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Role of *IL-1β* rs1143634 (+3954C>T) polymorphism in cancer risk: an updated meta-analysis and trial sequential analysis

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Abstract

Objective: Oxidative stress caused by the pro-inflammatory cytokine interleukin (IL)-1β has been widely investigated for cancer risk. In this study, we focused on the role of *IL-1β* rs1143634 polymorphism to reveal its impact on cancer development.

Methods: Related studies with fixed inclusion criteria were selected from electronic databases to May 2021. This meta-analysis was performed with odds ratios and 95% confidence intervals. Heterogeneity, publication bias and sensitivity analyses were also conducted. Trial sequential analysis (TSA) and *in-silico* gene expression analysis were performed.

Results: Forty-four case–control studies involving 18,645 patients with cancer and 22,882 controls were included. We observed a significant association of this single nucleotide polymorphism with overall cancer risk in the codominant model 3 (1.13-fold), recessive model (1.14-fold) and allelic model (1.08-fold). Subgroup analysis revealed that rs1143634 elevated the risk of gastric cancer, breast cancer and multiple myeloma. In addition, Asian and mixed populations and hospital-based controls had a significantly higher risk of cancer development. TSA confirmed our findings.

Conclusion: Our meta-analysis revealed that the presence of *IL-1β* rs1143634 polymorphism increases the risk of cancer development. Among polymorphism carriers, the Asian population has a higher risk than other ethnic populations.

This meta-analysis was registered retrospectively at INPLASY (https://inplasy.com/, INPLASY2021100044).

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Introduction

Currently, cancer is a leading cause of death worldwide. Oxidative stress induced by chronic inflammation plays a vital role in cancer development. Although inflammation is necessary for the immune system to protect the body against foreign infections, the overstimulation of inflammatory cytokines has been identified to be responsible for cancer progression.[1–6] Cancer cells often increase the release of cytokines that stimulate the activation of multiple genes involved in cellular migration, proliferation and survival. These cytokines help establish a favorable microenvironment for neoplastic initiation and DNA damage.[7,8] Interleukin-1 (IL-1) is a pro-inflammatory cytokine that exerts a wide range of biological actions, and several case–control studies have shown that *IL-1* polymorphisms are significantly associated with different cancers .[9]

The *IL-1β* gene encodes IL-1β, which is one of the most potent pro-inflammatory cytokines that initiates and amplifies both acute and chronic inflammation and is involved in various cellular actions, such as proliferation, differentiation and apoptosis. Upon stimulation, blood monocytes and tissue macrophages produce *IL-1β* proprotein, which is cleaved and activated by caspase 1.[10–15] According to genome-wide association studies, patients with three common characteristic polymorphisms of this gene, including rs16944, rs1143627 and rs1143634, are highly susceptible to cancer development.[16–18]

rs1143634, also known as +3954C>T, is a silent coding sequence polymorphism located in exon 5 of chromosome 2. This single nucleotide polymorphism (SNP) showed a significant association with increased IL-1β release from lipopolysaccharide-induced cells in previous *in vitro* studies.[19–21] Silent SNPs tend to produce truncated proteins that remain inactive or degrade faster than active proteins. This occurs when a silent SNP inactivates the splicing site and causes premature termination of mRNA transcription.[22] In the case of rs1143634, the presence of this polymorphism increases active IL-1β rather than inactive protein.[19–21] Excess IL-1β concentrations facilitate a suitable environment for cancer development by increasing the rate of uncontrolled cellular proliferation and differentiation and interfering with apoptosis. Over the past decades, several individual case–control studies on *IL-1β* rs1143634 polymorphism and cancer susceptibility have been conducted in different ethnic groups. Although some studies reported a significant link between this variant and different cancers, others failed to establish any significant association.[9] In this meta-analysis, we summarized previous studies to investigate the connection between *IL-1β* rs1143634 polymorphism and cancers and provide comprehensive outcomes.

Materials and methods

Literature search strategy

Multiple authorized electronic databases (PubMed, Google Scholar, CNKI, Web of Science and EMBASE) were comprehensively searched for related literature using

specific key terms up to May 2021. The selected key terms included cancer, interleukin-1 beta, rs1143634 (+3954C>T), *IL-1β* polymorphism and cancer, link between *IL-1β* rs1143634 and carcinogenesis and *IL-1β* polymorphism and cancer development in various ethnic populations. Additional studies were extracted from the references and citations of the selected studies and the 'similar studies' option of the respected websites. We selected published studies without restricting available languages.

Publication screening

The eligibility of the publications was determined based on the previously selected key terms, and the overall selection process was completed using a protocol designed by the authors. The authors (SJ and MAA) selected the eligible studies containing the related data and organized the extracted data for the meta-analysis by comprehensive screening. The overall study selection protocol was designed as a PRISMA flow diagram[23] using Review Manager (RevMan), Version 5.4 (The Cochrane Collaboration, 2020). The overall process was revised through final screening by another author (MSI).

This meta-analysis was retrospectively registered at INPLASY (https://inplasy.com/, INPLASY2021100044). Because no patients or controls were directly involved in this meta-analysis, patient consent and ethical approval were not necessary.

Inclusion and exclusion criteria

The main inclusion criteria of the selected studies were that they must contain comparative genotypic information and detailed data regarding *IL-1β* rs1143634 (+3954C>T) polymorphism in both patients with cancer and control populations. If the selected studies contained genotypic data on other SNPs, we only extracted the *IL-1β* rs1143634 (+3954C>T) data to include in this meta-analysis. We excluded studies without *IL-1β* rs1143634 genotypic data in patients with cancer as they were not eligible for this study. Publications containing incomplete genotypic data on rs1143634 were also excluded. Studies lacking control population data and those with incomplete information were avoided for further comparison in this meta-analysis.

Extraction and quality assessment of data

The study ID, publication year, country and ethnic background of the study population, cancer type, control type, genotypic method, sample and control size, clinical histories and basic characteristics, genotypic data for the selected SNP, Hardy–Weinberg equilibrium (HWE) *p*-value and Newcastle–Ottawa Scale (NOS) score were collected from each selected study by the authors.[23] Two authors (SJ and MAA) screened and processed the data using a previously designed protocol, and another author (MSI) reviewed the organized data by conducting the final screening.

Statistical analysis

We performed statistical analysis by comparing the frequency of *IL-1β* rs1143634 polymorphism among patients with different cancers and control populations to determine the connection between *IL-1β* rs1143634 variants and cancer development susceptibility. The meta-analysis used hospital-based (HB) and population-based (PB) control populations as the control arms and patients with various cancers carrying the *IL-1β* rs1143634 polymorphism as the experimental arm. We used Review Manager (RevMan 5.4) to perform the overall statistical data analysis. Estimation of cancer susceptibility was pooled as odds ratios (ORs) with 95% confidence intervals (CIs). Based on heterogeneity, both the

fixed-effect model and the random-effects model were used (Q-test). If heterogeneity was significant (p-value <0.10), a random-effect model was applied, and when heterogeneity was not significant, the fixed-effect model (Mantel–Haenszel) was applied.

The Begg & Mazumdar test and Egger's regression test were carried out to estimate publication biases. Sensitivity analysis was also performed to assess the reliability of the results by excluding individual studies one at a time. Ethnicity-based sub-group analyses (White, Asian, African and mixed) were conducted to analyze the role of *IL-1β* rs1143634 in patients with cancer among different ethnic populations. Cancer types with less than two studies were sub-grouped into 'other cancers' for further subgroup analysis.

We applied seven common genetic models, including the association-allele model (AM: T vs. C), codominant model 1 (COD1: TC vs. CC), codominant model 2 (COD2: TT vs. CC), codominant model 3 (COD3: TT vs. TC), dominant model (DM: TT+ TC vs. CC), recessive model (RM: TT vs. TC + CC) and over-dominant model (OD: TC vs. TT+ CC). TT, TC and CC indicate normal homozygotes, heterozygotes and mutant homozygotes, respectively.

