Technology in Cancer Research & Treatment
Volume 21: 1-19
© The Author(s) 2022
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/15330338221123109
journals.sagepub.com/home/tct
SAGE

Susceptibility of *TNFAIP8*, *TNFAIP8L1*, and *TNFAIP2* Gene Polymorphisms on Cancer Risk: A Comprehensive Review and Meta-Analysis of Case–Control Studies

Khokon Kanti Bhowmik, MPharm[1,2], Md Abdul Barek, MPharm[1,2], Md. Abdul Aziz, MPharm[3], and Mohammad Safiqul Islam, PhD[1,2]

Abstract

Objectives: The *TNFAIP8* gene family and *TNFAIP2* gene are inextricably linked to an elevated risk of cancer development. This systemic review and meta-analysis seeks to establish the relationship between *TNFAIP8* (rs11064, rs1045241, rs1045242, and rs3813308), *TNFAIP8L1* (rs1060555), and *TNFAIP2* (rs710100 and rs8126) polymorphisms with the risk of cancer. **Methods and Materials:** A systematic search of multiple databases from January 2022 to April 2022 was used to identify relevant studies. Odds ratios (ORs) with corresponding 95% CI and *p*-value were calculated to assess the association. Bonferroni correction was performed to correct *p*-values. Trial sequential analysis (TSA) and *in-silico* messenger RNA expression were also performed. Review Manager 5.4 software was used for performing this meta-analysis. **Results:** This study comprised 6909 cancer patients and 7087 healthy participants from 14 studies. Four genetic models of rs11064 (codominant 2 [COD2]: OR = 2.30, $p = 7.83 \times 10^{-5}$; codominant 3 [COD3]: OR = 2.10, $p = .0006$; recessive model [RM]: OR = 2.24, $p = .0001$; AC: OR = 1.47, $p = .037$), two genetic models of rs1045241 (codominant 1 [COD1]: OR = 1.27, $p = .009$; overdominant model [ODM]: OR = 1.24, $p = .018$), four genetic models of rs1045242 (COD1: OR = 1.52, $p = .005$; dominant model (DM): OR = 1.56, $p = .002$; OD: OR = 1.48, $p = .008$; AC: OR = 1.48, $p = .002$), and three genetic models of rs8126 (COD2: OR = 1.41, $p = .0005$; COD3: OR = 1.44, $p = .0002$; RM: OR = 1.43, $p = .0001$) were statistically linked to cancer risk. Only one genetic model of rs1060555 polymorphism showed a significant protective association with cancer (COD2: OR = 0.80, $p = .048$). The outcomes of TSA also validated the findings of the meta-analysis. **Conclusion:** This study summarizes that rs11064, rs1045241, and rs1045242 polymorphisms of *TNFAIP8* gene and rs8126 polymorphism of *TNFAIP2* gene are significantly linked with the risk of cancer development. This meta-analysis was registered at INPLASY (registration number: INPLASY202270073).

Keywords

TNFAIP8, *TNFAIP8L1*, *TNFAIP2*, polymorphism, meta-analysis

Abbreviations

AM, allele model; CI, confidence interval; COD1, codominant 1; COD2, codominant 2; COD3, codominant 3; DM, dominant model; mRNA, messenger RNA; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor kappa B; NOS, Newcastle–Ottawa scale; ODM, overdominant model; OR, odds ratio; RM, recessive model; SNP, single nucleotide polymorphism; TNF-α, tumor necrosis factor-alpha; *TNFAIP8*, tumor necrosis factor, alpha-induced protein 8; *TNFAIP8L1*, tumor necrosis factor, alpha-induced protein 8 like 1; *TNFAIP2*, tumor necrosis factor, alpha-induced protein 2; UTR, untranslated region.

Introduction

Cancer is one of the major public health crises at present, claiming more than 10 million lives with 19.3 million new incidences in 2020.[1] Increasing numbers of people are being diagnosed with cancer every day, and by 2040, global cancer-related deaths are estimated to touch 28 million.[1] Compared to developed countries, the status of cancer in developing countries may be more serious. Several genetic, epigenetic, and environmental risk factors

[1] Department of Pharmacy, Noakhali Science and Technology University, Noakhali, Bangladesh
[2] Laboratory of Pharmacogenomics and Molecular Biology, Department of Pharmacy, Noakhali Science and Technology University, Noakhali, Bangladesh
[3] Department of Pharmacy, State University of Bangladesh, Dhaka, Bangladesh

Corresponding Author:
Mohammad Safiqul Islam, Department of Pharmacy, Noakhali Science and Technology University, Noakhali-3814, Bangladesh.
Email: research_safiq@yahoo.com

contribute to cancer, including poor diet, lack of regular physical activity, smoking, use of oral contraceptives, exposure to ultraviolet radiation, and hormonal imbalance.[2] Because of the increasing frequency of cell divisions in mammals, there is an increased likelihood of genetic anomalies that also contribute to malignancy.[3,4]

Tumor necrosis factor-α induced protein 8 (TNFAIP8/TIPE) is a potent suppressor of TNF-α-mediated apoptosis, which is activated by nuclear factor kappa B (NF-κB).[5] TNFAIP8 is a protein family with four known members that convey high degrees of sequence homology and are critical regulators of immunological homeostasis, inflammation, cancer development, proliferation, and cell death. Moreover, its expression is elevated in numerous types of cancers. It has been found that the messenger RNA (mRNA) and protein for TNFAIP8 are highly concentrated in a wide variety of malignancies such as bladder, blood, bone, breast, cervix, colon, esophagus, endometrium, stomach, liver, lung, ovary, pancreas, prostate, and thyroid glands.[6]

Among the members, TNFAIP8 is the first discovered protein of this family, which is thought to be correlated with tumorigenesis. Oncogenesis has been linked to the TNFAIP8 death effector domain, which is capable of inhibiting caspase-mediated apoptosis. Moreover, TNF-α-induced caspase activation and apoptosis are inhibited by the TNFAIP8. Three single nucleotide polymorphisms (SNPs), including rs11064, rs1045241, and rs1045242 of the *TNFAIP8* gene, are present in the 3′-untranslated region (3′-UTR) region, which act as a binding site for microRNAs (miRNAs) to regulate gene expression, whereas rs3813308 C > G variant resides in the 5′-flanking region of the *TNFAIP8* gene.

The signaling molecule tumor necrosis factor, alpha-induced protein 8 like 1 (TNFAIP8L1), a *TNFAIP8* gene family member, has antiapoptotic and prooncogenic properties, which are critical in developing tumors and the immune system's ability to fight cancer. The variant rs1060555 is localized in the 3′-UTR of the *TNFAIP8L1* gene on chromosome 19.[7] Moreover, it is a vital polymorphism for developing various gynecological cancers, including breast and cervical cancers.[8–11]

Chromosome 14q32 contains the tumor necrosis factor, alpha-induced protein 2 (*TNFAIP2*) gene, which encodes 654 amino acid residues, and more than 13,000 nucleotides of *TNFAIP2* are encoded by its 11 exons and 10 intergenic regions.[12] TNF-α induces human endothelial cells to produce more of the *TNFAIP2* gene, a consequential responder to the B94 protein.[13] When *TNFAIP2* was coimmunoprecipitated with actin, it was found to be involved in producing actin-based protrusions in nasopharyngeal carcinoma-TW02 cells.[14,15] SNP rs8126 T > C was found to be located in the miR-184 binding region and rs710100 G > A was found to be located in the miR-155 binding area of the *TNFAIP2* gene, and studies showed that human cancer risk could be linked to these SNPs.[13,16]

One of the most effective methods of reducing cancer burden is early identification and treatment, tobacco and alcohol management, vaccination injection, and a balanced diet of fruits and vegetables.[17] A few studies have looked at the relationship between *TNFAIP8* (rs11064, rs1045241, rs1045242, and rs3813308), *TNFAIP8L1* (rs1060555), and *TNFAIP2* (rs710100 and rs8126) gene polymorphisms and cancer risk. However, these results were ambiguous and conflicting. This meta-analysis aimed to determine whether or not these variants are associated with the risk of cancer.

Methods and Materials

The present meta-analysis was performed following the updated guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2020.[18] We have also registered the meta-analysis at the International Platform for Registration of Systematic Review and Meta-analysis Protocols (INPLASY; available at https://inplasy.com/, registration number: INPLASY202270073).

Literature Search Strategy

PubMed, Science Direct, Google Scholar, EMBASE, and CNKI databases were explored for related articles using designated key phrases spanning from January 2022 to April 2022. Key phrases include: "cancer," "*TNFAIP8*," "*TNFAIP8L1*," "*TNFAIP2*," "*TNFAIP2* polymorphisms and cancer," "*TNFAIP8L1* polymorphisms and cancer," "*TNFAIP8* polymorphisms and cancer," "rs11064 and cancer," "rs1045241 and cancer," "rs1045242 and cancer," "rs3813308 and cancer," "rs1060555 and cancer," "rs710100 and cancer," and "rs8126 and cancer." There was no language restriction for including the studies.

Selecting Literature and Assessing Eligibility

Two authors (KKB and MAB) searched and selected publications from databases and conducted an extensive assessment of titles, abstracts, and full-text of articles to determine their eligibility for inclusion in a meta-analysis. The PRISMA flow diagram depicts the entire procedure of study selection (Figure 1). Another 2 authors (MAA and MSI) solved any disputes concerning the literature selection.

Only the studies that investigated *TNFAIP8* (rs11064, rs1045241, and rs1045242), *TNFAIP8L1* (rs1060555), and *TNFAIP2* (rs710100, rs8126) gene polymorphisms and cancer risk were included. To corroborate the association, every study must provide information on one of the specified SNPs. Furthermore, studies must contain genotypic and allelic frequencies of both cases and controls and an odds ratio (OR) with 95% confidence intervals (CIs) and *p*-value for inclusion.

Studies without the selected polymorphism of *TNFAIP8*, *TNFAIP8L1*, or *TNFAIP2* genes were excluded from this study because they were deemed ineligible. Studies that lacked or had incomplete data on a control population were omitted from this meta-analysis. Furthermore, review articles, letters, and correspondents were also excluded.

Extracting Data and Assessing Methodological Standard

Study ID, publication year, country, ethnicity, cancer type, genotyping technique, sample size (cases and controls), as well as genotypic data for selected SNPs were collected for each study. The Newcastle–Ottawa Scale (NOS) standard and the

