Meta Analysis

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
2022, Vol. 50(10) 1–25

DOI: 10.1177/03000605221133173
journals.sagepub.com/home/imr
SAGE

Association between *TP73 G4C14-A4T14* polymorphism and different cancer types: an updated meta-analysis of 55 case–control studies

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Abstract

Objective: The *TP73 G4C14-A4T14* variant has been associated with elevated cancer risk, but the evidence is inconclusive. We performed a meta-analysis to clarify the role of this variant in cancer development.

Methods: Eligible literature was selected by searching PubMed, Google Scholar, Cochrane Library, and Embase. The meta-analysis was performed using Review Manager 5.4.

Results: A meta-analysis of 55 case–control studies showed that the *G4C14-A4T14* variant was significantly associated with overall cancer development in five genetic models, including the allele model (AM), codominant model 1 (COD1), COD2, dominant model (DM), and over-dominant model (OD). Sub-group analysis based on ethnicity showed significantly higher risks in Africans in COD2 and RM and in Whites in AM, COD2, DM, and recessive model (RM). Cancer-specific subgroup analysis identified significant risks of gynecological (ovarian, cervical, and endometrial cancer), colorectal, oral, head and neck, and other cancers. Moreover, hospital-based controls revealed significant cancer risks in the AM, COD1, COD2, DM, and RM genetic models. Our findings were confirmed by trial sequential analysis.

Conclusion: This meta-analysis confirmed that *TP73 G4C14-A4T14* significantly elevates the overall cancer risk, especially in White, African, and hospital-based populations, and specifically predisposes individuals to gynecological, colorectal, oral, and head and neck cancers.

This meta-analysis was registered at INPLASY (registration number: INPLASY202210070).

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Keywords
TP73, G4C14-A4T14, polymorphism, cancer, meta-analysis, ethnic group

Date received: 14 January 2022; accepted: 28 September 2022

Introduction

Cancer is an evolving health problem and a major cause of death worldwide, with 19.3 million new cancer cases in 2020, and 10 million deaths due to various cancers.[1] Malignancies involve the accumulation of multiple genetic mutations, and scientists have discovered more than 10,000 genetic risk variants associated with susceptibility to cancer development. Mutations in tumor suppressor genes such as the *TP53* family, especially loss of function mutations that suppress the actions of the genes, are among the most important factors associated with carcinogenesis. *TP53* is the most widely investigated and common tumor suppressor gene, and has been found to be associated with almost all types of cancers. Researchers are now focusing on rare genetic variants to provide more specific information on cancer genetics.[2,3]

TP73 is a vital gene that encodes p73, an essential member of the p53 family that is structurally and functionally homologous to p53 (63% homologous amino acid sequence). This protein, also known as p53-like transcription factor, is involved in cellular proliferation, programmed cell death (apoptosis), cell cycle regulation or arrest, and transactivation of overlapping target genes such as the p21 gene.[4–8] However, unlike *TP53*, mutations in *TP73* are rare. During DNA damage, p73 is overexpressed in malignancies resulting from p53 mutation. It mimics the tumor suppression function of p53 by initiating the transcription of genes involved in cell cycle regulation, which are usually responsive to p53, repairing damaged DNA, promoting apoptosis, and preventing uncontrolled cellular growth and proliferation via blocking the G1 cell cycle checkpoint.[9–14] p73 thus helps to maintain cellular homeostasis through compensating for the *TP53* loss of function polymorphism.[7,14,15] Although mutations in *TP73* have been detected in less than 2% of all cancers, the gene is highly polymorphic and loss of heterozygosity polymorphisms have been reported in different types of tumors. *TP73* is located at chromosomal region 1p36-33, which is deleted in many human cancers. This suggests that p73 might be strongly related to cancer susceptibility.[16–18]

Nineteen exonic and intronic single nucleotide polymorphisms (SNPs) have been identified in *TP73*, but none of these result in miscoded amino acids.[19,20] Two common SNPs, *rs2273953* and *rs1801173*, are located at positions 4 (G>A) and 14 (C>T), respectively, within a noncoding 5′-untranslated region upstream of the *TP73* promoter in exon 2. The distance between the two polymorphisms is short, with a tendency for non-random associations between them. The two polymorphisms are in complete disequilibrium with each other and are jointly referred to as *G4C14-A4T14*. This set of polymorphisms is located just above the translation initiation site and has been shown to affect *TP73* gene expression levels by forming a stem-loop-like structure.[19,21–23]