Trial sequential analysis (TSA)

TSA was performed to reduce the random error risk. We first determined the required information size (RIS) and defined the monitoring boundaries by setting the following criteria: 1) 95% CI with a p-value <0.05, 2) 20% relative risk reduction, 3) 80% statistical power and 4) 5% type I error. We used TSA software (version 0.9.5.10 beta)[24] for conducting TSA. The statistical summary (Z values) was plotted on the Z-curve, which showed the TSA boundary. If the cumulative Z-curve crossed the TSA boundary or RIS, this meta-analysis was considered to have achieved a reasonable and sufficient degree of evidence, confirming that no additional studies are required.

In silico gene expression analysis

To evaluate the overall impact of rs1143634 polymorphism on the *IL-1β* gene expression level, we conducted an important *in silico* gene expression analysis termed expression quantitative trait loci (eQTL) analysis through the GTEx portal website (http://www.gtexportal.org/). Two skin samples from the GTEx database were analyzed, including sun-exposed skin samples and non-sun exposed skin samples (suprapubic). Sun-exposed skin samples were taken from the lower leg, and non-sun-exposed skin samples were taken from the suprapubic area. The skin samples were obtained as slices with the subcutaneous fat removed, avoiding pubic hair in the suprapubic region.

Results

Selection of the individual studies

Figure 1 outlines the complete study selection process in this meta-analysis. Forty-four studies[17,25–67] were selected from 970 primary studies acquired from the searched databases following the eligibility criteria. Comprehensive screening of the titles, abstracts and full texts for each study was conducted to include or exclude the studies. The quality of the studies was determined using the NOS quality assessment score, and low-quality studies (score <6) were excluded. Among the 44 studies, there were 18 on gastric cancer (GC), 8 on lung cancer (NSCLC), 7 on breast cancer (BC), 4 on colorectal cancer (CRC), 3 on prostate cancer (PCa) and 4 on other cancers.

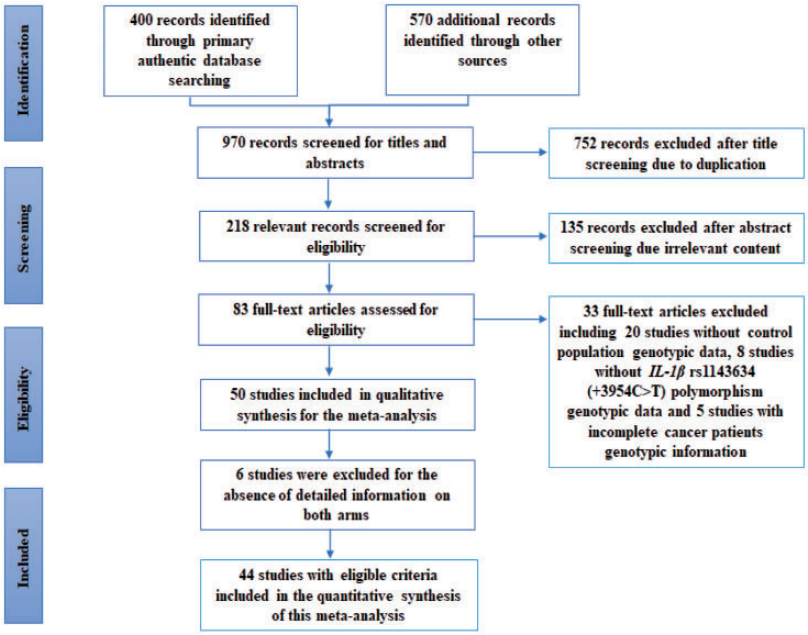

Figure 1. PRISMA flow diagram for study selection.
IL-1β: interleukin-1 beta.

Study characteristics

The basic demographic information of the 44 selected case–control studies involving 18,645 patients with cancer and 22,882 controls is summarized in Table 1. Among them, 16 studies were from the Asian population, 23 studies were from the White population, 2 studies were from the African population, and the other 5 studies were from mixed populations. One association study recruited both African and White populations for the *IL-1β* rs1143634 polymorphism. Most studies reported the HWE *p*-value.

Association of IL-1β *rs1143634 with cancers*

The overall meta-analysis of the total study population showed a significantly elevated risk in patients with cancer carrying the *IL-1β* rs1143634 variant in three different genetic models, including COD3 (TT vs. TC: OR = 1.13, 95% CI = 1.02–1.25, $p = 0.016$), RM (TT vs. TC + CC: OR = 1.14, 95% CI = 1.04–1.25, $p = 0.006$) and AM (T vs. C: OR = 1.08, 95% CI = 1.0–1.17, $p = 0.039$). According to the ethnicity-based subgroup analysis, the White population did not show any significant link between rs1143634 and cancer risk. In contrast, the Asian population showed a significantly increased risk of cancer among the variant carriers in several genetic models, including COD1 (TC vs. CC: OR = 1.54, 95% CI = 1.12–2.11, $p = 0.008$), DM (TT + TC vs. CC: OR = 1.54, 95% CI = 1.14–2.09, $p = 0.005$), OD (TC vs. TT+CC: OR = 1.48, 95% CI = 1.07–2.03, $p = 0.017$) and AM (T vs. C: OR = 1.50, 95% CI = 1.15–1.95, $p = 0.003$). In the African population, there was no significant association between cancer risk and the rs1143634 variant. Other studies with mixed populations showed a significant risk in COD2

Table 1. Baseline characteristics of all studies evaluating *IL-1β* rs1143634 included in this meta-analysis.[17,24–66]

Study ID	Year	Country	Ethnicity	Cancer type	Control type	Genotyping method	Cases	Controls	Cases			Controls			HWE *p*-value	NOS score
									TT	TC	CC	TT	TC	CC		
Abazis-Stamboulieh et al.	2007	Greece	White	MM	HB	PCR-SSP	74	160	12	39	23	8	62	90	0.518	8
AL-Eitan et al.	2020	Jordan	Asian	BC	HB	PCR-RFLP	148	187	78	57	13	74	92	21	0.339	9
Al-Moundhri et al.	2006	Oman	Asian	GC	PB	TaqMan	118	245	9	48	61	27	91	127	0.089	8
Alpízar-Alpízar et al.	2005	Costa Rica	White	GC	HB	PCR-RFLP	45	45	0	20	25	0	8	37	0.513	9
Balasubramanian et al.	2006	UK	White	BC	PB	TaqMan	691	420	39	242	410	22	167	231	0.243	9
Burada et al	2013	Romania	White	CRC	HB	TaqMan	144	233	11	46	87	18	93	122	0.962	9
Chen et al.	2005	China	Asian	HC	PB	PCR-RFLP	573	385	2	20	551	0	10	375	0.796	7
Cigrovski Berković et al.	2012	Croatia	White	PNT	HB	TaqMan	60	60	1	31	28	3	25	32	0.499	8
Crusius et al.	2008	Netherlands	White	GC	PB	RT-PCR	237	1125	13	88	136	70	412	643	0.713	9
Eaton et al.	2018	USA	Mixed	LC	PB	TaqMan	623	623	29	233	361	27	213	383	0.702	9
El-Omar et al.	2000	Poland	White	GC	PB	TaqMan	366	429	14	140	212	29	158	242	0.643	9
Glas et al	2004	Germany	White	GC	PB	PCR-RFLP	88	145	3	26	59	5	53	87	0.368	9
Gonzalez-Hormazabal et al	2014	Chile	White	GC	HB	TaqMan	147	172	5	31	111	4	46	122	0.891	8
Gordeeva et al.	2018	Russia	White	SQLC	HB	TaqMan	324	175	14	119	191	14	64	97	0.457	9
Hartland et al.	2004	UK	White	GC	HB	TaqMan	59	286	4	27	28	11	97	178	0.621	8
He et al.	2014	China	Asian	OS	HB	PCR-RFLP	120	120	13	30	77	9	32	79	0.036	9
Hefler et al.	2005	Germany	White	BC	HB	Pyrosequencing	269	227	13	97	159	9	99	119	0.035	8
Kaarvatn et al.	2012	Croatia	White	BC	HB	TaqMan	191	117	7	74	110	5	44	68	0.522	8
Kiyohara et al.	2010	Japan	Asian	LC	PB	TaqMan	462	379	9	70	383	3	42	334	0.200	8
Landvik et al.	2009	Norway	White	NSCLC	PB	TaqMan	357	430	24	136	197	30	144	256	0.122	9
Lee et al.	2007	China	Asian	LC	PB	RT-PCR	119	110	0	3	116	0	3	107	0.885	8
Michaud et al.	2006	USA	Mixed	PCa	PB	TaqMan	486	614	28	162	296	27	212	375	0.667	9
Ohmiya et al.	2001	Japan	Asian	GC	PB	ND	143	428	0	13	130	0	39	389	0.323	6
Palli et al.	2005	Italy	White	GC	PB	TaqMan	185	546	14	57	114	33	182	331	0.238	8
Pérez-Ramírez et al.	2017	Spain	White	NSCLC	PB	TaqMan	174	298	3	57	114	19	117	162	0.728	8
Persson et al._HB	2010	Sweden	White	GC	HB	Seminested	65	297	2	16	47	13	66	218	0.009	6
Persson et al._PB	2009	Sweden	White	GC	PB	Seminested	284	242	18	66	200	16	57	169	0.001	6
Pooja et al.	2012	India	Asian	BC	HB	PCR-RFLP	200	200	8	46	146	12	12	176	<001	7
Qian et al.	2018	China	Asian	CRC	HB	SMA	526	637	8	119	399	22	168	447	0.213	8

(continued)

Table 1. Continued.