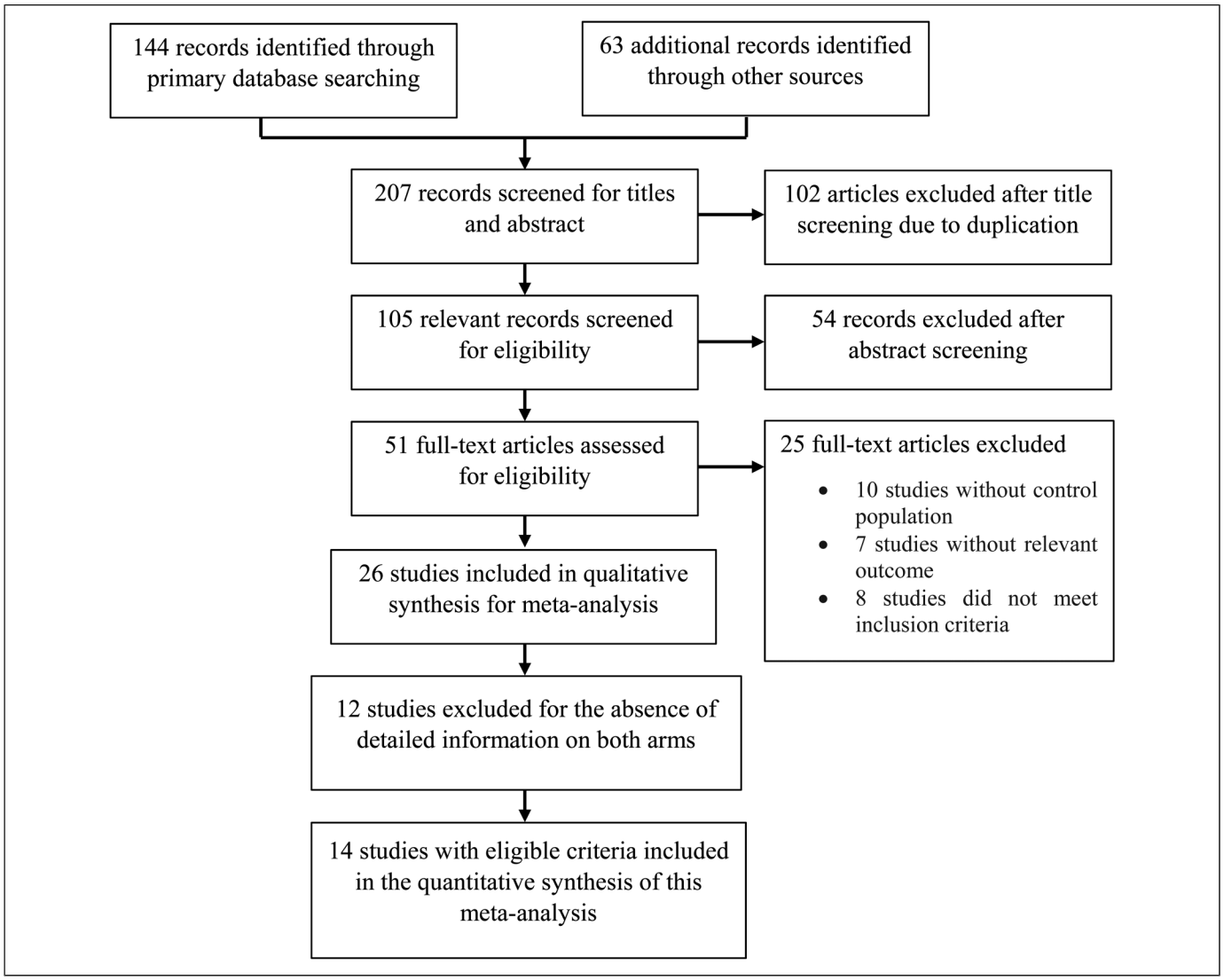

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram of the study selection process.

Jadad scale were employed to assess specified observational cohort studies[19] and determine sampling accuracy in controlled trials with randomization.[20]

Statistical Analysis, Trial Sequential Analysis, and In-Silico Analysis

Review Manager software (RevMan version 5.4) was employed for all statistical analyses. The association of genetic polymorphisms and cancer risk was estimated using 7 distinct genotypic models, including the codominant 1-3 models (COD1, COD2, and COD3), dominant model (DM), overdominant model (ODM), recessive model (RM), and the allele model (AM). The χ^2-based I^2-statistic and Q-test were performed to determine whether there was any possible heterogeneity. If the p-value is low ($p < .1$) or I^2 is >50%, the Q-test shows considerable heterogeneity. The sensitivity analysis was conducted by excluding the studies one by one. By constructing funnel plots, we determined if there was any publication bias. The publication bias was determined using Begg–Mazumdar's test and Egger's regression test. The random effects model was used for pooled OR estimation. When the p-value is <.05, the association was considered statistically significant. Bonferroni correction was also conducted for the p-values, and a p-value of <.007 is considered statistically significant. Moreover, we performed trial sequential analysis (TSA) to evaluate whether the case number is enough to produce a significant outcome[21] and analyzed the levels of mRNA expression[22] of the included polymorphisms by applying the Genotype-Tissue Expression (GTEx, release v7 and human genome build 37) portal (https://gtexportal.org/home/). We constructed violin plots to visualize the gene expression.

Results

Characteristics of the Included Articles

Overall, 6909 cancer patients and 7087 controls from 14 studies were enrolled in this study. Four studies presented genotypic

Table 1. Characteristics of Included Studies for the Meta-Analysis of the Association of *TNFAIP8* (rs11064, rs1045241, rs1045242, and rs3813308), *TNFAIP8L1* rs1060555, and *TNFAIP2* (rs710100 and rs8126) Polymorphisms with Cancer Risk

Study ID	Year	Country	Ethnicity	Cancer type	Genotyping method	Cases	Controls	GG	GA	AA	GG	GA	AA	HWE (p)
***TNFAIP8* rs11064**														
Gao et al (2020)	2020	China	Asian	OC	SNaPshot	210	160	3	62	145	0	15	145	0.534
Han et al (2017)	2017	China	Asian	CC	TaqMan	783	691	19	175	589	8	164	519	0.211
Liu et al (2019)	2019	China	Asian	EC	SNaPshot	226	248	18	70	138	10	60	178	0.096
Shi et al (2013)	2013	China	Asian	CC	TaqMan	1567	1380	39	350	1178	15	326	1039	0.057
Subtotal						2786	2479	79	657	2050	33	565	1881	
***TNFAIP8* rs1045241**														
						Cases	Controls	TT	TC	CC	TT	TC	CC	HWE (p)
Al-Khatib et al (2020)	2020	Jordan	Arab	DLBCL	MassARRAY	114	218	4	41	69	17	78	123	0.354
Gao et al (2020)	2020	China	Asian	OC	SNaPshot	210	231	6	67	137	13	64	154	0.076
Liu et al (2019)	2019	China	Asian	EC	SNaPshot	226	248	12	71	143	9	72	167	0.721
Zhang et al (2012)	2012	China	Asian	NHL	TaqMan	514	557	41	180	293	20	156	381	0.420
Subtotal						1064	1254	63	359	642	59	370	825	
***TNFAIP8* rs1045242**														
						Cases	Controls	GG	GA	AA	GG	GA	AA	HWE (p)
Gao et al (2020)	2020	China	Asian	OC	SNaPshot	210	231	8	67	135	4	52	175	0.952
Liu et al (2019)	2019	China	Asian	EC	SNaPshot	226	248	8	74	144	6	65	177	0.991
Subtotal						436	479	16	141	279	10	117	352	
***TNFAIP8* rs3813308**														
						Cases	Controls	GG	GC	CC	GG	GC	CC	HWE (p)
Han et al (2017)	2017	China	Asian	CC	TaqMan	783	690	198	377	208	181	341	168	0.768
Shi et al (2013)	2013	China	Asian	CC	TaqMan	1567	1380	397	754	416	362	681	337	0.637
Subtotal						2350	2070	595	1131	624	543	1022	505	
***TNFAIP8L1* rs1060555**														
						Cases	Controls	GG	GC	CC	GG	GC	CC	HWE (p)
Han et al (2017)	2017	China	Asian	CC	TaqMan	783	690	45	305	433	49	263	378	0.725
Han et al (2019)	2019	China	Asian	CC	MassARRAY	342	498	20	123	199	34	218	246	0.122
Shi et al (2013)	2013	China	Asian	CC	TaqMan	1567	1380	91	609	867	98	525	757	0.594
Subtotal						2692	2568	156	1037	1499	181	1006	1381	
***TNFAIP2* rs710100**														
						Cases	Controls	AA	AG	GG	AA	AG	GG	HWE (p)
Ainiwaer et al (2020)	2020	China	Asian	CC	MassARRAY	342	490	53	171	118	69	211	210	0.177
Guo et al (2020)	2020	China	Asian	GC	MassARRAY	543	572	75	251	217	73	285	214	0.145
Han et al (2017)	2017	China	Asian	CC	TaqMan	782	690	107	370	305	89	339	262	0.203
Liu et (2011)	2011	USA	Mixed	HNSCC	TaqMan	1077	1073	111	474	492	99	459	515	0.821
Slaby et al (2013)	2013	Czech Republic	Caucasian	CRC	TaqMan	212	197	23	89	100	26	86	85	0.566
Xu et al (2013)	2013	China	Asian	GC	TaqMan	301	313	40	141	120	41	137	135	0.503
Subtotal						3257	3335	409	1496	1352	397	1517	1421	
***TNFAIP2* rs8126**														
						Cases	Controls	CC	CT	TT	CC	CT	TT	HWE (p)
Chen et al (2022)	2022	China	Asian	GC	PCR-RFLP	90	90	29	30	31	15	40	35	0.538
Guo et al (2020)	2020	China	Asian	GC	MassARRAY	587	538	80	235	272	63	270	205	0.067
Liu et (2011)	2011	USA	Mixed	HNSCC	TaqMan	1077	1073	106	483	488	84	441	548	0.717
Xu et al (2013)	2013	China	Asian	GC	TaqMan	301	313	33	98	170	18	130	165	0.245
Zhang et al (2014)	2014	China	Asian	ESCC	TaqMan	588	600	57	266	265	37	243	320	0.306
Subtotal						2643	2614	305	1112	1226	217	1124	1273	
Total of 14 individual studies						6909	7087							

Abbreviations: CC, cervical cancer; CRC, colorectal cancer; DLBCL, diffuse large B-cell lymphoma; EC, endometrial cancer; ESCC, esophageal cancer; GC, gastric cancer; HNSCC, head and neck squamous cell carcinoma; NHL, non-Hodgkin lymphoma; OC, ovarian cancer; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism.

Table 2. Meta-Analysis of the Association of *TNFAIP8* (rs11064, rs1045241, rs1045242, and rs3813308), *TNFAIP8L1* rs1060555, and *TNFAIP2* (rs710100 and rs8126) Polymorphisms with Cancer Risk.

