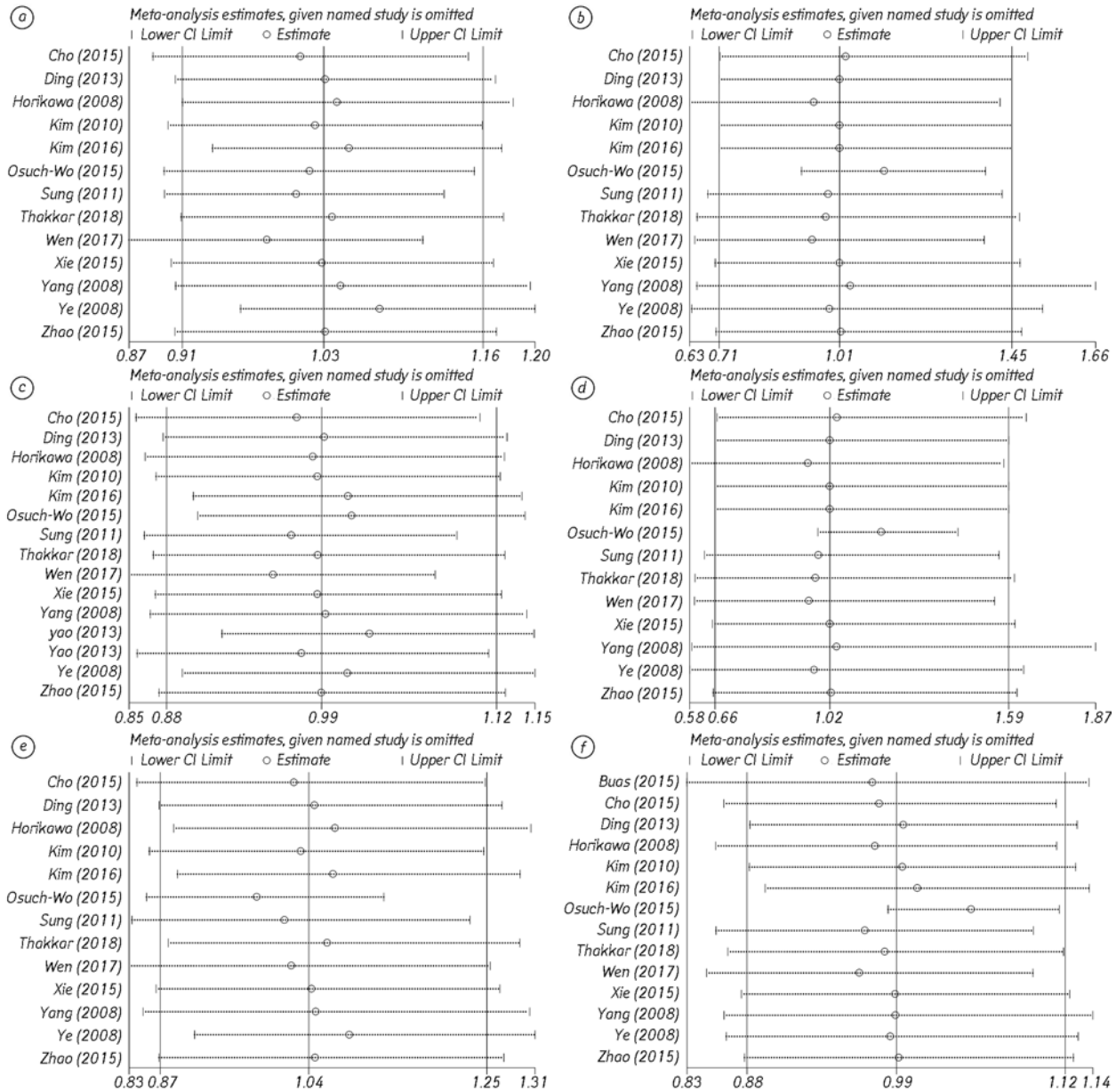

Fig. 4. Sensitivity analyses for studies on *XPO5* rs11077 A>C using different genetic models; *a* — AC *vs* AA, *в* — CC *vs* AA, *c* — AC+CC *vs* AA, *d* — CC *vs* AC+AA, *e* — AC *vs* AA+CC, and *f* — C *vs* A

association between rs11077 variant and risk of gastric cancer was observed in Chinese population [20]. Yang *et al.* [21] findings revealed no significant association between rs11077 polymorphism and bladder cancer in American population. Ye *et al*. [22] reported that rs11077 variant significantly increased the risk of esophageal cancer.

XPO5 gene is mapped to a short arm of chromosome 6 (6p21.1) and encodes XPO5 protein which is involved in export of pre-miRNA from nucleus into the cytoplasm. Hoti *et al.* [29] reported that a *XPO5* knockdown resulted in downregulation of 20 mature miRNAs and overexpression of six miRNAs.

Several studies evaluated the expression levels of *XPO5* in various cancers and the findings were controversial. The expression levels of *XPO5* were found to be higher in several tumors including breast, ovary, prostate, bladder, and melanoma compared to the normal adjacent tissues, while the lower expression level of *XPO5* in kidney, adrenal gland, and hepatocellular carcinoma tumors proposing oncogenic or tumor-suppressor features in different cancer types [29–32].

There are some limitations in our meta-analysis needed to be addressed. First, heterogeneity was observed among the studies possibly resulting from the differences of ethnicity, source of control, and cancer type. Second, this study focused on the effect of rs11077 polymorphism and cancer risk. Gene-gene and gene-environment interactions might also impact in cancer risk. Third, the characteristics of included studies such as age and sex which might affect the results of meta-analysis were not evaluated due to the lack of relevant data across the included studies. Fourth, the majority of the individuals studied were Asian, further studies on other ethnicity groups are needed. Finally, the sample size of our meta-analysis is relatively small espe-

cially in subgroup analyses by cancer types (5 studies for gastrointestinal cancer, 3 studies for breast cancer, and 2 studies for lung cancer) and ethnicities (9 studies for Asian and 3 studies for Caucasian). Accordingly, the statistical power of the study is limited and the results should be interpreted with caution.

In conclusion, the results of our meta-analysis based on 16 case-control studies suggested that there is no significant association between the *XPO5* rs11077 polymorphism and cancer risk. Statistical power can be improved by pooling analysis from more studies. Considering the limitations mentioned above, further well-designed multicenter studies with large sample sizes, more diverse ethnic groups and cancer types are warranted to verify the findings.

CONFLICT OF INTEREST

The authors have declared that no competing interests exist.

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