Study ID	Year	Country	Ethnicity	Cancer type	Control type	Genotyping method	Cases	Controls	Cases			Controls			HWE *p*-value	NOS score
									TT	TC	CC	TT	TC	CC		
Sakuma et al.	2005	Japan	Asian	GC	HB	PCR-RFLP	140	103	0	27	113	0	10	93	0.605	7
Sanabria-Salas et al.	2017	Colombia	Mixed	CRC	HB	TaqMan	500	306	14	123	363	4	77	225	0.363	8
Schonfeld et al.	2010	USA	Mixed	BC	PB	TaqMan	834	1074	57	314	463	53	385	636	0.590	9
Sicinschi et al.	2006	Mexico	White	GC	HB	TaqMan	137	262	4	18	115	4	35	223	0.067	8
Snoussi et al.	2005	Tunisia	African	BC	HB	PCR-RFLP	305	200	34	114	157	14	66	120	0.245	9
Song et al.	2021	China	Asian	GC	HB	SMA	190	186	3	19	168	0	8	178	0.764	8
Sousa et al.	2016	Portugal	White	NPC	HB	TaqMan	131	687	4	39	88	38	254	395	0.734	9
Ter-Minassian et al.	2008	USA	White	NSCLC	PB	TaqMan	2150	1492	113	775	1262	69	551	872	0.124	9
Truong et al.	2010	Mixed	Mixed	LC	Mixed	TaqMan	5438	7322	319	1744	3375	367	2407	4548	0.037	6
Wang et al.	2007	China	Asian	GC	HB	ALM-ASA	97	141	0	5	92	0	3	138	0.898	7
Wang et al.	2015	China	Asian	CRC	HB	SMA	203	296	1	17	185	0	13	283	0.699	7
Wen et al.	2014	China	Asian	GC	HB	SMA	308	308	1	18	289	0	10	298	0.772	8
Zabaleta et al._AF	2008	USA	African	PCa	HB	TaqMan	67	125	3	11	53	3	31	91	0.853	8
Zabaleta et al._Cau	2008	USA	White	PCa	HB	TaqMan	470	389	23	178	269	21	141	227	0.883	8
Zeng et al.	2003	China	Asian	GC	HB	PCR-RFLP	170	361	1	15	154	0	45	316	0.207	9
Zhang et al.	2000	Sweden	White	MM	HB	PCR-RFLP	73	129	5	25	43	6	46	77	0.793	9
Zhang et al.	2005	China	Asian	GC	PB	PCR-RFLP	154	166	0	40	114	0	8	158	0.750	8
Total							**18,645**	**22,882**	**963**	**5595**	**12,087**	**1089**	**6898**	**14,895**		

SMA: Sequenom MassARRAY; RT-PCR: reverse transcription-polymerase chain reaction; SSP: sequence-specific amplification; RFLP: restriction fragment length polymorphism; ALM-ASA: adapter-ligation mediated allele-specific amplification; HB: hospital-based; PB: population-based; HWE: Hardy–Weinberg Equilibrium; NOS: Newcastle–Ottawa Scale; GC: gastric cancer; CRC: colorectal cancer; BC: breast cancer; LC: lung cancer; NSCLC: non-small cell lung cancer; SQLC: squamous cell lung cancer; MM: multiple myeloma; PCa: prostate cancer; PNT: pancreatic neuroendocrine tumor; NPC: nasopharyngeal cancer; OS: osteosarcoma, ND: not defined.

(TT vs. CC: OR = 1.22, 95% CI = 1.07–1.40, $p = 0.004$), COD3 (TT vs. TC: OR = 1.22, 95% CI = 1.06–1.40, $p = 0.006$), RM (TT vs. TC + CC: OR = 1.22, 95% CI = 1.07–1.39, $p = 0.004$) and AM (T vs. C: OR = 1.05, 95% CI = 1.0–1.11, $p = 0.050$) genetic models.

In the sub-group analysis of different cancer types, patients with *IL-1β* rs1143634 polymorphism showed a significant risk of GC in COD1 (TC vs. CC: OR = 1.25, 95% CI = 1.00–1.56, $p = 0.048$), DM (TT + TC vs. CC: OR = 1.25, 95% CI = 1.01–1.56, $p = 0.039$), OD (TC vs. TT+CC: OR = 1.25, 95% CI = 1.00–1.55, $p = 0.045$) and AM (T vs. C: OR = 1.21, 95% CI = 1.00–1.46, $p = 0.044$) models. For BC, patients with this polymorphism showed a significantly increased cancer risk in two genetic models, including COD2 (TT vs. CC: OR = 1.31, 95% CI = 1.03–1.67, $p = 0.029$) and RM (TT vs. TC + CC: OR = 1.35, 95% CI = 1.08–1.67, $p = 0.008$). The carriers of *IL-1β* rs1143634 polymorphism showed a significant risk for multiple myeloma (MM) in the RM model (TT vs. TC + CC: OR = 2.64, 95% CI = 1.25–5.57, $p = 0.011$). No significant association was found for the other types of cancers. Subgroup analysis of HB control populations showed a significantly increased risk in two genetic models: DM (TT + TC vs. CC: OR = 1.18, 95% CI = 1.00–1.40, $p = 0.049$) and AM (T vs. C: OR = 1.17, 95% CI = 1.02–1.35, $p = 0.030$). PB controls with rs1143634 polymorphism did not show any association with cancer risk. The overall findings were summarized in Table 2 and Figure 2.

Heterogeneity

The *Q*-test was performed to determine the degree of heterogeneity (Table 2). Heterogeneity was significant in maximum subgroup analysis models (p-value <0.1), and random-effect models were applied for these analyses. All subgroup analyses showed significant heterogeneity (p-value < 0.1), except the subgroup analysis with the mixed population and patients with PCa. The overall analysis with the total study population did not show significant heterogeneity in COD3 ($I^2 = 19.52$) and RM ($I^2 = 22.46$) genetic models.

Sensitivity and publication bias analyses

To confirm the reliability of the outcomes, we performed a sensitivity analysis by the sequential omission of each study. The influence of each included study on the final outcome of this meta-analysis was analyzed, and none of the studies interfered with the pooled ORs. The sensitivity analysis revealed the stability and robustness of this meta-analysis (Table 3).

Publication bias was tested using Egger's test and Begg & Mazumdar's test. The funnel plots are shown in Figure 3, and the bias parameters are presented in Table 4. The bias analysis was conducted for overall studies, and no visual asymmetry was found for COD2, COD3 and RM, indicating the absence of publication bias. The rest of the analysis model showed potential publication biases (p-value <0.05).

TSA results

TSA plots revealed that the cumulative Z-curve for rs1143634 crossed conventional and/or trial sequential monitoring boundaries and achieved the RIS in the overall analysis, GC, BC and HB controls, demonstrating that an adequate level of evidence was achieved, and no further studies are required to confirm the results of the present meta-analysis (Figure 4 A–F). For the Asian subgroup of overall cancer, the Z-curve surpassed the trial sequential monitoring boundary but failed to attain the RIS.

Table 2. Meta-analysis of the association between *IL-1β* rs1143634 polymorphisms and cancer susceptibility.