	Test of association			Test of heterogeneity			Publication bias (*p*-value)	
Genetic models	**OR**	**95% CI**	***p*-value**	**Model**	***p*-value**	**I^2 (%)**	**Egger's test**	**Begg–Mazumdar's test**
***TNFAIP8* rs11064**								
Codominant 1 (GA vs AA)	1.40	0.91-2.17	.131	Random	0	87.78	.070	**.042**
Codominant 2 (GG vs AA)	2.30	1.52-3.47	**7.83×10^{-5}***	Fixed	.899	0	.132	.497
Codominant 3 (GG vs GA)	2.10	1.37-3.22	**.0006***	Fixed	.862	0	.625	.497
Dominant model (GG + GA vs AA)	1.48	0.97-2.28	.071	Random	0	88.1	.060	**.042**
Recessive model (GG vs GA + AA)	2.24	1.48-3.37	**.0001***	Fixed	.938	0	.253	.497
Overdominant (GA vs GG + AA)	1.35	0.88-2.08	.165	Random	0	87.4	.077	**.042**
Allele contrast (G vs A)	1.47	1.03-2.12	**.037**	Random	0	86.74	.053	**.042**
***TNFAIP8* rs1045241**								
Codominant 1 (TC vs CC)	1.27	1.06-1.50	**.009**	Fixed	.327	13.14	**.013**	.174
Codominant 2 (TT vs CC)	1.05	0.42-2.63	.909	Random	.004	77.58	.058	**.042**
Codominant 3 (TT vs TC)	0.92	0.44-1.92	.814	Random	.042	63.53	.109	.174
Dominant model (TT + TC vs CC)	1.20	0.90-1.60	.223	Random	.052	61.11	**.009**	**.042**
Recessive model (TT vs TC + CC)	1.00	0.43-2.35	.991	Random	.008	74.77	.070	.174
Overdominant (TC vs TT + CC)	1.24	1.04-1.48	**.018**	Fixed	.636	0.00	.054	.174
Allele contrast (T vs C)	1.13	0.82-1.55	.472	Random	.004	77.61	**.029**	**.042**
***TNFAIP8* rs1045242**								
Codominant 1 (GA vs AA)	1.52	1.14-2.03	**.005***	Fixed	.553	0	–	.317
Codominant 2 (GG vs AA)	2.00	0.89-4.50	.092	Fixed	.582	0	–	.317
Codominant 3 (GG vs GA)	1.33	0.58-3.04	.506	Fixed	.742	0	–	.317
Dominant model (GG + GA vs AA)	1.56	1.18-2.07	**.002***	Fixed	.485	0	–	.317
Recessive model (GG vs GA + AA)	1.78	0.80-3.98	.161	Fixed	.614	0	–	.317
Overdominant (GA vs GG + AA)	1.48	1.11-1.98	**.008**	Fixed	.583	0	–	.317
Allele contrast (G vs A)	1.48	1.16-1.90	**.002***	Fixed	.430	0	–	.317
***TNFAIP8* rs3813308**								
Codominant 1 (GC vs GG)	0.90	0.78-1.04	.135	Fixed	.977	0	–	.317
Codominant 2 (GG vs CC)	0.89	0.75-1.05	.154	Fixed	.976	0	–	.317
Codominant 3 (GG vs GC)	0.99	0.86-1.14	.893	Fixed	.995	0	–	.317
Dominant model (GG + GC vs CC)	0.89	0.78-1.02	.101	Fixed	.974	0	–	.317
Recessive model (GG vs GC + CC)	0.95	0.83-1.09	.489	Fixed	.986	0	–	.317
Overdominant (GC vs GG + CC)	0.95	0.85-1.07	.409	Fixed	.990	0	–	.317
Allele contrast (G vs C)	0.94	0.87-1.02	.150	Fixed	.976	0	–	.317
***TNFAIP8L1* rs1060555**								
Codominant 1 (GC vs CC)	0.92	0.75-1.13	.423	Random	.07	62.86	.365	.117
Codominant 2 (GG vs CC)	0.80	0.63-1.00	**.048**	Fixed	.95	0	.279	.117
Codominant 3 (GG vs GC)	0.83	0.66-1.05	.117	Fixed	.72	0	.392	.117
Dominant model (GG + GC vs CC)	0.90	0.75-1.08	.269	Random	.09	57.68	.361	.117
Recessive model (GG vs GC + CC)	0.81	0.65-1.01	.063	Fixed	.98	0	.517	.602
Overdominant (GC vs GG + CC)	0.94	0.78-1.15	.569	Random	.07	62.2	.367	.117
Allele contrast (G vs **C**)	0.92	0.85-1.01	.078	Fixed	.25	27.38	.355	.117
***TNFAIP2* rs710100**								
Codominant 1 (AG vs GG)	1.04	0.94-1.15	.480	Fixed	.133	40.88	.889	.851
Codominant 2 (AA vs GG)	1.09	0.93-1.28	.264	Fixed	.713	0	.399	.348
Codominant 3 (AA vs AG)	1.05	0.90-1.23	.519	Fixed	.939	0	**.049**	.188
Dominant model (AA + AG vs GG)	1.05	0.95-1.16	.338	Fixed	.137	40.29	.968	.573
Recessive model (AA vs AG + GG)	1.07	0.93-1.24	.351	Fixed	.949	0	**.035**	.091
Overdominant (AG vs AA + GG)	1.02	0.92-1.12	.731	Fixed	.240	25.87	.764	.851
Allele contrast (A vs G)	1.04	0.97-1.12	.246	Fixed	.342	11.48	.704	.348
***TNFAIP2* rs8126**								
Codominant 1 (CT vs TT)	0.94	0.69-1.28	.695	Random	.0001	83.74	.434	.327
Codominant 2 (CC vs TT)	1.41	1.16-1.71	**.0005***	Fixed	.121	45.14	.320	.327
Codominant 3 (CC vs CT)	1.44	1.19-1.75	**.0002***	Fixed	.151	40.51	**.012**	.142
Dominant model (CC + CT vs TT)	1.05	0.79-1.39	.737	Random	.0002	81.6	.675	.624
Recessive model (CC vs CT + TT)	1.43	1.19-1.72	**.0001***	Fixed	.273	22.27	**.019**	**.050**
Overdominant (CT vs CC + TT)	0.86	0.64-1.16	.337	Random	.0001	83.7	.274	.327
Allele contrast (C vs T)	1.14	0.96-1.36	.144	Random	.005	73.38	.864	.624

Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval. Bold values indicate statistically significant ($p < .05$).
*Indicates significant after Bonferroni correction.

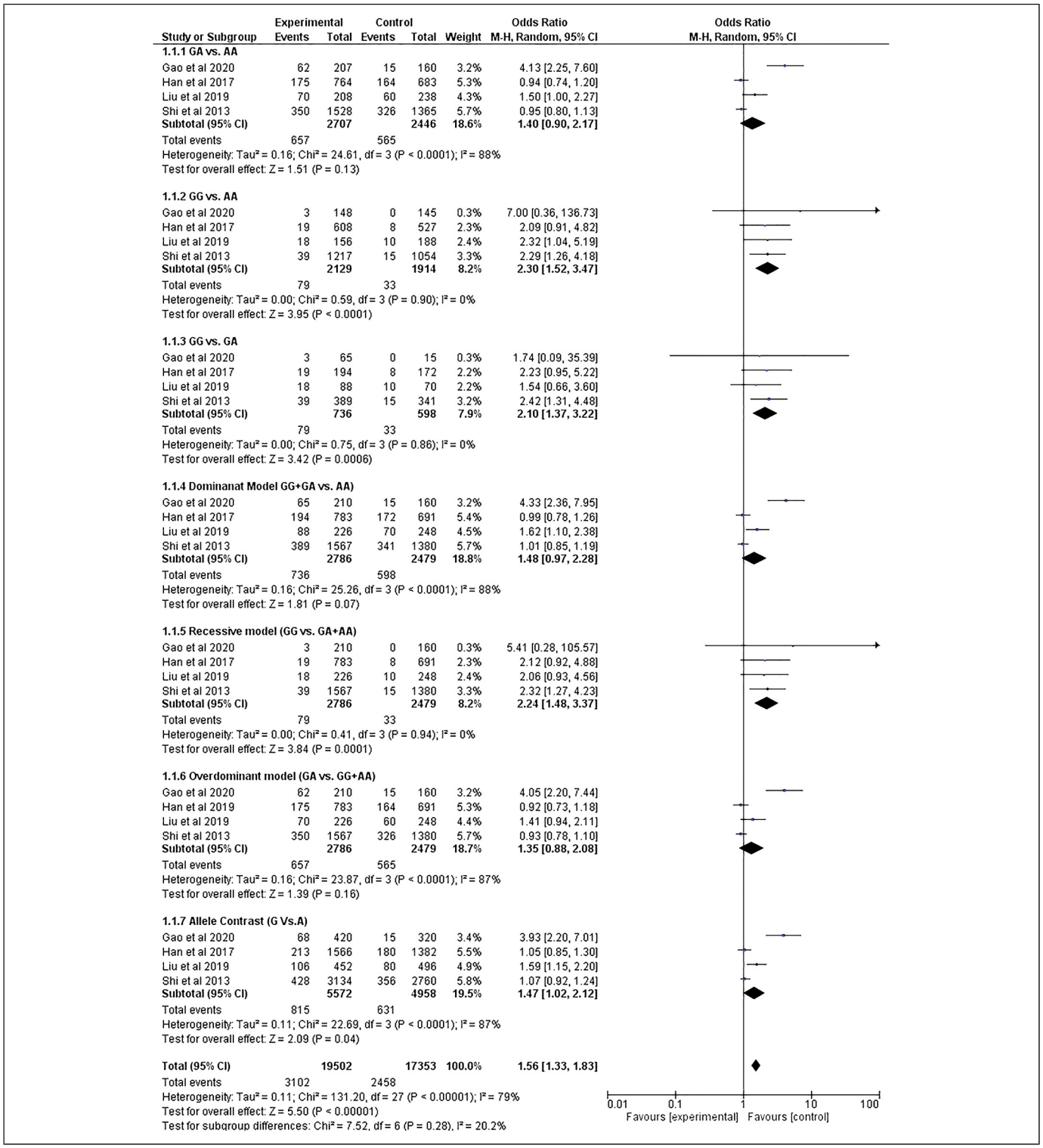

Figure 2. Forest plot for the meta-analysis of the association of *TNFAIP8* rs11064 polymorphism with cancer risk.

data of both rs11064[11,23–25] and rs1045241,[23,24,26,27] whereas 2 studies provided genotypic data of rs1045242[23, 24] and rs3813308.[11,25] Three, 6, and 5 studies provided genotypic information on the rs1060555,[7,11,25] rs710100,[12,14,25,28–30] and rs8126,[12,14,28,31,32] respectively (Table 1). The studies were on 9 cancers, the most common of which is cervical cancer, with 3034 patients, and the least common is ovarian cancer, with just 210 cancer patients. A total of 1077 cases

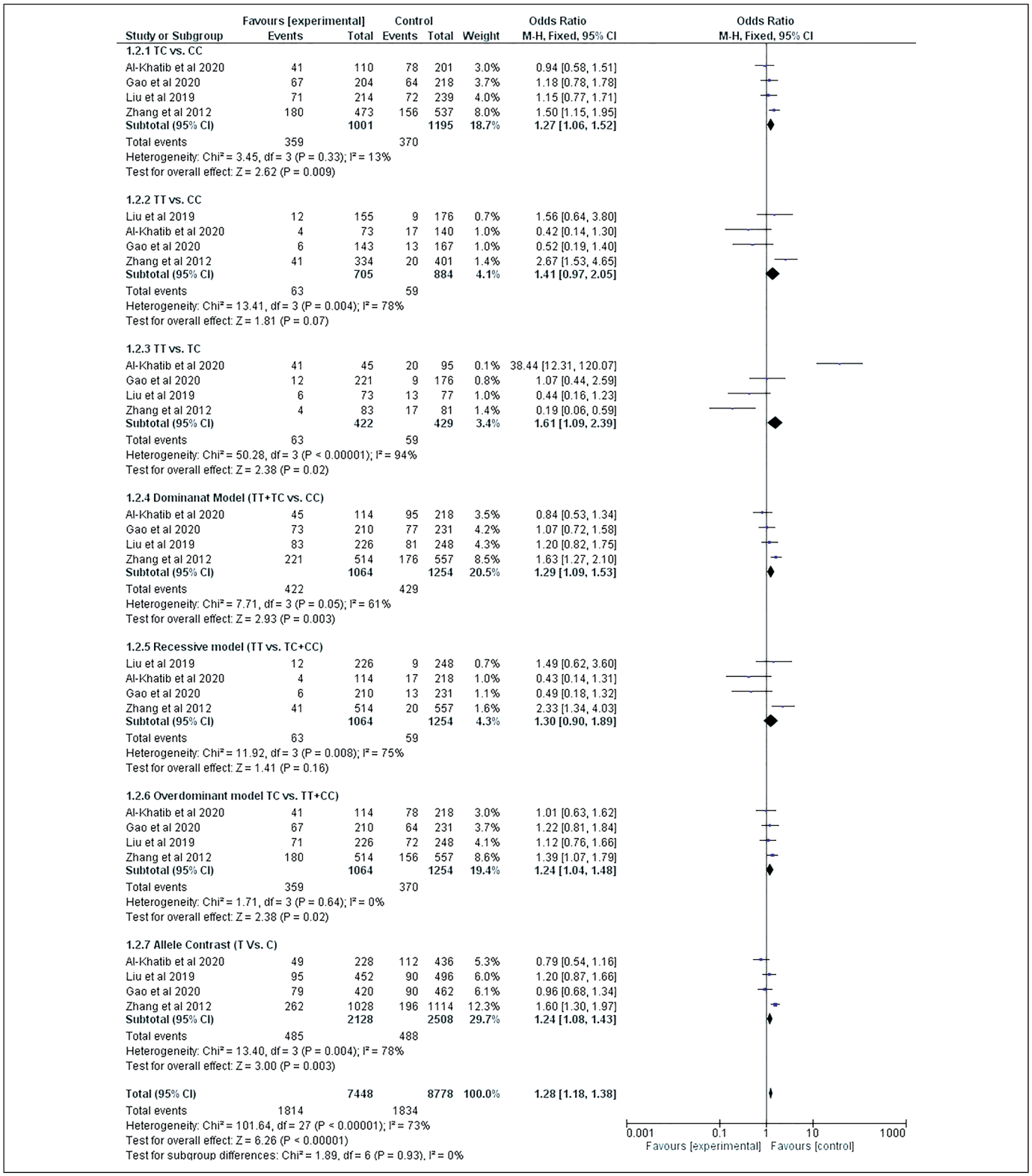

Figure 3. Forest plot for the meta-analysis of the association of *TNFAIP8* rs1045241 polymorphism with cancer risk.

of head and neck squamous cell carcinoma have been reported, while 978 cases have been identified in terms of gastric cancer. Others were esophageal cancer, non-Hodgkin lymphoma, endometrial cancer, colorectal cancer, and diffuse large B-cell lymphoma which accounted for 588, 514, 226, 212, and 114 cases, respectively. According to the quality assessment by NOS, the maximum included studies scored ≥6 (high quality) (Table S1).