Given its ability to modify the tumor suppression activity of *TP73*, the association between *G4C14-A4T14* and

carcinogenesis has recently been investigated in genome-wide association studies in multiple cancer types, including lung, colorectal, breast, cervical, gastric, esophageal, endometrial, oral, and ovarian cancer, in addition to head and neck squamous cell carcinoma, lymphoma, and cutaneous melanoma.[2,24–74] However, the findings of these studies were inconsistent. Although previous meta-analyses have summarized the evidence regarding the roles of the *G4C14-A4T14* polymorphism in different cancers, the numbers of studies included in those meta-analyses were limited,[75–78] While a larger sample size provides firmer evidence in population-based genetic association studies.

In this study, we performed a comprehensive meta-analysis of 55 case–control studies to resolve previous controversies and provide systematic evidence for the association between the *TP73 G4C14-A4T14* polymorphism and cancer development.

Materials and methods

This meta-analysis was performed following the updated PRISMA 2020 guidelines (available at https://www.bmj.com/content/372/bmj.n160). The need for obtaining informed consent from patients or controls was not applicable as no participants were directly involved in this study.

Literature search strategy

We carried out a comprehensive literature search of the PubMed, Google Scholar, Embase, Cochrane Library, Web of Science, and China National Knowledge Infrastructure electronic databases up to 20 July 2021, using the following key terms: '*TP73* or *p73'*, 'Cancer or tumor', '*G4C14-A4T14* polymorphism', '*rs2273953* and *rs1801173'*, '*TP73* polymorphism and cancer', and 'association between *TP73 G4C14-A4T14* polymorphism and cancer'. Additional studies were extracted from the reference lists of the selected literature. We also screened the 'similar studies' options in the above databases. Finally, published studies were included avoiding any language barriers.

Publication selection and eligibility criteria

The overall selection process was completed according to the authors' predesigned protocol. Eligible studies containing the required data were selected and the data were organized for further analysis by comprehensive screening. The overall study selection method is outlined in a PRISMA flow diagram (Figure 1). Two authors (SJ and MAA) carefully revised the whole procedure, and the other author (MSI) conducted a final screening to reduce the chances of disagreement. This meta-analysis was retrospectively registered at INPLASY (https://inplasy.com/, registration number: INPLASY202210070).

The inclusion criteria of the selected studies were case–control studies examining the association between *TP73 G4C14-A4T14* polymorphism and cancer susceptibility, studies with detailed comparative genotypic information for both controls and patients, and study population in agreement with the Hardy–Weinberg equilibrium (HWE) after adjustments. If the selected studies contained genotypic data on other SNPs, as well as the selected SNP, we only extracted data on the selected SNP for inclusion in this meta-analysis. We excluded studies without *G4C14-A4T14* genotypic data for cancer patients and controls, studies lacking a control population data or with incomplete genotypic information, systematic reviews and meta-analyses, and studies conducted on cell lines or animal models.