Variables	Test types	Parameters	COD1 (TC vs. CC)	COD2 (TT vs. CC)	COD3 (TT vs. TC)	DM (TT + TC vs. CC)	RM (TT vs. TC + CC)	OD (TC vs. TT + CC)	AM (T vs. C)
Overall	Association	OR	1.08	1.10	1.13	1.09	1.14	1.06	1.08
		95% CI	0.98–1.18	0.95–1.27	1.02–1.25	1.0–1.19	1.04–1.25	1.0–1.16	1.0–1.17
		p-value	0.110	0.202	0.016	0.061	0.006	0.210	0.039
	Heterogeneity	Model	Random	Random	Fixed	Random	Fixed	Random	Random
		p-value	<0.001	0.048	0.143	<0.001	0.106	<0.001	<0.001
		I^2 (%)	48.35	28.86	19.52	52.59	22.46	45.92	56.4
White	Association	OR	0.97	0.97	1.01	0.97	1.00	0.97	0.98
		95% CI	0.87–1.09	0.78–1.20	0.86–1.19	0.87–1.09	0.85–1.166	0.88–1.07	0.89–1.08
		p-value	0.633	0.783	0.872	0.649	0.979	0.599	0.673
	Heterogeneity	Model	Random	Random	Fixed	Random	Fixed	Random	Random
		p-value	0.016	0.073	0.550	0.003	0.241	0.069	0.002
		I^2 (%)	42.87	32.41	0	50.42	16.47	32.34	52.6
Asian	Association	OR	1.54	1.08	1.00	1.54	1.19	1.48	1.50
		95% CI	1.12–2.11	0.76–1.53	0.55–1.81	1.14–2.09	0.74–1.92	1.07–2.03	1.15–1.95
		p-value	0.008	0.679	0.996	0.005	0.481	0.017	0.003
	Heterogeneity	Model	Random	Fixed	Random	Random	Random	Random	Random
		p-value	<0.001	0.131	0.012	<0.001	0.064	<0.001	<0.001
		I^2 (%)	73.87	33.45	55.86	73.69	42.88	76.7	74.49
African	Association	OR	0.97	1.84	1.55	1.07	1.70	1.06	1.26
		95% CI	0.46–2.03	0.99–3.40	0.81–2.94	0.55–2.09	0.93–3.10	0.75–1.48	0.97–1.64
		p-value	0.927	0.054	0.184	0.837	0.086	0.753	0.079
	Heterogeneity	Model	Random	Fixed	Fixed	Random	Fixed	Fixed	Fixed
		p-value	0.077	0.931	0.467	0.088	0.881	0.102	0.147
		I^2 (%)	67.95	0	0	65.73	0	62.68	52.39
Mixed	Association	OR	1.00	1.22	1.22	1.03	1.22	0.99	1.05
		95% CI	0.94–1.07	1.07–1.40	1.06–1.40	0.97–1.10	1.07–1.39	0.93–1.05	1.0–1.11
		p-value	0.892	0.004	0.006	0.315	0.004	0.726	0.050
	Heterogeneity	Model	Fixed	Fixed	Fixed	Fixed	Fixed	Fixed	Fixed
		p-value	0.505	0.679	0.753	0.505	0.726	0.549	0.574
		I^2 (%)	0	0	0	0	0	0	0

(continued)

Table 2. Continued.

Variables	Test types	Parameters	COD1 (TC vs. CC)	COD2 (TT vs. CC)	COD3 (TT vs. TC)	DM (TT + TC vs. CC)	RM (TT vs. TC + CC)	OD (TC vs. TT + CC)	AM (T vs. C)
GC	Association	OR	1.25	0.97	0.95	1.25	0.96	1.25	1.21
		95% CI	1.00–1.56	0.74–1.27	0.72–1.26	1.01–1.56	0.73–1.25	1.00–1.55	1.00–1.46
		p-value	0.048	0.803	0.710	0.039	0.751	0.045	0.044
	Heterogeneity	Model	Random	Fixed	Fixed	Random	Fixed	Random	Random
		p-value	0.0001	0.533	0.663	<0.001	0.558	0.0001	0.0001
		I^2 (%)	64.23	0	0	65.89	0	63.76	65.61
BC	Association	OR	1.15	1.31	1.13	1.16	1.35	1.06	1.15
		95% CI	0.85–1.56	1.03–1.67	0.76–1.69	0.89–1.50	1.08–1.67	0.79–1.43	0.96–1.38
		p-value	0.365	0.029	0.545	0.267	0.008	0.703	0.120
	Heterogeneity	Model	Random	Fixed	Random	Random	Fixed	Random	Random
		p-value	0.0001	0.604	0.021	0.001	0.513	<0.001	0.006
		I^2 (%)	78.5	0	59.69	73.39	0	80.84	66.6
LC	Association	OR	1.00	1.02	1.12	1.02	1.02	0.99	1.02
		95% CI	0.94–1.06	0.78–1.33	0.98–1.28	0.91–1.15	0.79–1.31	0.93–1.05	0.91–1.13
		p-value	0.893	0.903	0.090	0.679	0.907	0.702	0.781
	Heterogeneity	Model	Fixed	Random	Fixed	Random	Random	Fixed	Random
		p-value	0.164	0.054	0.160	0.058	0.073	0.236	0.018
		I^2 (%)	33.05	51.55	35.19	48.76	48.02	24.2	58.77
CRC	Association	OR	0.92	0.94	1.01	0.94	1.00	0.89	0.98
		95% CI	0.68–1.25	0.41-2.20	0.60–1.70	0.67–1.32	0.44–2.26	0.74–1.06	0.71–1.36
		p-value	0.594	0.894	0.965	0.738	1.00	0.192	0.911
	Heterogeneity	Model	Random	Random	Fixed	Random	Random	Fixed	Random
		p-value	0.079	0.079	0.195	0.030	0.091	0.102	0.012
		I^2 (%)	55.86	55.83	36.19	66.37	53.63	51.61	72.7
PCa	Association	OR	0.98	1.15	1.17	1.00	1.15	0.97	1.02
		95% CI	0.82–1.18	0.77–1.72	0.78–1.76	0.84–1.19	0.78–1.71	0.81–1.17	0.88–1.18
		p-value	0.843	0.484	0.452	0.986	0.474	0.768	0.784
	Heterogeneity	Model	Fixed	Fixed	Fixed	Fixed	Fixed	Fixed	Fixed
		p-value	0.403	0.626	0.349	0.597	0.533	0.351	0.796
		I^2 (%)	0	0	4.9	0	0	4.59	0

(continued)

Table 2. Continued.

Variables	Test types	Parameters	COD1 (TC vs. CC)	COD2 (TT vs. CC)	COD3 (TT vs. TC)	DM (TT + TC vs. CC)	RM (TT vs. TC + CC)	OD (TC vs. TT + CC)	AM (T vs. C)
MM	Association	OR	1.55	3.11	2.03	1.72	2.64	1.32	1.60
		95% CI	0.62–3.85	0.82–11.88	0.93–4.42	0.64–4.64	1.25–5.57	0.88–1.99	0.77–3.33
		p-value	0.346	0.096	0.076	0.287	0.011	0.184	0.211
	Heterogeneity	Model	Random	Random	Fixed	Random	Fixed	Fixed	Random
		p-value	0.035	0.093	0.592	0.016	0.258	0.133	0.020
		I^2 (%)	77.43	64.5	0	82.79	21.98	55.61	81.39
Others	Association	OR	0.91	0.91	0.99	0.92	0.95	0.93	1.01
		95% CI	0.69–1.21	0.48–1.72	0.50–1.95	0.70–1.20	0.50–1.79	0.70–1.23	0.71–1.45
		p-value	0.516	0.762	0.976	0.533	0.863	0.602	0.950
	Heterogeneity	Model	Fixed	Fixed	Fixed	Fixed	Fixed	Fixed	Random
		p-value	0.234	0.277	0.427	0.137	0.300	0.253	0.095
		I^2 (%)	29.73	22.25	0	45.73	18.06	26.55	52.9
HB	Association	OR	1.16	1.20	1.12	1.18	1.18	1.12	1.17
		95% CI	0.98–1.38	0.90-1.60	0.85–1.47	1.00–1.40	0.92–1.52	0.95–1.32	1.02–1.35
		p-value	0.088	0.215	0.428	0.049	0.199	0.192	0.030
	Heterogeneity	Model	Random	Random	Random	Random	Random	Random	Random
		p-value	<0.001	0.035	0.069	<0.001	0.086	<0.001	<0.001
		I^2 (%)	64.38	37.35	31.86	66.03	29.77	63.41	66.96
PB	Association	OR	1.05	1.07	1.06	1.05	1.07	1.05	1.04
		95% CI	0.93–1.18	0.92–1.25	0.90–1.24	0.93–1.18	0.92–1.24	0.93–1.18	0.93–1.15
		p-value	0.447	0.357	0.477	0.445	0.382	0.426	0.498
	Heterogeneity	Model	Random	Fixed	Fixed	Random	Fixed	Random	Random
		p-value	0.002	0.233	0.487	0.001	0.289	0.003	0.0003
		I^2 (%)	55.62	19.78	0	59.72	14.68	53.97	61.57