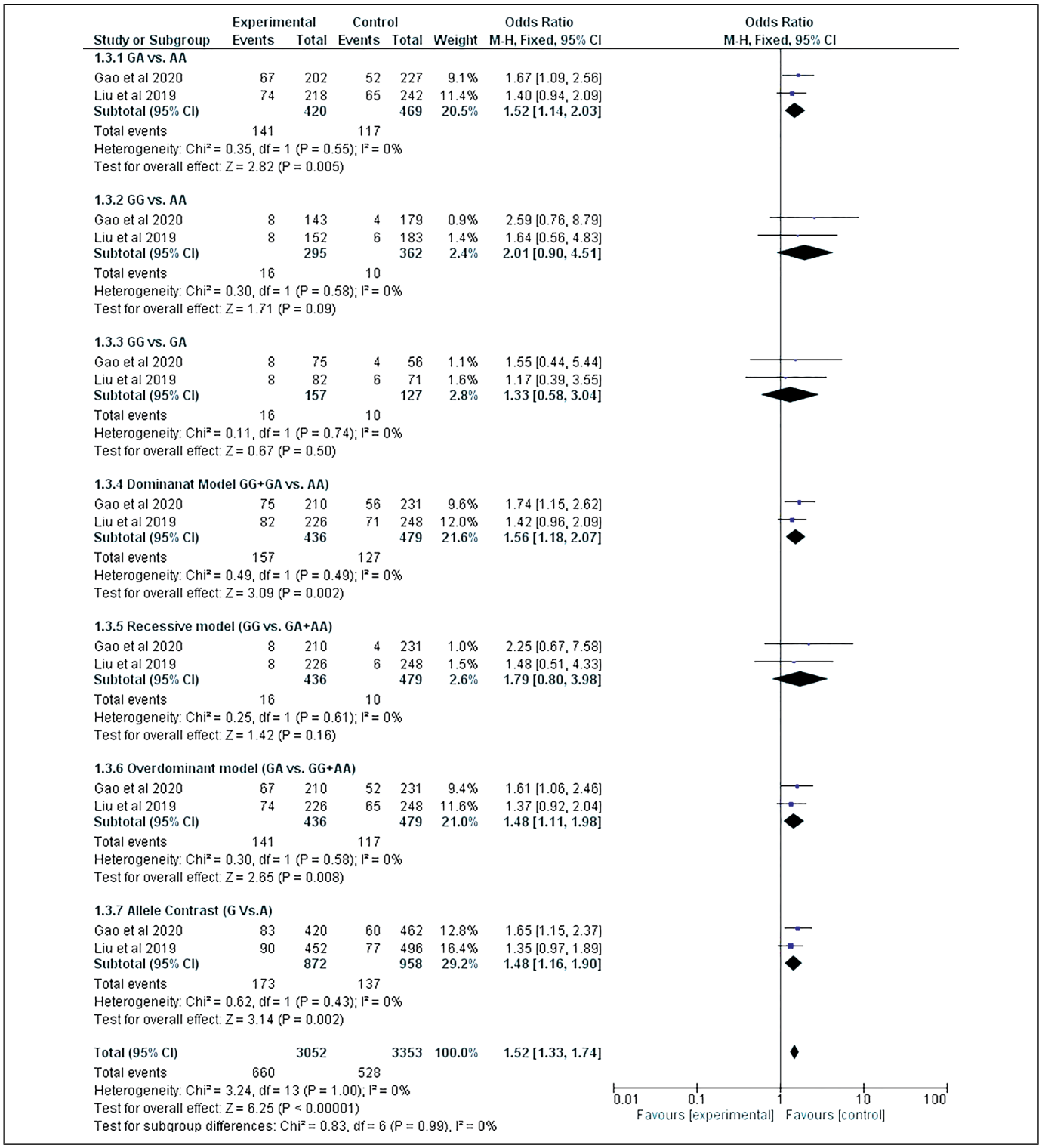

Figure 4. Forest plot for the meta-analysis of the association of *TNFAIP8* rs1045242 polymorphism with cancer risk.

Association of TNFAIP8 Polymorphisms with Cancer

Four studies evaluated the association of rs11064 polymorphism with cancer risk. For this polymorphism, 4 different genetic models such as COD2 (GG vs AA: OR = 2.30, 95% CI = 1.52–3.47, $p = 7.83 \times 10^{-5}$), COD3 (GG vs GA: OR = 2.10, 95% CI = 1.37–3.22, $p = .0006$), RM (GG vs GA + AA: OR = 2.24, 95% CI = 1.48–3.37, $p = .0001$), and AM (G vs A: OR = 1.47, 95% CI = 1.03–2.12, $p = .037$) significantly increased the probability of developing cancer. The *p*-values of the COD2, COD3, and RM remained significant after the Bonferroni

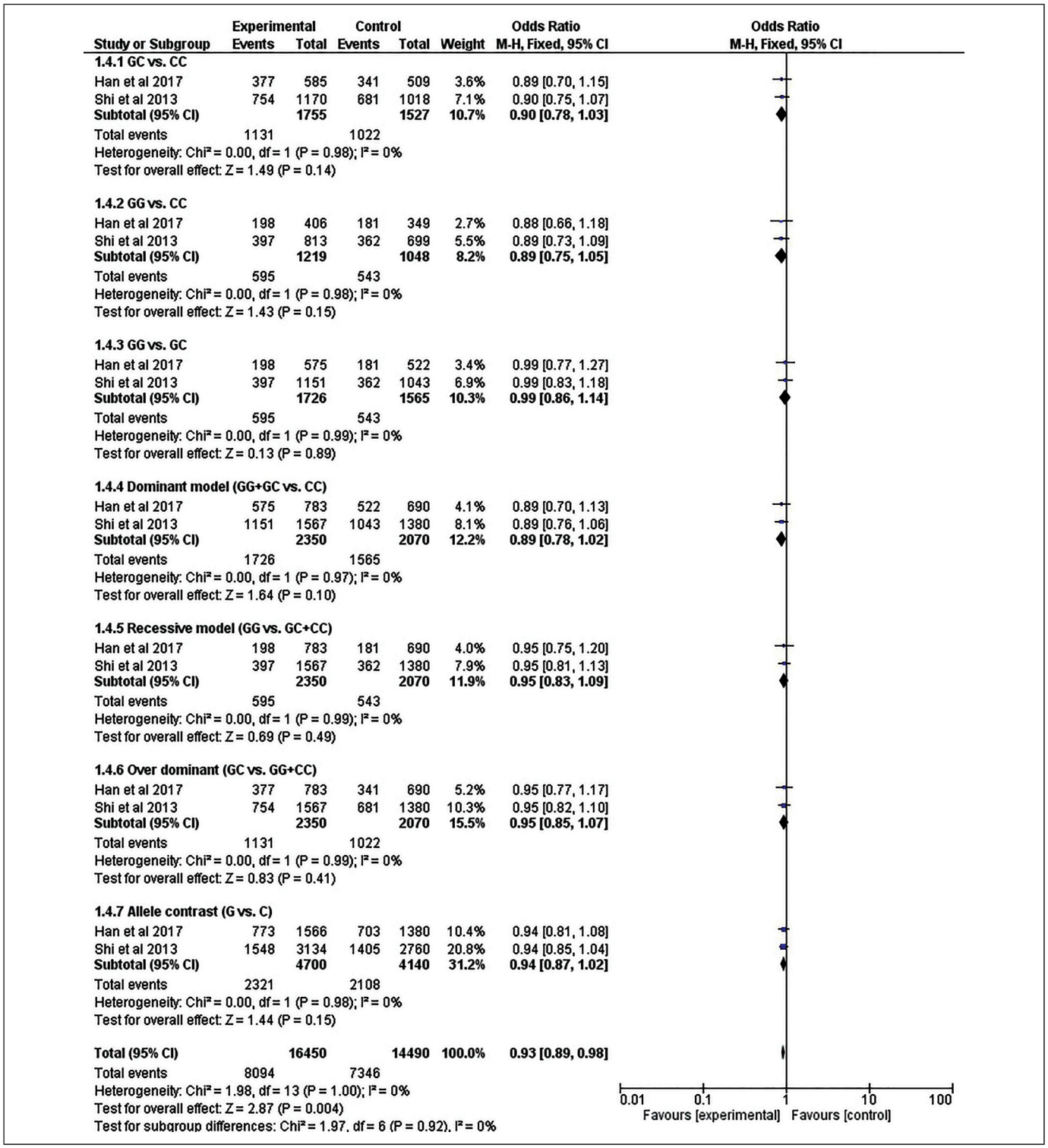

Figure 5. Forest plot for the meta-analysis of the association of *TNFAIP8* rs3813308 polymorphism with cancer risk.

correction. The COD1 and ODM failed to demonstrate a statistically significant link with cancer ($p > .05$; Table 2 and Figure 2). For rs1045241, 2 genetic models, COD1 (TC vs CC: OR = 1.27, 95% CI = 1.06–1.5, $p = .009$) and ODM (TC vs TT + CC: OR = 1.24, 95% CI = 1.04–1.48, $p = .018$) showed a significant correlation with cancer (Table 2 and Figure 3).

The *TNFAIP8* rs1045242 polymorphism was investigated in ovarian and esophageal cancer in 2 separate studies on the Asian population that included 436 cancer patients and 479 controls (Table 1). Four distinct genetic models, including COD1, DM, ODM, and AM (GA vs AA: OR = 1.52, 95% CI = 1.14–2.03, $p = .005$; GG + GA vs AA: OR = 1.56,