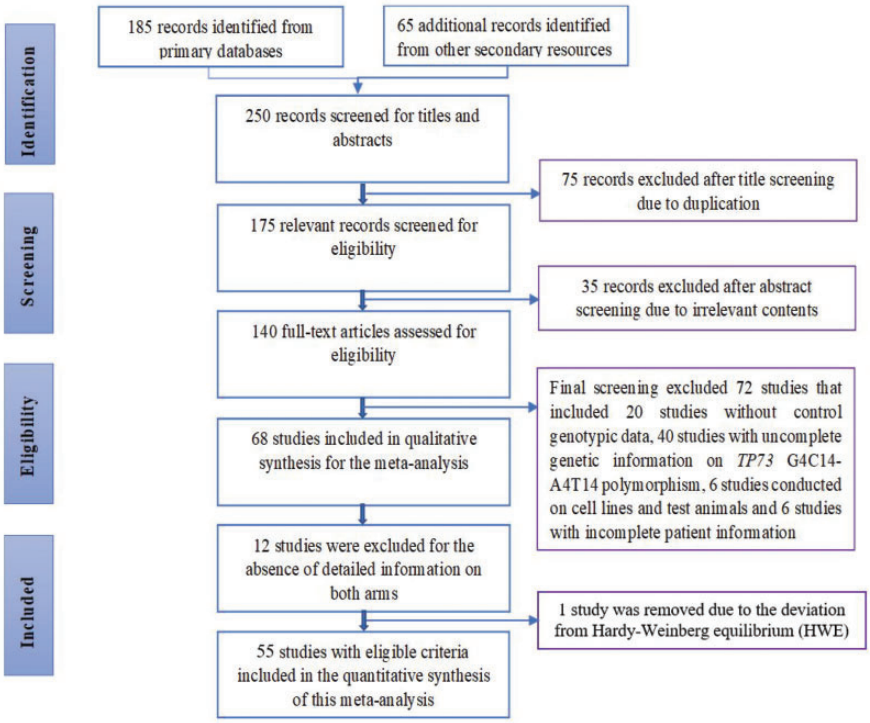


Figure 1. Systematic flow diagram of study selection process.

Data extraction and quality assessment

We extracted the following information from the selected studies: study ID, date of publication, country, ethnicity or region of the recruited population, type of cancer, category of control population, type of genotyping method used, sample and control sizes, and genotypic data for the selected SNP. In addition, the HWE *p*-value was collected and adjusted (corrected) by Benjamini and Hochberg's (1995) false discovery rate,[79] and the Newcastle–Ottawa Scale (NOS) score[80] was calculated from each selected study by the authors to maintain the quality of the selected studies. Two authors (SJ and MAA) extracted the above data from each study, and the other author (MSI) carried out a final screening of the organized data to avoid mistakes and misinterpretation.

Statistical analysis

The overall statistical analysis was carried out using Review Manager (RevMan) software version 5.4 (Cochrane Collaboration, 2020) to elucidate the impact of the *TP73 G4C14-A4T14* variant on susceptibility to different cancers. We applied seven genetic association models to evaluate the association: the allele model (AM) (AT vs. GC), codominant model 1 (COD1) (GC/AT vs. GC/GC), codominant model 2 (COD2) (AT/AT vs. GC/GC), codominant model 3 (COD3) (AT/AT vs. GC/AT), dominant model (DM) (AT/AT + GC/AT vs. GC/GC), recessive model (RM) (AT/AT vs. GC/AT + GC/GC), and over-dominant model (OD) (GC/AT vs. AT/AT + GC/GC). We also conducted a subgroup analysis in which the controls were divided into hospital-based (HB) and population-based

(PB) control populations, while the case or experimental arm included patients with different cancers carrying the *TP73 G4C14-A4T14* variant. We also conducted subgroup analysis according to ethnicity in Asian, White, and African populations. The degree of cancer risk was estimated as an odds ratio (OR) with 95% confidence intervals (CIs), and the significance level (P_z) was set to $P_z<0.05$. A fixed-effects or random-effects model was applied based on the results of the heterogeneity test (Q-test): when heterogeneity was significant ($P_H<0.10$), the random-effects model (DerSimonian–Laird) was applied, and when heterogeneity was non-significant, the fixed-effects model (Mantel–Haenszel) was applied. Visual inspection of funnel plots as well as the results of Egger's regression and Begg–Mazumdar tests were used to estimate publication bias. Sensitivity analysis was performed to assess the reliability of the results by subtracting the studies one by one. Trial sequential analysis (TSA) was performed using TSA software (version 0.9.5.10 Beta), maintaining an overall 5% risk of a type I error, a relative risk reduction of 20%, and a power of 80%.

Results

Study characteristics

Fifty-five case–control studies[2,24–74] including 15,648 cancer cases and 19,159 controls met the eligibility criteria and were finally included in this meta-analysis (Figure 1). A total of 194 studies were excluded after screening the title, abstract and full-text, because of irrelevant information, incomplete genetic data, or duplicate contents. Among the 55 included studies, 11 focused on lung cancer (LC), 10 on gynecological cancers [cervical cancer (CC), endometrial cancer (EM) and ovarian cancer (OVC)], six on colorectal cancer (CRC), five on gastric cancer (GC), four each on esophageal cancer (EC), breast cancer (BC), and oral cancer (OC), three on prostate cancer (PC), one on bladder cancer (UBC), and the others on hepatocellular carcinoma (HCC), non-Hodgkin's lymphoma (NHL), and neuroblastoma (NB). The included studies were grouped according to ethnicity, including 38 studies of Asian populations, 13 in White populations, three in African populations, and one in a mixed population. In addition, 31 studies recruited controls from HB sources and 24 recruited controls from PB sources. Regarding quality assessment, we determined the NOS score and excluded studies that scored less than 6 points. Detailed demographic information on the included studies is presented in Table 1.