OR: odds ratio, 95% CI: 95% confidence interval, COD1: codominant model 1, COD2: codominant model 2, COD3: codominant model 3, DM: dominant model, RM: recessive model, OD: over-dominant model, AM: allelic model; GC: gastric cancer; BC: breast cancer; LC: lung cancer; CRC: colorectal cancer; PCa: prostate cancer; MM: multiple myeloma; HB: hospital-based; PB: population-based. Bold values indicate statistically significant differences ($p < 0.05$).

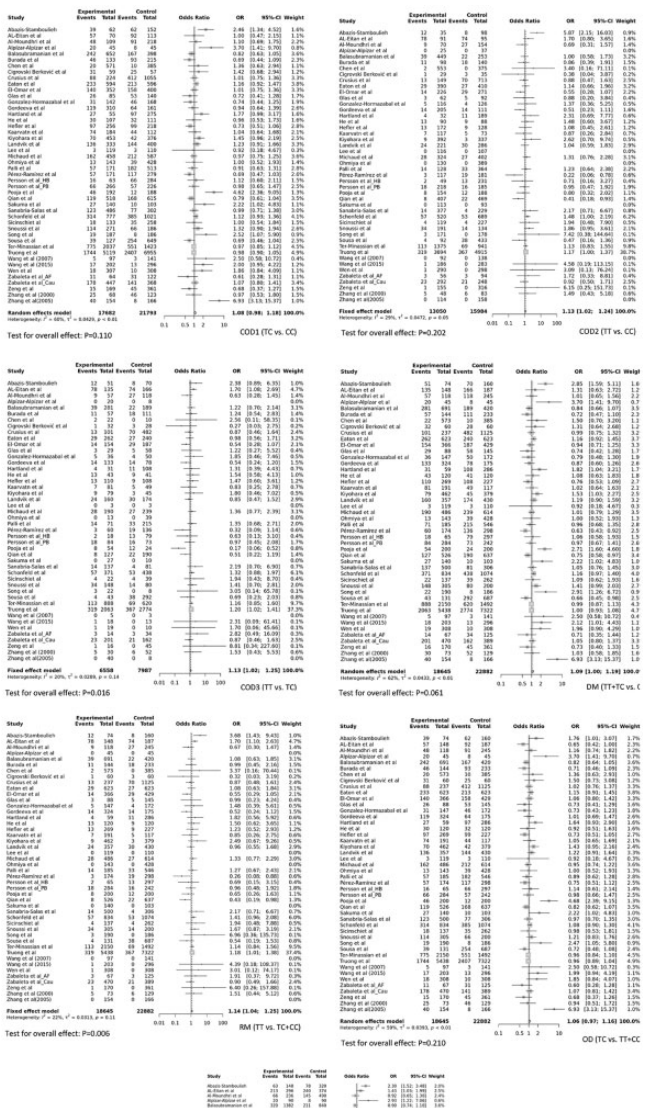

Figure 2. Forest plots describing the association between *IL-1β* rs1143634 (+3954C>T) polymorphism and cancer susceptibility.

IL-1*β*: interleukin-1 beta, OR: odd's ratio, CI: confidence interval, COD1: codominant model 1, COD2: codominant model 2, COD3: codominant model 3, DM: dominant model, RM: recessive model, OD: overdominant model, AM: allelic model.

Table 3. Sensitivity analysis of the meta-analysis.

Study ID	COD1 (TC vs. CC)	COD2 (TT vs. CC)	COD3 (TT vs. TC)	DM (TT + TC vs. CC)	RM (TT vs. TC + CC)	OD (TC vs. TT + CC)	AM (T vs. C)
Overall	1.08 (0.98–1.18)	1.10 (0.95–1.27)	1.13 (1.02–1.25)	1.09 (1.00–1.19)	1.14 (1.04–1.25)	1.06 (1.00–1.16)	1.08 (1.00–1.17)
Abazis-Stamboulieh et al.	1.06 (0.97–1.16)	1.08 (0.95–1.23)	1.12 (1.02–1.24)	1.07 (0.98–1.16)	1.13 (1.02–1.24)	1.05 (0.96–1.14)	1.06 (0.99–1.14)
AL-Eitan et al.	1.08 (0.98–1.18)	1.09 (0.94–1.26)	1.11 (1.00–1.23)	1.09 (0.99–1.19)	1.12 (1.01–1.23)	1.07 (0.98–1.17)	1.07 (1.00–1.16)
Al-Moundhri et al.	1.08 (0.98–1.18)	1.11 (0.96–1.29)	1.14 (1.03–1.26)	1.09 (1.00–1.20)	1.15 (1.04–1.26)	1.06 (0.97–1.16)	1.09 (1.01–1.18)
Alpízar-Alpízar et al.	1.06 (0.97–1.16)	1.1 (0.95–1.27)	1.13 (1.02–1.25)	1.08 (0.99–1.18)	1.14 (1.04–1.25)	1.05 (0.96–1.14)	1.07 (1.00–1.16)
Balasubramanian et al.	1.09 (0.99–1.20)	1.1 (0.95–1.29)	1.13 (1.02–1.25)	1.1 (1.00–1.21)	1.14 (1.04–1.26)	1.07 (0.98–1.17)	1.09 (1.01–1.18)
Burada et al.	1.09 (0.99–1.19)	1.11 (0.95–1.29)	1.13 (1.02–1.25)	1.1 (1.00–1.20)	1.14 (1.04–1.26)	1.07 (0.98–1.17)	1.09 (1.01–1.18)
Chen et al.	1.07 (0.98–1.18)	1.1 (0.95–1.27)	1.13 (1.02–1.25)	1.09 (0.99–1.19)	1.14 (1.04–1.25)	1.06 (0.97–1.15)	1.08 (1.00–1.16)
Cigrovski Berković et al.	1.07 (0.98–1.18)	1.1 (0.95–1.28)	1.13 (1.03–1.25)	1.09 (0.99–1.19)	1.14 (1.04–1.26)	1.05 (0.96–1.15)	1.08 (1.00–1.17)
Crusius et al.	1.08 (0.98–1.19)	1.11 (0.95–1.29)	1.14 (1.03–1.26)	1.09 (1.00–1.20)	1.15 (1.04–1.26)	1.06 (0.97–1.16)	1.09 (1.01–1.18)
Eaton et al.	1.08 (0.98–1.18)	1.1 (0.94–1.28)	1.14 (1.03–1.26)	1.09 (0.99–1.19)	1.14 (1.04–1.26)	1.06 (0.96–1.16)	1.08 (1.00–1.17)
El-Omar et al.	1.08 (0.98–1.19)	1.13 (0.98–1.30)	1.15 (1.04–1.27)	1.1 (1.00–1.20)	1.16 (1.05–1.27)	1.06 (0.97–1.16)	1.09 (1.01–1.18)
Glas et al.	1.08 (0.99–1.19)	1.1 (0.95–1.28)	1.13 (1.02–1.25)	1.1 (1.00–1.20)	1.14 (1.04–1.25)	1.06 (0.97–1.16)	1.09 (1.01–1.18)
Gonzalez-Hormazabal et al.	1.09 (0.99–1.19)	1.1 (0.95–1.27)	1.13 (1.02–1.24)	1.1 (1.00–1.20)	1.14 (1.04–1.25)	1.07 (0.97–1.16)	1.09 (1.01–1.17)
Gordeeva et al.	1.08 (0.99–1.19)	1.12 (0.97–1.30)	1.14 (1.03–1.26)	1.1 (1.00–1.20)	1.15 (1.05–1.27)	1.06 (0.97–1.16)	1.09 (1.01–1.18)

(continued)

Table 3. Continued.