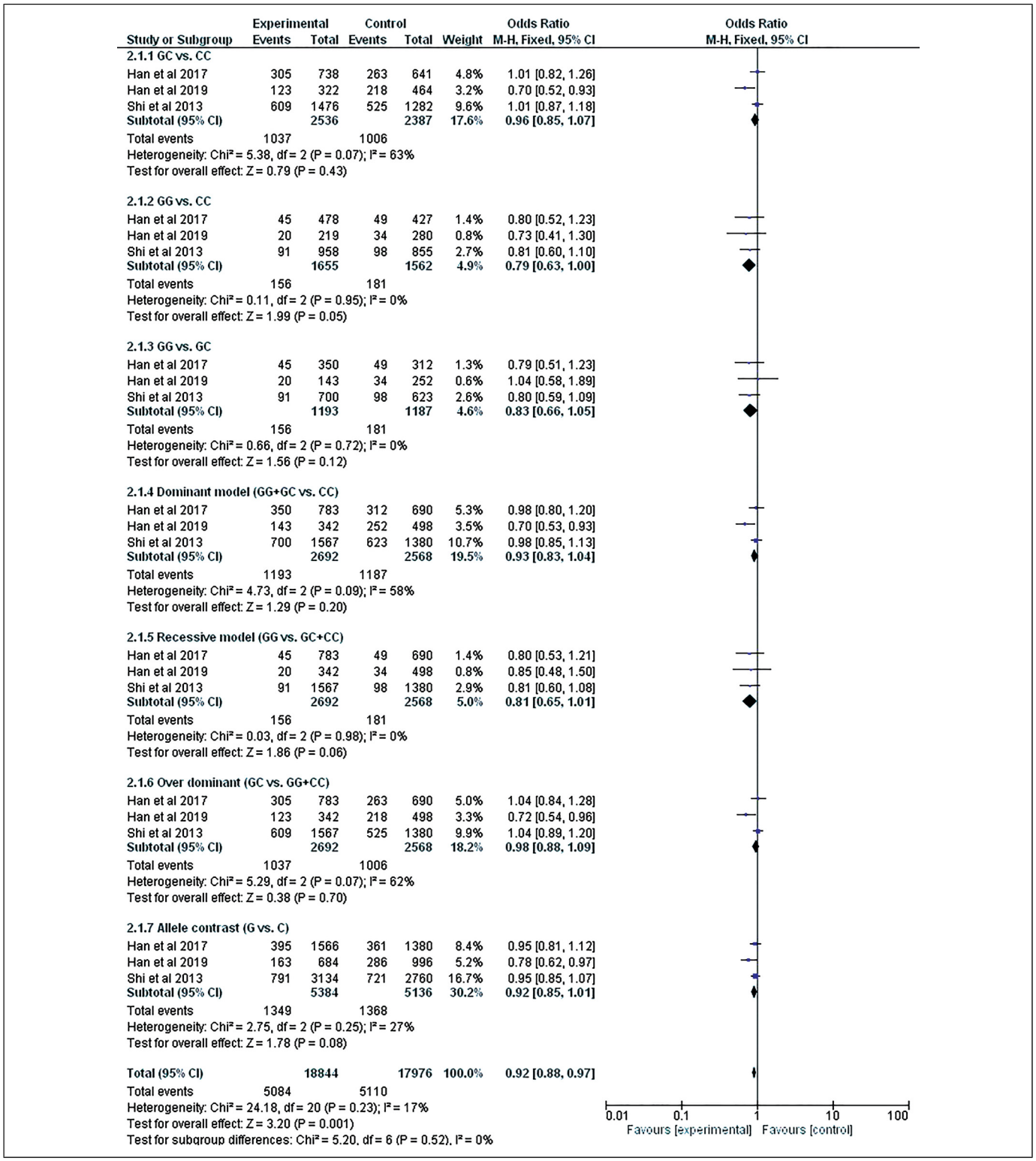

Figure 6. Forest plot for the meta-analysis of the association of *TNFAIP8L1* rs1060555 polymorphism with cancer risk.

95% CI = 1.18–2.07, $p = .002$; GA vs GG + AA: OR = 1.48, 95% CI = 1.11–1.98, $p = .008$; G vs A: OR = 1.48, 95% CI = 1.16–1.90, $p = .002$) showed a significant association with cancer, respectively, and the associations remained significant even after Bonferroni correction except the ODM (Table 2 and Figure 4). SNP rs3813308 was analyzed by 2 studies on Asian women with cervical cancer, with 2350 patients and 2070 controls. This SNP did not demonstrate any significant correlation with cancer in any genetic models (Table 2 and Figure 5).

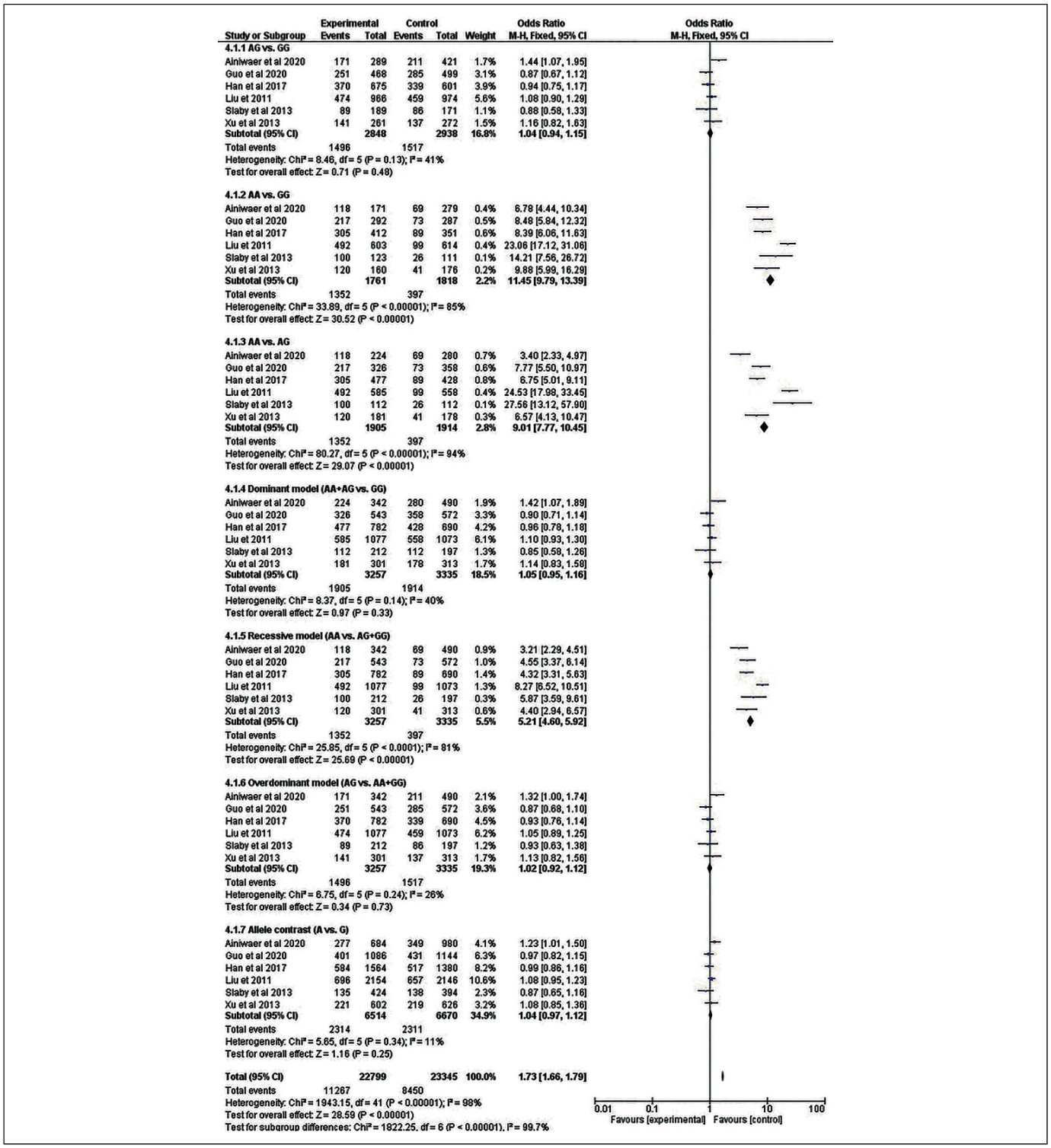

Figure 7. Forest plot for the meta-analysis of the association of *TNFAIP2* rs710100 polymorphism with cancer risk.

Association of TNFAIP8L1 Polymorphism with Cancer

For this SNP, 3 studies involving 2692 Asian cervical cancer patients and 2568 controls were included. Only 1 genetic model, COD2, depicted a significantly protective effect against cancer (GG vs CC: OR = 0.80, 95% CI = 0.63–1.0, $p = .048$; as shown in Table 2 and Figure 6).

Association of TNFAIP2 Polymorphisms with Cancer

Six studies with 4 different cancers were included in the meta-analysis of rs710100. However, none of the genetic models demonstrated a statistically significant connection of rs710100 with cancer. For rs8126, 3 models—COD2 (CC vs TT: OR = 1.41, 95% CI = 1.16–1.71, $p = .0005$), COD3 (CC vs CT: OR = 1.44,

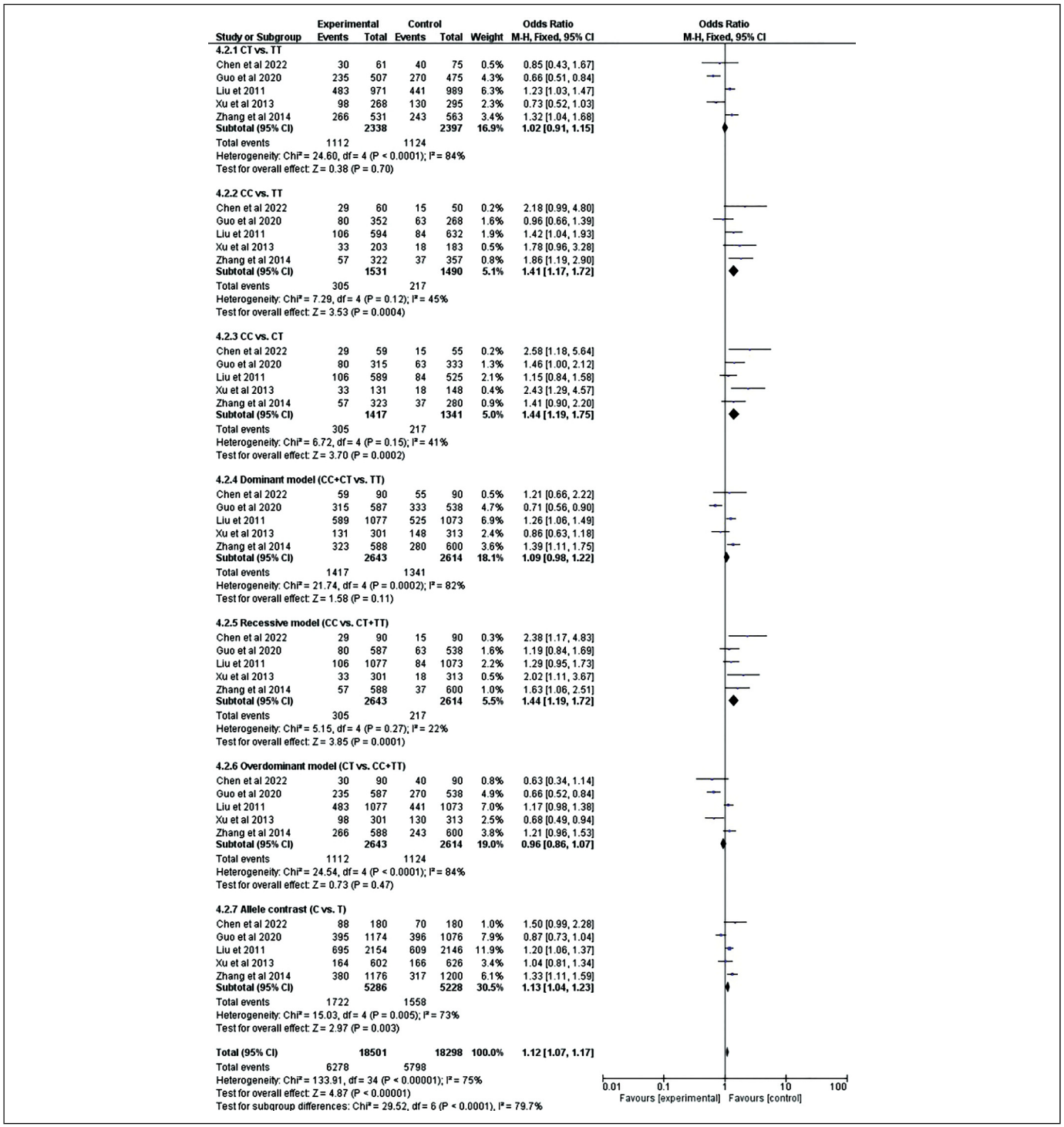

Figure 8. Forest plot for the meta-analysis of the association of *TNFAIP2* rs8126 polymorphism with cancer risk.

95% CI = 1.19–1.75, $p = .0002$), and RM (CC vs CT + TT: OR = 1.44, 95% CI = 1.19–1.72, $p = .0001$) revealed a statistically significant association with cancer. All of the associations were found to be significant after the Bonferroni correction (Table 2). Forest plots regarding the association of *TNFAIP2* rs710100 and rs8126 gene polymorphisms with cancer risk are presented in Figures 7 and 8, respectively.