Association of TP73 G4C14-A4T14 variant with cancer

We evaluated the overall impact of the *TP73 G4C14-A4T14* variant on cancer in a meta-analysis of 55 studies, using seven common genetic models. Five of the genetic models showed significant risk associations with overall cancer, including AM, COD1, COD2, DM, and OD. COD3 and RM did not confirm a significant association between *TP73 G4C14-A4T14* and cancer susceptibility (Table 2, Figure 2).

Subgroup analysis based on ethnicity

We compared the results of the seven genetic models among the three ethnic populations: Asian, African, and White (Table 2). There was no significant association between *TP73 G4C14-A4T14* and cancer susceptibility in the Asian population. Only the COD2 and RM models showed significant high-risk associations in African populations, while the AM, COD2, DM, and RM models showed significantly increased cancer risks in carriers of the *TP73 G4C14-A4T14* in White

Table 1. Baseline demographic information of the included studies.

Study ID	Country	Ethnicity	Genotyping method	Control type	Cancer type	Cases	Controls	Cases			Controls			HWE (*p*)		NOS score
								EE	DE	DD	EE	DE	DD	Crude	Adjusted	
Ahomadegbe et al.[37]	France	White	PCR	HB	BC	59	34	1	22	36	0	7	27	0.503	0.940	7
Arfaoui et al.[42]	Tunisia	White	PCR	PB	CRC	150	204	26	47	77	22	73	109	0.074	0.344	8
Carastro et al.[39]	USA	White	TaqMan	HB	PC	1232	586	65	417	750	27	202	357	0.817	0.998	9
Carastro et al.[39]	USA	African	TaqMan	HB	PC	60	85	2	9	49	1	16	68	0.957	0.998	6
Chen et al.[51]	USA	White	PCR-RFLP	PB	OC	326	349	20	111	195	20	115	214	0.387	0.885	7
Chen et al.[69]	USA	White	PCR-RFLP	PB	OC	188	349	14	60	114	20	114	215	0.349	0.849	7
Choi et al.[47]	Korea	Asian	PCR-CTPP	HB	LC	582	582	41	221	320	32	212	338	0.869	0.998	8
Craveiro et al.[26]	Portugal	White	PCR	PB	CC	141	176	8	38	95	9	48	119	0.164	0.483	7
De Feo et al.[36]	Italy	White	PCR	HB	GC	114	295	8	22	84	10	71	214	0.183	0.513	7
Ebeid et al.[66]	Egypt	African	PCR-CTPP	HB	BC	80	80	13	29	38	5	15	60	0.010	0.183	6
Feng et al.[38]	China	Asian	PCR	HB	CC	180	180	10	67	103	11	55	114	0.220	0.588	7
Ge et al.[67]	China	Asian	PCR-RFLP	HB	GC	259	630	14	99	146	29	210	391	0.906	0.998	7
Ge et al.[49]	China	Asian	PCR-RFLP	HB	EC	348	583	21	113	214	28	184	371	0.403	0.885	8
Guo et al.[52]	China	Asian	HRMPCR	HB	CC	175	189	22	46	107	10	70	109	0.775	0.998	7
Hamajima et al.[31]	Japan	Asian	PCR-CTPP	HB	EC	102	241	6	29	67	10	98	133	0.122	0.400	7
Hamajima et al.[31]	Japan	Asian	PCR-CTPP	HB	GC	144	241	9	51	84	10	98	133	0.122	0.400	7
Hamajima et al.[31]	Japan	Asian	PCR-CTPP	HB	CRC	147	241	10	50	87	10	98	133	0.122	0.400	6
Han et al.[63]	USA	Mixed	TaqMan	HB	SC	753	832	37	259	457	34	273	525	0.841	0.998	8
Hiraki et al.[43]	Japan	Asian	PCR-CTPP	HB	LC	189	235	12	68	109	10	95	130	0.151	0.470	7
Hishida et al.[65]	Japan	Asian	PCR-CTPP	HB	NHL	103	440	11	43	49	27	152	261	0.442	0.885	6
Hu et al.[60]	China	Asian	PCR-SSCP	PB	LC	425	588	21	149	255	45	248	295	0.472	0.911	6
Huang et al.[62]	Japan	Asian	PCR-CTPP	PB	BC	200	282	18	64	118	17	112	153	0.556	0.998	7
Huang et al.[54]	China	Asian	HRM	PB	LC	642	354	22	222	398	26	136	192	0.777	0.998	7
Jaiswal et al.[56]	India	Asian	PCR-CTPP	HB	UBC	200	200	16	67	117	6	57	137	0.981	0.998	8
Jha et al.[28]	India	Asian	PCR	PB	CC	101	100	2	28	71	4	19	77	0.062	0.317	8
Jun et al.[55]	Korea	Asian	PCR-RFLP	PB	LC	582	582	41	221	320	32	212	338	0.869	0.998	8
Kang et al.[48]	China	Asian	PCR	PB	OVC	257	257	19	74	164	14	92	151	0.998	0.998	9
Lee et al.[35]	Korea	Asian	PCR-CTPP	PB	CRC	383	469	29	171	183	25	173	271	0.701	0.998	7
Li et al.[32]	USA	White	PCR	HB	LC	1054	1139	67	394	593	53	365	721	0.436	0.885	7
Li et al.[54]	USA	White	PCR-CTPP	HB	HNC	708	1229	38	271	399	69	387	773	0.028	0.197	8
Li et al.[61]	USA	White	PCR-CTPP	HB	SC	805	838	50	287	468	39	302	497	0.422	0.885	8
Li et al.[71]	China	Asian	PCR-CTPP	HB	LC	186	196	12	80	94	27	71	98	0.020	0.197	6