Study ID	COD1 (TC vs. CC)	COD2 (TT vs. CC)	COD3 (TT vs. TC)	DM (TT + TC vs. CC)	RM (TT vs. TC + CC)	OD (TC vs. TT + CC)	AM (T vs. C)
Hartland et al.	1.07 (0.97–1.17)	1.09 (0.94–1.26)	1.13 (1.02–1.25)	1.08 (0.99–1.18)	1.14 (1 .03–1.25)	1.05 (0.96–1.15)	1.07 (1.00–1.16)
He et al.	1.08 (0.98–1.18)	1.09 (0.94–1.27)	1.13 (1.02–1.24)	1.09 (1.00–1.19)	1.14 (1.03–1.25)	1.06 (0.97–1.16)	1.08 (1.00–1.17)
Hefler et al.	1.09 (0.99–1.19)	1.1 (0.95–1.28)	1.13 (1.02–1.24)	1.1 (1.00–1.20)	1.14 (1.04–1.25)	1.07 (0.98–1.17)	1.09 (1.01–1.18)
Kaarvatn et al.	1.08 (0.98–1.18)	1.1 (0.95–1.28)	1.13 (1.03–1.25)	1.09 (1.00–1.20)	1.14 (1.04–1.26)	1.06 (0.97–1.16)	1.09 (1.01–1.17)
Kiyohara et al.	1.07 (0.97–1.17)	1.09 (0.94–1.26)	1.13 (1.02–1.24)	1.08 (0.99–1.18)	1.14 (1.03–1.25)	1.05 (0.96–1.15)	1.07 (0.99–1.16)
Landvik et al.	1.07 (0.98–1.18)	1.1 (0.95–1.28)	1.14 (1.03–1.26)	1.09 (0.99–1.19)	1.15 (1.04–1.26)	1.05 (0.96–1.15)	1.08 (1.00–1.17)
Lee et al.	1.08 (0.98–1.18)	1.1 (0.95–1.27)	1.13 (1.02–1.25)	1.09 (1.00–1.19)	1.14 (1.04–1.25)	1.06 (0.97–1.16)	1.08 (1.00–1.17)
Michaud et al.	1.08 (0.99–1.19)	1.09 (0.94–1.27)	1.12 (1.02–1.24)	1.09 (1.00–1.20)	1.13 (1.03–1.25)	1.06 (0.97–1.17)	1.09 (1.00–1.17)
Ohmiya et al.	1.08 (0.98–1.18)	1.1 (0.95–1.27)	1.13 (1.02–1.25)	1.09 (1.00–1.19)	1.14 (1.04–1.25)	1.06 (0.97–1.16)	1.08 (1.00–1.17)
Palli et al.	1.08 (0.99–1.19)	1.09 (0.94–1.27)	1.13 (1.02–1.24)	1.09 (1.00–1.20)	1.14 (1.03–1.25)	1.06 (0.97–1.16)	1.09 (1.00–1.17)
Pérez-Ramírez et al.	1.09 (0.99–1.19)	1.12 (0.98–1.29)	1.14 (1.03–1.26)	1.1 (1.01–1.21)	1.15 (1.05–1.26)	1.07 (0.98–1.17)	1.1 (1.02–1.18)
Persson et al._HB	1.08 (0.98–1.18)	1.1 (0.95–1.28)	1.13 (1.03–1.25)	1.09 (1.00–1.19)	1.14 (1.04–1.26)	1.06 (0.97–1.16)	1.08 (1.00–1.17)
Persson et al._PB	1.08 (0.98–1.19)	1.1 (0.95–1.28)	1.13 (1.03–1.25)	1.09 (1.00–1.20)	1.14 (1.04–1.26)	1.06 (0.97–1.16)	1.09 (1.01–1.17)
Pooja et al.	1.05 (0.96–1.14)	1.11 (0.95–1.28)	1.15 (1.04–1. 27)	1.07 (0.98–1.16)	1.15 (1.04–1.26)	1.03 (0.95–1.12)	1.07 (0.99–1.15)
Qian et al.	1.09 (0.99–1.20)	1.13 (0.98–1.30)	1.14 (1.03–1.26)	1.1 (1.01–1.21)	1.16 (1.05–1.27)	1.07 (0.98–1.17)	1.1 (1.02–1.18)
Sakuma et al.	1.07 (0.97–1.17)	1.1 (0.95–1.27)	1.13 (1.02–1.25)	1.08 (0.99–1.18)	1.14 (1.04–1.25)	1.05 (0.96–1.14)	1.08 (1.00–1.16)

(continued)

Table 3. Continued.

Study ID	COD1 (TC vs. CC)	COD2 (TT vs. CC)	COD3 (TT vs. TC)	DM (TT + TC vs. CC)	RM (TT vs. TC + CC)	OD (TC vs. TT + CC)	AM (T vs. C)
Sanabria-Salas et al.	1.08 (0.98–1.19)	1.09 (0.94–1.26)	1.12 (1.02–1.24)	1.09 (1.00–1.20)	1.14 (1.03–1.25)	1.06 (0.97–1.16)	1.08 (1.00–1.17)
Schonfeld et al.	1.08 (0.98–1.19)	1.08 (0.93–1.25)	1.12 (1.01–1.24)	1.09 (0.99–1.19)	1.12 (1.02–1.24)	1.06 (0.97–1.16)	1.08 (1.00–1.17)
Sicinschiet al.	1.08 (0.98–1.18)	1.09 (0.94–1.27)	1.13 (1.02–1.24)	1.09 (1.00–1.19)	1.14 (1.03–1.25)	1.06 (0.97–1.16)	1.08 (1.00–1.17)
Snoussi et al.	1.07 (0.98–1.18)	1.08 (0.93–1.25)	1.12 (1.02–1.24)	1.08 (0.99–1.18)	1.13 (1.03–1.24)	1.05 (0.96–1.15)	1.07 (1.00–1.16)
Song et al.	1.07 (0.97–1.17)	1.1 (0.95–1.27)	1.13 (1.02–1.25)	1.08 (0.99–1.18)	1.14 (1.04–1.25)	1.05 (0.96–1.14)	1.07 (1.00–1.15)
Sousa et al.	1.09 (0.99–1.19)	1.12 (0.97–1.29)	1.13 (1.03–1.25)	1.1 (1.01–1.21)	1.15 (1.04–1.26)	1.07 (0.98–1.17)	1.09 (1.01–1.18)
Ter-Minassian et al.	1.09 (0.99–1.20)	1.1 (0.94–1.28)	1.13 (1.01–1.25)	1.1 (1.00–1.21)	1.14 (1.03–1.26)	1.07 (0.97–1.17)	1.09 (1.01–1.18)
Truong et al.	1.09 (0.99–1.21)	1.09 (0.93–1.29)	1.09 (0.96–1.24)	1.11 (1.00–1.22)	1.12 (0.99–1.26)	1.07 (0.97–1.18)	1.1 (1.01–1.19)
Wang et al. (2007)	1.07 (0.98–1.18)	1.1 (0.95–1.27)	1.13 (1.02–1.25)	1.09 (0.99–1.19)	1.14 (1.04–1.25)	1.05 (0.97–1.15)	1.08 (1.00–1.17)
Wang et al. (2015)	1.07 (0.98–1.17)	1.1 (0.95–1.27)	1.13 (1.02–1.25)	1.08 (0.99–1.18)	1.14 (1.04–1.25)	1.05 (0.96–1.15)	1.08 (1.00–1.16)
Wen et al.	1.07 (0.98–1.17)	1.1 (0.95–1.27)	1.13 (1.02–1.25)	1.08 (0.99–1.18)	1.14 (1.04–1.25)	1.05 (0.96–1.15)	1.08 (1.00–1.16)
Zabaleta et al._AF	1.08 (0.99–1.19)	1.1 (0.94–1.27)	1.13 (1.02–1.24)	1.1 (1.00–1.20)	1.14 (1.04–1.25)	1.06 (0.97–1.16)	1.09 (1.01–1.17)
Zabaleta et al._Cau	1.08 (0.98–1.19)	1.11 (0.95–1.29)	1.14 (1.03–1.26)	1.09 (1.00–1.20)	1.15 (1.04–1.26)	1.06 (0.97–1.16)	1.09 (1.01–1.18)
Zeng et al.	1.08 (0.99–1.19)	1.1 (0.95–1.27)	1.13 (1.02–1.25)	1.1 (1.00–1.20)	1.14 (1.04–1.25)	1.06 (0.97–1.16)	1.09 (1.01–1.17)
Zhang et al. (2000)	1.08 (0.98–1.18)	1.1 (0.94–1.27)	1.13 (1.02–1.25)	1.09 (1.00–1.19)	1.14 (1.04–1.25)	1.06 (0.97–1.16)	1.08 (1.00–1.17)
Zhang et al. (2005)	1.05 (0.96–1.14)	1.1 (0.95–1.27)	1.13 (1.02–1.25)	1.06 (0.98–1.15)	1.14 (1.04–1.25)	1.03 (0.95–1.12)	1.06 (0.99–1.14)