Sensitivity Analysis and Publication Bias

The funnel plots exhibited no considerable asymmetry (Figure 9). As per the Begg–Mazumdar's test and Egger's regression test (Table 2), for rs11064, 4 genetic models (COD1: $p = .042$, DM: $p = .042$, OD: $p = .042$, and AM: $p = .042$) showed a significant publication bias. SNP rs1045241 also depicted a significant

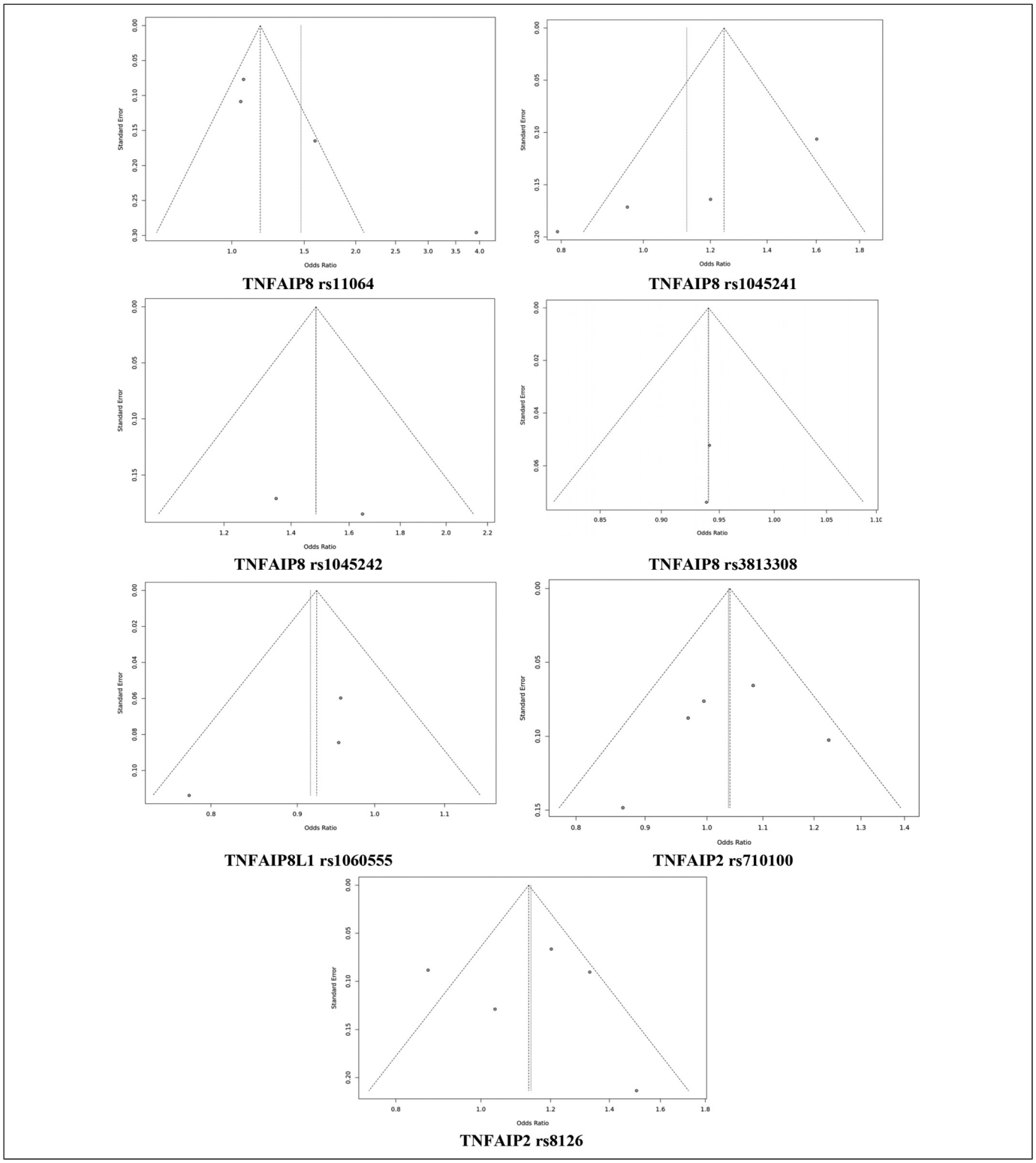

Figure 9. Funnel plots indicating the publication bias for detecting the association of studied polymorphism with cancer risk in the allele model.

publication bias in 3 different genetic models, according to both Egger's test (COD1: $p = .013$, DM: $p = .009$, and AM: $p = .029$) and Begg–Mazumdar's test (COD2: $p = .042$, DM: $p = .042$, and AM: $p = .042$). The *TNFAIP2* rs710100 also showed publication bias in 2 genetic models (COD3: $p = .049$ and RM: $p = .035$) for Egger's test, while Begg–Mazumdar's test did not demonstrate any publication bias. Our meta-analysis found significant publication bias in 2 genetic models (COD3:

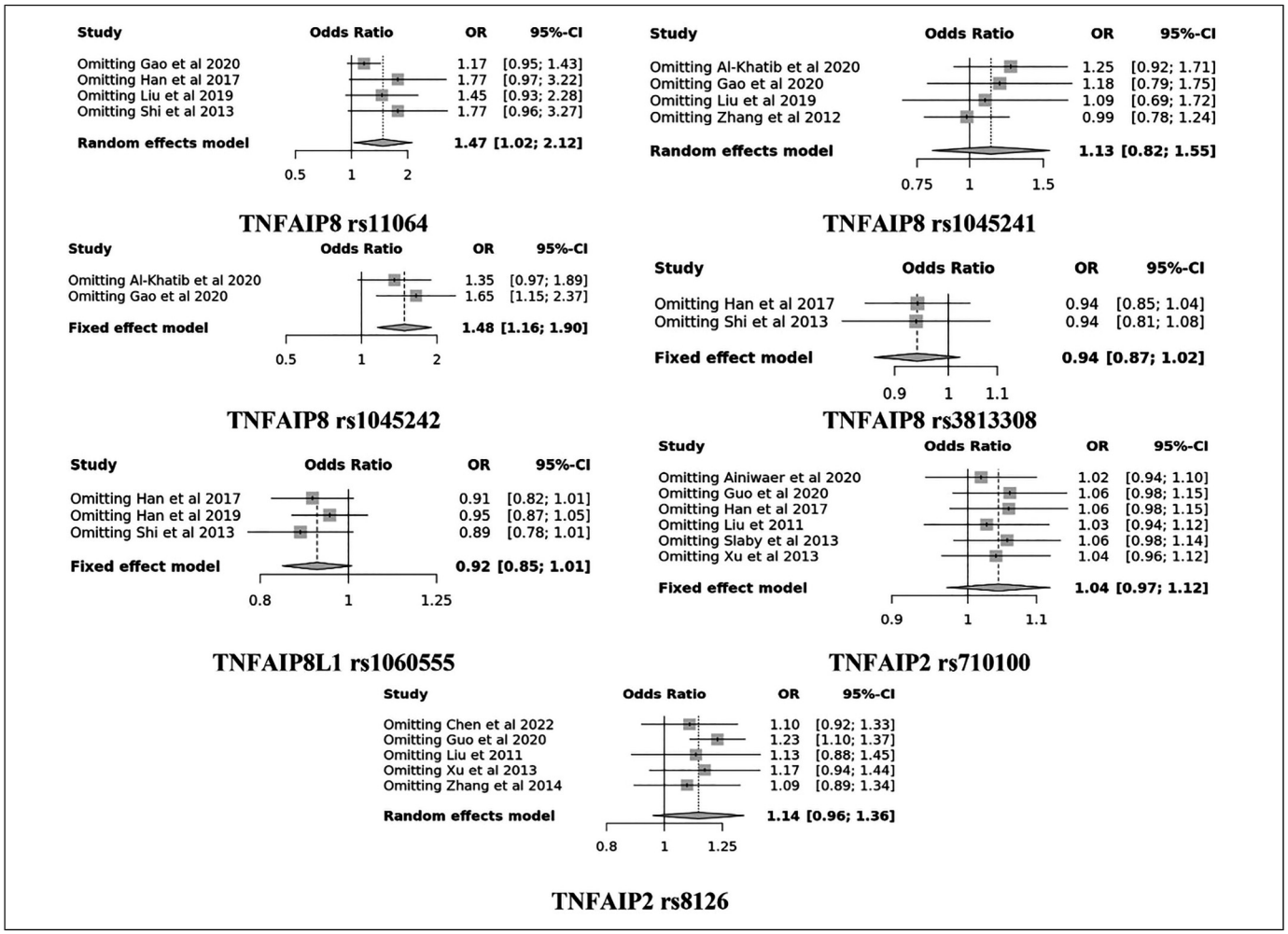

Figure 10. Sensitivity analysis for the meta-analysis of the association of studied polymorphism with cancer risk in the allele model.

$p = .012$ and RM: $p = .019$) as determined by Egger's p-values for rs8126 and 1 genetic model (RM: $p = .050$) defined by Begg–Mazumdar's test revealed publication bias. The sensitivity analysis for the association of studied polymorphisms with cancer risk using AM was conducted by excluding the studies one by one, which revealed no significant changes, confirming the reliability and stability of the findings (Figure 10).

TSA and In-Silico Analysis

As shown in Figure 11(A to G), we conducted TSA for the meta-analysis of the association of studied polymorphism with cancer risk in *TNFAIP8* rs11064 (G vs A), *TNFAIP8* rs1045241 (TC vs CC), *TNFAIP8* rs1045242 (GA vs AA), *TNFAIP8* rs3813308 (GG vs GC + CC), *TNFAIP8L1* rs1060555 (GG vs CC), *TNFAIP2* rs710100 (AA vs AG + GG), and *TNFAIP2* rs8126 (CC vs CT + TT) incorporating sample size of 31,499, 1,896, 2,196, 3,736, 5,450, 5,301, and 10,132, respectively. In the figures, the uppermost curves represent trial sequential monitoring boundary lines for the benefit and the lowermost curves represent trial sequential monitoring boundary lines for the harm. Two horizontal lines represent the traditional boundaries, and the crossing of Z-curves of these lines indicates statistically significant outcomes, and the futility boundaries are represented by triangular lines (red lines). According to Figure 11A, C, and E, Z-curves crossed the traditional sequential boundary, indicating the significant outcomes, but the required information size (RIS) did not reach, whereas, for Figure 11D, the RIS reached, although the outcome is not significant. In the case of Figure 11B and F, the Z-curves crossed the traditional sequential boundary, futility boundary, and RIS, indicating that our outcomes are supported with sufficient evidence, and no more studies are required. In contrast, in the case of Figure 11G, the Z-curve crossed the traditional and futility boundaries, verifying our significant outcome, but the RIS is not reached.

According to the result of GTEx portal data (Figure 12), we found that *TNFAIP8* rs11064 and rs3813308, *TNFAIP8L1* rs1060555, and *TNFAIP2* rs710100 and rs8126 were detected in cultured fibroblasts. Only *TNFAIP8* rs1045241 and rs1045242 were detected in mammary tissues. The constructed violin plots indicated the mRNA expression of rs11064 ($p = 1.7 \times 10^{-9}$), rs1045241 ($p = .032$), rs1045242 ($p = .048$), rs3813308 ($p = .0027$), rs710100 ($p = .00047$), and rs8126 ($p = .017$) while no significant difference in mRNA expression between the mutant and wild alleles was found for rs1060555 ($p = .41$).