(continued)

Table 1. Continued.

Study ID	Country	Ethnicity	Genotyping method	Control type	Cancer type	Cases	Controls	Cases			Controls			HWE (*p*)		NOS score
								EE	DE	DD	EE	DE	DD	Crude	Adjusted	
Liu et al.[44]	China	Asian	PCR-RFLP	HB	CRC	60	60	15	19	26	3	21	36	0.978	0.998	6
Misra et al.[74]	India	Asian	PCR	HB	OC	303	319	15	176	112	9	124	186	0.028	0.197	7
Mittal et al.[50]	India	Asian	PCR-RFLP	PB	PC	177	265	0	56	121	7	66	192	0.645	0.998	6
Niwa et al.[41]	Japan	Asian	PCR-CTPP	HB	CC	112	442	3	52	57	22	150	270	0.843	0.998	6
Niwa et al.[27]	Japan	Asian	PCR	HB	EMC	114	442	14	39	61	22	150	270	0.843	0.998	6
Pfeifer et al.[57]	Sweden	White	PCR-RFLP	PB	CRC	179	260	12	54	113	5	96	159	0.027	0.197	6
Rao et al.[33]	India	Asian	PCR-CTPP	PB	OC	204	212	8	40	156	4	49	159	0.921	0.998	7
Romani et al.[24]	Italy	White	PCR	PB	NB	73	150	3	39	31	7	49	94	0.850	0.998	6
Ryan et al.[46]	Ireland	White	PCR	PB	EC	84	152	1	41	42	15	65	72	0.953	0.998	6
Shirai et al.[70]	Japan	Asian	PCR-CTPP	HB	GC	388	419	26	142	220	24	156	239	0.826	0.998	7
Sun et al.[84]	China	Asian	PCR-CTPP	PB	CC	218	220	11	100	107	12	80	128	0.914	0.998	8
Umar et al.[72]	Indian	Asian	PCR	PB	EC	255	255	11	70	174	4	51	200	0.719	0.998	7
Wang et al.[59]	China	Asian	PCR-CTPP	HB	LC	168	195	8	59	101	25	68	102	0.015	0.197	6
Wang et al.[64]	China	Asian	PCR-CTPP	HB	LC	186	198	10	68	108	26	68	104	0.009	0.183	6
Wang et al.[73]	China	Asian	MALDI-TOF	HB	HCC	100	100	7	31	62	7	28	65	0.119	0.400	7
Wu et al.[45]	China	Asian	TaqMan	HB	LC	460	922	17	149	294	71	361	490	0.691	0.998	7
Yazici et al.[30]	Turkey	White	PCR-CTPP	PB	CRC	104	113	1	43	60	1	38	74	0.101	0.400	7
Zhang et al.[40]	China	Asian	PCR-CTPP	PB	GC	373	412	82	168	123	116	194	102	0.246	0.626	8
Zhang et al.[68]	China	Asian	PCR-RFLP	HB	LC	293	380	14	116	163	13	120	247	0.735	0.998	8
Zhang et al.[25]	China	Asian	PCR	PB	HNC	569	479	26	220	323	17	147	315	0.977	0.998	9
Zheng[34]	China	Asian	PCR-RFLP	PB	CC	82	100	2	22	58	4	19	77	0.062	0.317	6
Zheng et al.[29]	China	Asian	PCR-CTPP	PB	CC	101	100	2	28	71	4	19	77	0.062	0.317	6
Zhou & Wu[2]	China	Asian	MALDI-TOF	PB	BC	170	178	5	59	106	11	67	100	0.960	0.998	6
Totals						15,648	19,159	978	5620	9050	1111	6566	11,482			