COD1: codominant model 1, COD2: codominant model 2, COD3: codominant model 3, DM: dominant model, RM: recessive model, OD: over-dominant model, AM: allelic model.

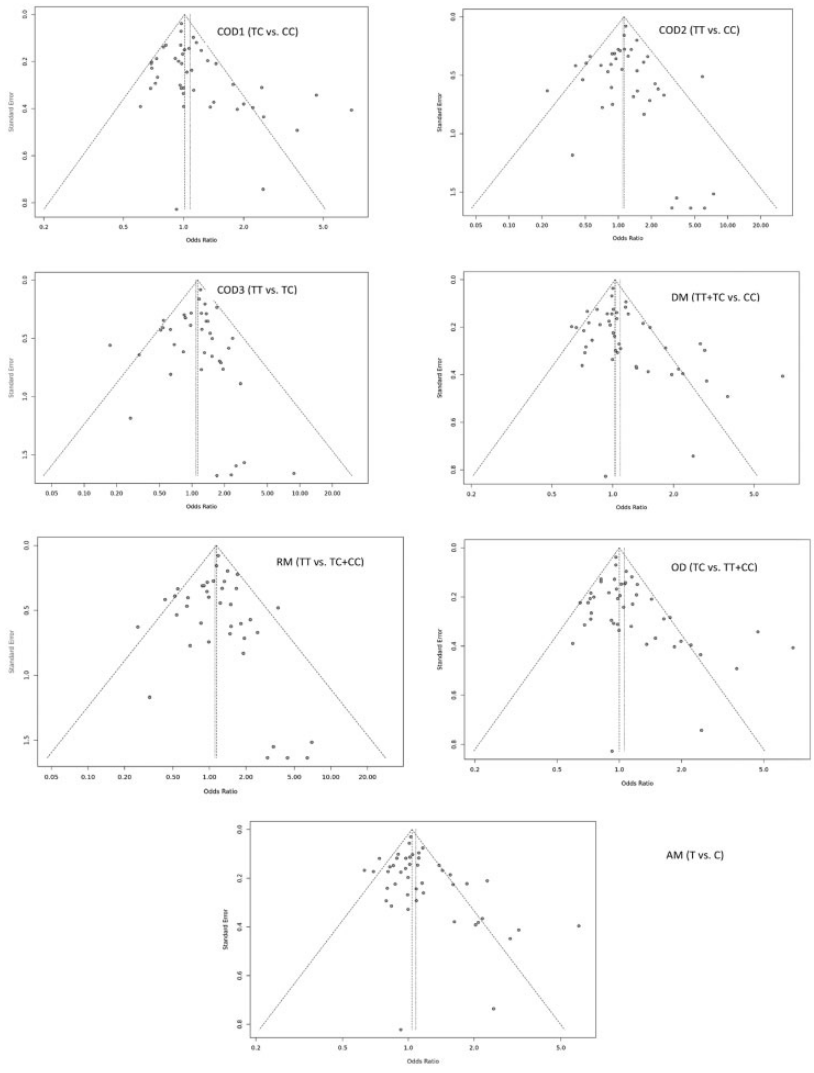

Figure 3. Funnel plots indicating publication bias.
COD1: codominant model 1, COD2: codominant model 2, COD3: codominant model 3, DM: dominant model, RM: recessive model, OD: over-dominant model, AM: allelic model.

*IL-1*β *gene expression*

The eQTL analysis from GTEx revealed that the mutant allele of *IL-1β* rs1143634 leads to increased *IL-1β* mRNA expression in the colon ($p = 0.00095$) and skin ($p = 0.0032$) (Figure 5A & B).

Discussion

Previous reports suggest that cancer and inflammatory cytokines are closely related. For example, the elevated expression of *IL-1β* in most human cancer types indicates its crucial impact on carcinogenesis.

Table 4. Outcome of publication bias analysis.

Study population and cancer	Comparison type	Egger's test		Begg & Mazumdar's Test	
		t	*p*	Z	*p*
Overall	COD1 (TC vs. CC)	2.44	0.019	2.96	0.003
	COD2 (TT vs. CC)	0.25	0.805	0.71	0.478
	COD3 (TT vs. TC)	−0.90	0.374	−0.24	0.813
	DM (TT + TC vs. CC)	2.22	0.027	2.96	0.003
	RM (TT vs. TC + CC)	−0.07	0.947	0.60	0.551
	OD (TC vs. TT + CC)	2.42	0.020	2.83	0.005
	AM (T vs. C)	2.08	0.044	2.49	0.013

COD1: codominant model 1, COD2: codominant model 2, COD3: codominant model 3, DM: dominant model, RM: recessive model, OD: over-dominant model, AM: allelic model.

In addition, the increased level of *IL-1β* restricts improvement in many cancer cases.[35,68,69] Because some previous studies provided controversial reports, we attempted to collect and analyze all evidence to understand the role of *IL-1β* rs1143634 in different cancers.

IL-1β inhibits gastric acid secretion and potentiates chronic inflammation in GC, worsening the disease.[70,71] As *IL-1β* rs1143634 polymorphism increases the production of active IL-1β, this SNP is thought to play a critical role in GC. Zhang et al. showed that the heterozygote model of *IL-1β* +3954C>T was related to a significantly increased risk of GC.[61] Another study also demonstrated that C>T genotype carriers showed a significantly increased risk of this cancer.[58] Wen et al. reported an elevated risk and added that environmental factors potentiated the chance of cancer development.[57] Similarly, Sakuma et al. provided evidence that polymorphism carriers in the Japanese population might have an increased risk of GC development in the corpus.[45] In contrast, a number of studies showed that the *IL-1β* rs1143634 variant is not associated with an elevated risk of GC.[27,28,40,47,60,67] Moreover, El-Omar et al. stated that this variant might have a protective effect against GC, although the result was statistically non-significant.[17] Persson et al. conducted both PB and HB case–control studies but did not find any connection.[42]

IL-1β binds to the estrogen receptor of BC cells and activates transcription. Pooja et al. reported that variant alleles of *IL-1β* rs1143634 elevated the risk of BC[43], whereas other previous studies did not find any significant correlations.[32,33,63] Two case–control studies reported that this variant might not be related to lung cancer,[26,54] whereas Kiyohara et al. and Ter-Minassian et al. indicated that smokers who are mutant T allele carriers of rs1143634 might have a higher risk of lung cancer.[34,53] This SNP did not show any association with NSCLC and small cell lung cancer in men.[29,35,41] For CRC, only polymorphism carriers among the Chinese Han population showed an increased risk,[56] but other studies reported a negative association.[44,64] Patients with MM carrying CT and TT alleles of the *IL-1β* +3954C>T polymorphism exhibited improved survival rates and survival conditions compared with the CC allele carriers.[25] However, another study in patients with MM did not find any possible association with this polymorphism.[62] Excess IL-1β potentiates inflammation caused by oxidative stress in