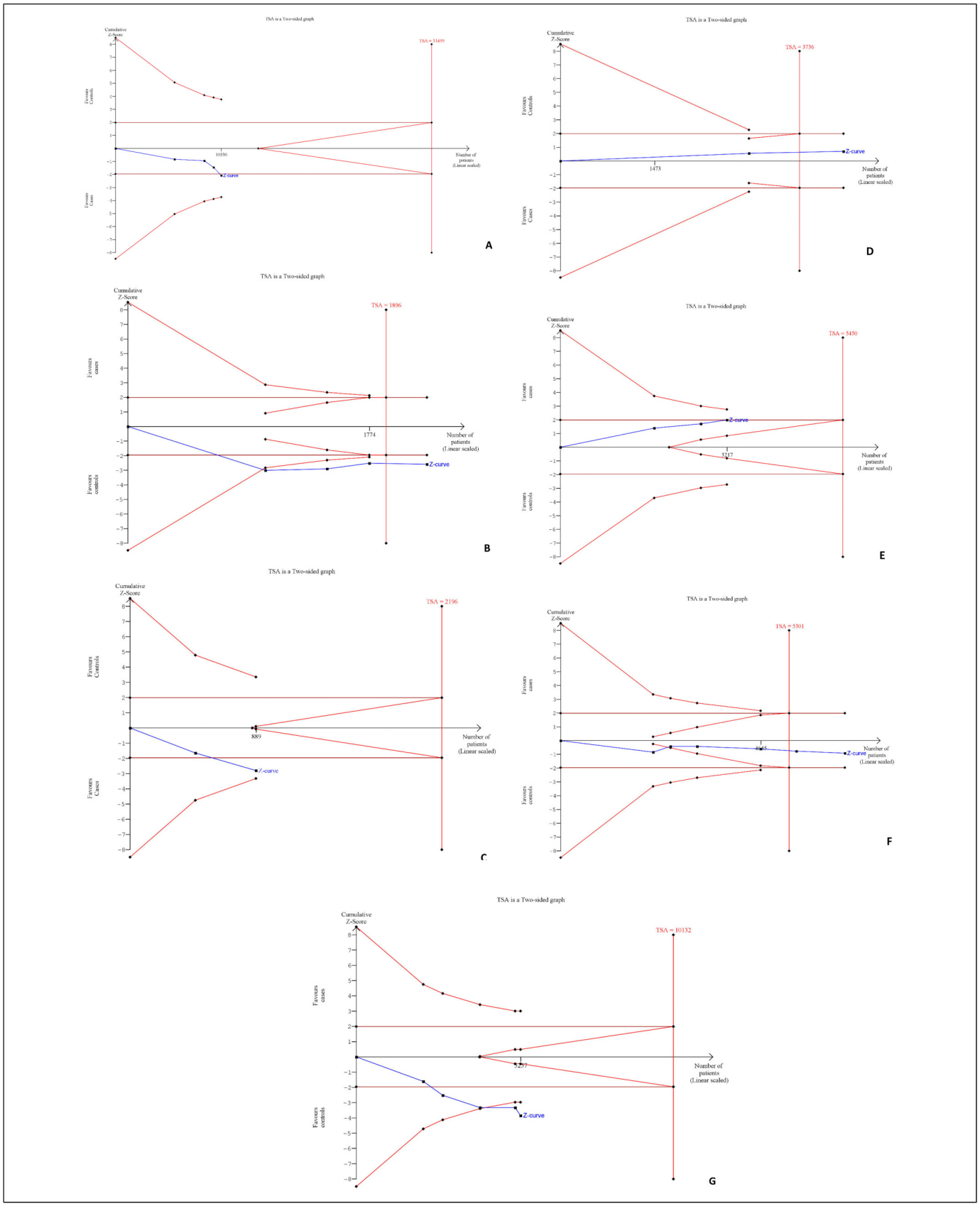

Figure 11. Trial sequential analysis (TSA) for the meta-analysis of the association of studied polymorphism with cancer risk in (A) *TNFAIP8* rs11064 (G vs A); (B) *TNFAIP8* rs1045241 (TC vs CC); (C) *TNFAIP8* rs1045242 (GA vs AA); (D) *TNFAIP8* rs3813308 (GG vs GC + CC); (E) *TNFAIP8L1* rs1060555 (GG vs CC); (F) *TNFAIP2* rs710100 (AA vs AG + GG); and (G) *TNFAIP2* rs8126 (CC vs CT + TT).

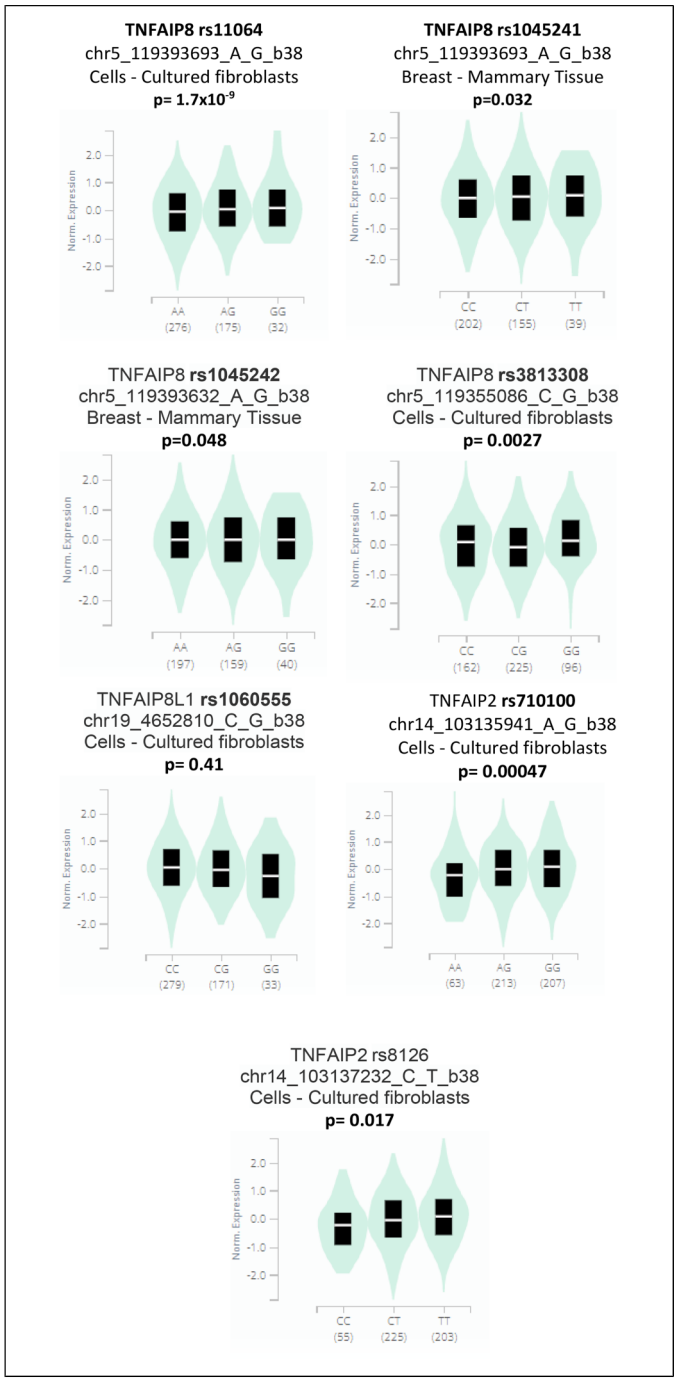

Figure 12. In-silico analysis (violin plots) of *TNFAIP8* rs11064, *TNFAIP8* rs1045241, *TNFAIP8* rs1045242, *TNFAIP8* rs3813308, *TNFAIP8L1* rs1060555, *TNFAIP2* rs710100, and *TNFAIP2* rs8126 expression using the Genotype-Tissue Expression (GTEx) database. The teal area denotes the density distribution of the samples in each genotype and the white line in the box plot (black) indicates the median value of the expression of each genotype.

Discussion

Cancer is a group of disorders in which cells divide uncontrollably and abnormally.[33] Investigations into the causes of human malignancy have been continuously done for decades, and experts continue to analyze the importance of genetic and epigenetic aberrations in cancer development. In this meta-analysis, a total of 14 case–control studies on multiple cancers were included, and the association was analyzed using seven genetic models for the *TNFAIP8* (rs11064, rs1045241, rs1045242, and rs3813308), *TNFAIP8L1* (rs1060555), and *TNFAIP2* (rs710100 and rs8126) gene polymorphisms.

Data shows that one of the most consequential regulators of apoptosis in both typical and malignant tissues is *TNFAIP8*, which is situated on chromosome 5q23.1. By inhibiting tumor cell growth and proliferation by modulating the Hippo signaling pathway, *TNFAIP8* works as a cellular "pilot" for tumor cell migration by boosting local phosphatidylinositol 3 kinase-protein kinase B and Rac signals on the cell membrane encountering chemoattractants.[34,35] In addition, TNF-α activates the NF-κB pathway to promote its expression, and *TNFAIP8* mRNA expression is found in the head and neck, esophagus, breast, and lung tumors.[5,36–38] SNP rs11064 was found to be correlated to a greater risk of cervical cancer in women from the Eastern Chinese region as reported by Shi et al.[11] Additionally, the results of the study imply that *TNFAIP8* may serve as a valuable marker for reckoning platinum resistance and clinical outcomes in cervical cancer.[11] Polymorphisms in the *TNFAIP8* gene were also reported to be associated with a greater risk of contracting ovarian cancer in another investigation. According to the results, the ovarian cancer risk was increased by rs1045242, whereas the risk was reduced by rs11064. They found no correlation between the *TNFAIP8* rs1045241 and the likelihood of ovarian cancer.[21]

In this meta-analysis, we found that 4 distinct genetic models of SNP rs11064, including COD2, COD3, RM, and AM (OR = 2.30, $p = 7.83 \times 10^{-5}$; OR = 2.10, $p = .0006$; OR = 2.24, $p = .0001$; and OR = 1.47, $p = .037$, respectively) and SNP rs1045242, including COD1, DM, ODM, and AM (OR = 1.52, $p = .005$; OR = 1.56, $p = .002$; OR = 1.48, $p = .008$; and OR = 1.48, $p = .002$, respectively), and 2 genetic models of SNP rs1045241, including COD1 and ODM (OR = 1.27, $p = .009$ and OR = 1.24, $p = .018$, respectively) are connected to increased cancer risk. This result is congruent with another recent study which reveals that rs11064 is not correlated to cancer.[39] The present study also revealed that rs1045241 polymorphism is associated with cancer risk in COD1 (OR = 1.27, $p = .009$) and ODM (OR = 1.24, $p = .018$), and rs1045242 is associated with cancer in 3 genetic models such as COD1 (OR = 1.52, $p = .005$), DM (OR = 1.56, $p = .002$), and AM (OR = 1.48, $p = .002$). Our meta-analysis found no evidence linking *TNFAIP8* rs3813308 to an increased cancer risk, which is in line with prior studies.[11,25]

TNFAIP8L1 has a crucial function in the development and progression of malignant tumors. By binding to Rac1 and activating the caspases, TNFAIP8L1 causes cell death in hepatocellular carcinoma cells.[40,41] According to research on neural cell lines, oxidative stress induces the production of the transcription factor TNFAIP8L1, which then inhibits the mammalian target of rapamycin (mTOR).[42] According to our data, *TNFAIP8L1*

rs1060555 is not associated with an increased risk of cancer; rather, one genetic model shows that it has a significant protective association with cancer (OR = 0.80, $p = .048$), which is consistent with recent research showing that this SNP has a protective role against cancer development.[7,11]

TNFAIP2, the principal responder gene of TNF-α, is phosphorylated by polo-like kinases in response to lipopolysaccharide stimulation, regulating the cellular inflammatory response via the NF-κB signaling pathway governing cell inflammatory, angiogenesis, cell aggrandization, relocation, and invasion.[43–46] *TNFAIP2* knockdown halted cell growth in the G_0/G_1 phase in esophageal squamous cell carcinoma cells and inhibiting *TNFAIP2* expression diminishes proliferation and colony formation.[47] This meta-analysis confirms previous findings that the *TNFAIP2* rs710100 genetic model is not correlated to an elevated risk of malignancy.[14,28] In contrast, Ainiwaer et al[29] demonstrated that cervical cancer risk has been attributed to rs710100 in Chinese Uygur women (OR = 1.44, $p = .018$). Our study showed a significant link between rs8126 and cancer in 3 genetic models (COD2: OR = 1.41, $p = .0005$; COD3: OR = 1.44, $p = .0002$; and RM: OR = 1.43, $p = .0001$). Several studies have suggested that rs8126 has a link with stomach cancer, epidermis carcinomas, and squamous cell carcinomas of the head and neck.[12,14,31] The results of TSA and sensitivity analysis also confirm the findings of our meta-analysis.