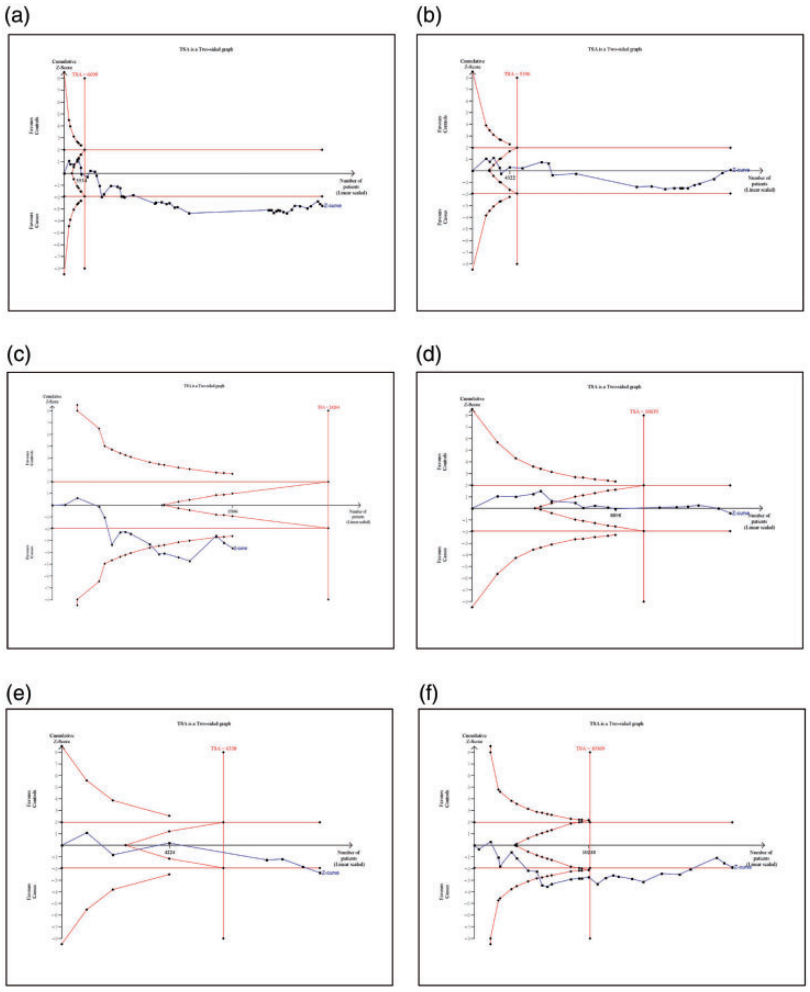

Figure 4. Trial sequential analysis for *IL-1β* rs1143634 in allele models. (a) Overall, (b) White, (c) Asian, (d) Gastric cancer, (e) Breast cancer and (f) Hospital-based controls. The blue line represents the cumulative Z curve, and the red lines indicate the futility boundaries.
TSA: trial sequential analysis, *IL-1β*: interleukin-1 beta.

cancerous pancreatic beta cells, leading to cell destruction and restricted insulin release. It also controls adhesion, invasion and chemoresistance by triggering various signaling pathways, such as nuclear factor kappa B and extracellular signal-regulated kinase.[72–75] Cigrovsk Berkovic et al. found a possible association between rs1143634 variant and pancreatic neuroectoderm tumors, although the results were not statistically significant.[66] This SNP did not show a significant association with PCa,[38,59] and prior studies[31,65] reported no risk for other cancer types. This polymorphism was found to have varied relationships with malignancies in different ethnic populations.[9,39]

In this meta-analysis, the *IL-1β* rs1143634 variant showed a significantly elevated association with cancers in three

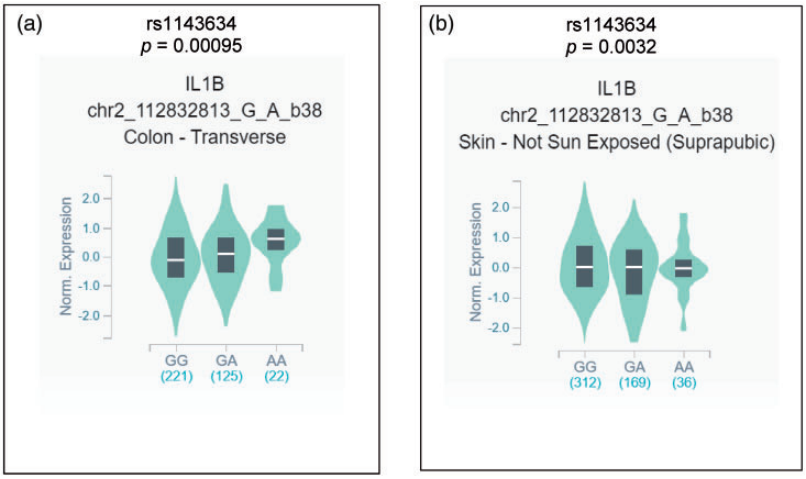

Figure 5. *In silico* expression analysis of *IL-1β* in relation to different variants of the rs1143634 polymorphism. (a) There was a significant difference in the expression of *IL-1β* mRNA in colon tissues depending on the three genotypes, and the variant allele showed higher expression. (b) There was a significant difference in the expression of *IL-1β* mRNA in the non-sun exposed skin samples, and the variant allele showed lower expression. The values in the brackets represent the frequency of different genotype carriers.
IL-1β: interleukin-1 beta.

genetic models, COD3 (1.13-fold), RM (1.14-fold) and AM (1.08-fold). The Asian population showed a significantly enhanced risk of cancer in various genetic models, such as COD1 (1.54-fold), DM (1.54-fold), OD (1.48-fold) and AM (1.50-fold). African and White populations did not show any connection between the *IL-1β* rs1143634 variant and cancer susceptibility. Populations with other mixed ethnicities were significantly associated with cancer risk in COD2 (1.22-fold), COD3 (1.22-fold), RM (1.22-fold) and AM (1.05-fold) models.

We also performed a subgroup analysis with different cancer types. *IL-1β* rs1143634 polymorphism showed a significant risk association with GC in COD1, DM, OD and AM (1.25-, 1.25-, 1.25-, and 1.21-fold, respectively), BC in COD2 and RM (1.31- and 1.35-fold, respectively) and MM in RM (2.64-fold) models. We found no significant association for the other types of cancers. The selection of controls slightly affected the outcomes according to our sub-group analysis with HB and PB control populations. The analysis with HB controls showed a significantly increased risk in DM (1.18-fold) and AM (1.17-fold) models. No risk association was revealed for the *IL-1β* rs1143634 variant with cancers in the case of PB controls. The presence of variant alleles of *IL-1β* rs1143634 might increase the risk of various cancers.

The analysis of sensitivity confirmed the stability and robustness of the present meta-analysis. Moreover, TSA demonstrated that the cumulative Z-curve for the rs1143634 SNP crossed the conventional monitoring boundaries and achieved the RIS, demonstrating that adequate evidence was achieved for this meta-analysis and that no additional studies are needed to verify the results. However, in the Asian population, the Z-curve surpassed the trial sequential monitoring boundary but failed to attain the RIS. Furthermore, we conducted *IL-1β* gene expression analysis through

eQTL, which revealed that mutant alleles of *IL-1β* rs1143634 lead to increased *IL-1β* mRNA expression in both colon tissues.

Our meta-analysis had some limitations that could not be avoided. Some of the subgroup analyses showed significant heterogeneity based on the *Q*-test analysis. Visual asymmetry, Egger's and Begg & Mazumdar's tests reported the presence of possible publication bias in a few models. Finally, because of missing information, we failed to provide additional data for individuals, such as their age, sex or disease duration, that may have enriched the quality of the investigation.

Conclusions

Our meta-analysis revealed that the presence of *IL-1β* rs1143634 variant might elevate the cancer risk in the overall population. Among rs1143634 polymorphism carriers, the Asian population has a greater risk than other ethnic populations. Further studies with larger sample sizes, specific ethnicities and unbiased populations with detailed individual information should be conducted to confirm our findings.

Author contributions

Mohammad Safiqul Islam: conceptualization, supervision, data analysis, software and writing-reviewing and editing; Sarah Jafrin and Md. Abdul Aziz: literature search; Sarah Jafrin: writing-original draft preparation, methodology; Md. Abdul Aziz: writing-reviewing and editing. The final version of the manuscript has been reviewed and approved by all authors.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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