A few shortcomings should be made clear in light of the results of this investigation. First, the overall number of case–control studies is low (14 studies); for TNFAIP8 (rs1045242 and rs3813308), only 2 studies were included. Second, the number of patients and controls retained in the studies was low. Third, the controls in several pieces of research were not always designated as being of the same age and gender. Fourth, there is a significant publication bias observed in some genetic models, which may be attributed to the small number of studies as well as the small sample size. Finally, the genetic model demonstrated a publication bias. Even after these shortcomings, including case–control studies in this review, the meta-analysis is comprehensive, and the study's consequences are eminently conceivable.

Conclusion

This meta-analysis summarizes that rs11064, rs1045241, and rs1045242 polymorphisms of the *TNFAIP8* gene and rs8126 polymorphism of the *TNFAIP2* gene are significantly correlated to an elevated risk of cancer. Besides, *TNFAIP8L1* rs1060555 polymorphism may have a protective role in cancer development. Large-scale investigations incorporating more studies in diverse populations are recommended to determine the proper correlation of these polymorphisms with cancer.

Acknowledgments

The authors wish to thank the Laboratory of Pharmacogenomics and Molecular Biology, Department of Pharmacy, Noakhali Science and Technology University, Sonapur, Noakhali, Bangladesh for their generalized support, unwavering motivation, academic supervision, constructive comments, affectionate sensation, and positive recommendations.

Authors Contributions

Both KKB and MAB contributed equally to the review and conducted the first literature search. KKB, MAB, and MAA were all involved in the writing process, review, and editing. MSI came up with the idea, performed the data analysis, and reviewed and edited the final result for accuracy. The final paper was reviewed and approved by all of the researchers.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article

Data Availability

All data generated or analyzed during the present meta-analysis are accessible from the corresponding author upon reasonable request.

ORCID iDs

Khokon Kanti Bhowmik https://orcid.org/0000-0001-6101-4623
Mohammad Safiqul Islam https://orcid.org/0000-0003-4924-5319

Supplemental Material

Supplemental material for this article is available online.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA-Cancer J Clin*. 2021;71(3):209-249.
2. Aziz MA, Uddin MS, Millat MS, Islam MS. Vascular endothelial growth factor A (VEGFA) promoter rs2010963 polymorphism and cancer risk: an updated meta-analysis and trial sequential analysis. *Meta Gene*. 2022;31:101017.
3. Vincze O, Colchero F, Lemaitre JF, et al. Cancer risk across mammals. *Nature*. 2022;601(7892):263-267.
4. Leroi AM, Koufopanou V, Burt A. Cancer selection. *Nat Rev Cancer*. 2003;3(3):226-231.
5. Hadisaputri YE, Miyazaki T, Suzuki S, et al. TNFAIP8 overexpression: clinical relevance to esophageal squamous cell carcinoma. *Ann Surg Oncol*. 2012;19(3):589-596.
6. Lou Y, Tian X, Sun C, et al. TNFAIP8 protein functions as a tumor suppressor in inflammation-associated colorectal tumorigenesis. *Cell Death Dis*. 2022;13(4):1-10.
7. Han L, Husaiyin S, Ma C, et al. TNFAIP8L1 and FLT1 polymorphisms alter the susceptibility to cervical cancer amongst Uyghur females in China. *Biosci Rep*. 2019;39(7):BSR20191155.
8. Padmavathi G, Banik K, Monisha J, et al. Novel tumor necrosis factor-α induced protein eight (TNFAIP8/TIPE) family: functions

and downstream targets involved in cancer progression. *Cancer Lett*. 2018;432:260-271.
9. Lou Y, Liu S. The TIPE (TNFAIP8) family in inflammation, immunity, and cancer. *Mol Immunol*. 2011;49(1-2):4-7.
10. Goldsmith JR, Chen YH. Regulation of inflammation and tumorigenesis by the TIPE family of phospholipid transfer proteins. *Cell Mol Immunol*. 2017;14(6):482-487.
11. Shi TY, Cheng X, Yu KD, et al. Functional variants in TNFAIP8 associated with cervical cancer susceptibility and clinical outcomes. *Carcinogenesis*. 2013;34(4):770-778.
12. Xu Y, Ma H, Yu H, et al. The miR-184 binding-site rs8126 T>C polymorphism in TNFAIP2 is associated with risk of gastric cancer. *PLoS One*. 2013;8(5):e64973.
13. Sarma V, Wolf FW, Marks RM, et al. Cloning of a novel tumor necrosis factor-alpha-inducible primary response gene that is differentially expressed in development and capillary tube-like formation in vitro. *J Immunol*. 1992;148(10):3302-3312.
14. Liu Z, Wei S, Ma H, et al. A functional variant at the miR-184 binding site in TNFAIP2 and risk of squamous cell carcinoma of the head and neck. *Carcinogenesis*. 2011;32(11): 1668-1674.
15. Hase K, Kimura S, Takatsu H, et al. M-Sec promotes membrane nanotube formation by interacting with Ral and the exocyst complex. *Nat Cell Biol*. 2009;11(12):1427-1432.
16. Landi D, Gemignani F, Naccarati A, et al. Polymorphisms within micro-RNA-binding sites and risk of sporadic colorectal cancer. *Carcinogenesis*. 2008;29(3):579-584.
17. Rong G, Tang W, Wang Y, Qiu H, Chen S. Investigation of leptin receptor rs1137101 G > A polymorphism with cancer risk: evidence from 35936 subjects. *Biosci Rep*. 2019;39(6): BSR20182240.
18. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Br Med J.* 2021;372:n71.
19. Wells G, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2000.
20. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials*. 1996;17(1):1-12.
21. Meng J, Wang S, Zhang M, Fan S, Zhang L, Liang C. *TP73 G4C14-A4T14* polymorphism and cancer susceptibility: Evidence from 36 case-control studies. *Biosci Rep*. 2018;38(6): BSR20181452.
22. Fan S, Meng J, Zhang L, Zhang X, Liang C. CAV1 polymorphisms rs1049334, rs1049337, rs7804372 might be the potential risk in tumorigenicity of urinary cancer: a systematic review and meta-analysis. *Pathol Res Pract.* 2019;215(1): 151-158.
23. Gao H, Zhang Z, Jiang L, et al. TNFAIP8 variants as potential epidemiological and predictive biomarkers in ovarian cancer. *Cancer Cell Int*. 2020;20(1):1-8.
24. Liu T, Jiang L, Yu L, Ge T, Wang J, Gao H. Association of TNFAIP8 gene polymorphisms with endometrial cancer in northern Chinese women. *Cancer Cell Int*. 2019;19(1):1-7.
25. Han SX, Zhao JJ, Li XWA. Molecular epidemiological study on apoptosis related gene SNP mediated by TNF-α in pathogenesis of cervical cancer. *J Clin Exp Med*. 2017;16:851-854.
26. Zhang Y, Wang MY, He J, et al. Tumor necrosis factor-α induced protein 8 polymorphism and risk of non-Hodgkin's lymphoma in a Chinese population: a case–control study. *PLoS One*. 2012;7(5): e37846.
27. Al-Khatib SM, Abdo N, Al-Eitan LN, Al-Mistarehi AHW, Zahran DJ, Kewan TZ. LTA, LEP, and TNF-a gene polymorphisms are associated with susceptibility and overall survival of diffuse large B-cell lymphoma in an Arab population: a case–control study. *Asian Pac J Cancer Prev*. 2020;21(9):2783.
28. Guo F, Xu Q, Lv Z, et al. Correlation between TNFAIP2 gene polymorphism and prediction/prognosis for gastric cancer and its effect on TNFAIP2 protein expression. *Front Oncol*. 2020;10:1127.
29. Ainiwaer Z, Maisaidi R, Liu J, et al. Genetic polymorphisms of PGF and TNFAIP2 genes related to cervical cancer risk among Uygur females from China. *BMC Med Genet*. 2020; 21(1):1-7.
30. Slaby O, Sachlova M, Brezkova V, et al. Identification of microRNAs regulated by isothiocyanates and association of polymorphisms inside their target sites with risk of sporadic colorectal cancer. *Nutr Cancer*. 2013;65(2):247-254.
31. Zhang J, Yu H, Zhang Y, et al. A functional TNFAIP2 3′-UTR rs8126 genetic polymorphism contributes to risk of esophageal squamous cell carcinoma. *PLoS One*. 2014;9(11):e109318.
32. Chen Q, Guo D, Zheng J, Xu X. Effect of tumor necrosis factor alpha inducible protein 2 gene polymorphism on risk of Hp-positive non-cardia gastric cancer. *Chin J Nosocomiol*. 2022;7:1018-1022.
33. Matthews HK, Bertoli C, de Bruin RA. Cell cycle control in cancer. *Nat Rev Mol Cell Biol*. 2022;23(1):74-88.
34. Jones PA, Baylin SB. The epigenomics of cancer. *Cell*. 2007;128(4):683-692.
35. Li M, Li X, Goldsmith JR, et al. Decoupling tumor cell metastasis from growth by cellular pilot protein TNFAIP8. *Oncogene*. 2021;40(46):6456-6468.
36. Patel S, Wang F, Whiteside T, Kasid U. Identification of seven differentially displayed transcripts in human primary and matched metastatic head and neck squamous cell carcinoma cell lines: implications in metastasis and/or radiation response. *Oral Oncol*. 1997;33(3):197-203.
37. Horrevoets AJ, Fontijn RD, van Zonneveld AJ, de Vries CJ, ten Cate JW, Pannekoek H. Vascular endothelial genes that are responsive to tumor necrosis factor-α in vitro are expressed in atherosclerotic lesions, including inhibitor of apoptosis protein-1, stannin, and two novel genes. *Blood*. 1999;93(10): 3418-3431.
38. Dong QZ, Zhao Y, Liu Y, et al. Overexpression of SCC-S2 correlates with lymph node metastasis and poor prognosis in patients with non-small-cell lung cancer. *Cancer Sci*. 2010; 101(6):1562-1569.
39. Gao X, Xiong C, Wang D, et al. Association of TNFAIP8 gene polymorphisms with cancer risk in Chinese population. *Nucleos Nucleot Nucl*. 2022;41(5–6):1-11.

40. Zhang Z, Liang X, Gao L, et al. TIPE1 induces apoptosis by negatively regulating Rac1 activation in hepatocellular carcinoma cells. *Oncogene*. 2015;34(20):2566-2574.
41. Wu X, Ma Y, Cheng J, et al. TIPE1 function as a prognosis predictor and negative regulator of lung cancer. *Oncotarget*. 2017; 8(45):78496.
42. Ha JY, Kim JS, Kang YH, Bok E, Kim YS, Son JH. Tnfaip8 l1/ Oxi-β binds to FBXW 5, increasing autophagy through activation of TSC 2 in a Parkinson's disease model. *J Neurochem*. 2014; 129(3):527-538.
43. Chevrier N, Mertins P, Artyomov MN, et al. Systematic discovery of TLR signaling components delineates viral-sensing circuits. *Cell*. 2011;147(4):853-867.
44. Jia L, Shi Y, Wen Y, Li W, Feng J, Chen C. The roles of TNFAIP2 in cancers and infectious diseases. *J Cell Mol Med*. 2018;22(11): 5188-5195.
45. Thair SA, Topchiy E, Boyd JH, et al. TNFAIP2 Inhibits early TNFα-induced NF-κB signaling and decreases survival in septic shock patients. *J Innate Immun*. 2016;8(1):57-66.
46. Jia L, Zhou Z, Liang H, et al. KLF5 promotes breast cancer proliferation, migration and invasion in part by upregulating the transcription of TNFAIP2. *Oncogene*. 2016;35(16):2040-2051.
47. Xie Y, Wang B. Downregulation of TNFAIP2 suppresses proliferation and metastasis in esophageal squamous cell carcinoma through activation of the Wnt/β-catenin signaling pathway. *Oncol Rep*. 2017;37(5):2920-2928.