DD, GC/GC; DE, GC/AT; EE, AT/AT; NB, neuroblastoma; BC, breast cancer; EC, esophageal cancer; GC, gastric cancer; SC, skin cancer; CRC, colorectal cancer; LC, lung cancer; NHC, non-Hodgkin's lymphoma; HNC, head and neck cancer; EMC, endometrial cancer; OC, oral cancer; PC, prostate cancer; CC, cervical cancer; OVC, ovarian cancer; HCC, hepatocellular carcinoma; UBC, bladder cancer; HWE, Hardy–Weinberg equilibrium; PCT, polymerase chain reaction; RFLP, restriction fragment length polymorphism; HRM, high-resolution melting; CTPP, confronting two-pair primers.

Table 2. Associations of *TP73 G4C14-A4T14* polymorphism with cancer risk in different ethnicities.

Comparison	Subgroup	N	P_H	I^2	Model	OR	95% CI	P_Z
AM (E vs. D)	Overall	55	<0.0001	70.16	Random	1.10	1.02–1.18	**0.010**
	White	13	0.0001	18.7	Fixed	1.14	1.07–1.22	**0.0001**
	Asian	38	<0.0001	75.04	Random	1.07	0.97–1.18	0.161
	African	3	0.020	74.36	Random	1.55	0.86–2.79	0.150
COD1 (DE vs. DD)	Overall	55	<0.0001	63.91	Random	1.09	1.01–1.19	**0.035**
	White	13	0.025	48.7	Random	1.13	0.99–1.29	0.068
	Asian	38	<0.0001	68	Random	1.07	0.96–1.20	0.193
	African	3	0.016	75.77	Random	1.29	0.57–2.90	0.539
COD2 (EE vs. DD)	Overall	55	<0.0001	59.22	Random	1.18	1.00–1.40	**0.046**
	White	13	0.472	0	Fixed	1.30	1.08–1.55	**0.004**
	Asian	38	<0.0001	66.11	Random	1.10	0.89–1.38	0.381
	African	3	0.379	0	Fixed	2.12	1.24–3.64	**0.006**
COD3 (EE vs. DE)	Overall	55	0.0002	45.47	Random	1.10	0.95–1.27	0.211
	White	13	0.119	32.92	Fixed	1.14	0.95–1.37	0.168
	Asian	38	0.0001	51.69	Random	1.05	0.87–1.26	0.631
	African	3	0.778	0	Fixed	1.77	1.00–3.14	0.051
DM (EE + DE vs. DD)	Overall	55	<0.0001	67.98	Random	1.11	1.02–1.21	**0.015**
	White	13	0.081	37.94	Random	1.15	1.03–1.29	**0.016**
	Asian	38	<0.0001	72.62	Random	1.08	0.97–1.21	0.164
	African	3	0.012	77.27	Random	1.48	0.69–3.19	0.312
RM (EE vs. DE + DD)	Overall	55	<0.0001	53.83	Random	1.15	0.99–1.34	0.068
	White	13	0.335	10.97	Fixed	1.24	1.04–1.48	**0.019**
	Asian	38	<0.0001	60.87	Random	1.08	0.89–1.32	0.432
	African	3	0.684	0	Fixed	2.00	1.19–3.37	**0.009**
OD (DE vs. EE + DD)	Overall	56	<0.0001	59.88	Random	1.08	1.00–1.17	**0.044**
	White	13	0.014	52.57	Random	1.12	0.97–1.28	0.114
	Asian	38	<0.0001	63.33	Random	1.07	0.97–1.18	0.178
	African	3	0.030	71.53	Random	1.14	0.55–2.38	0.716

AM, allele model; COD1, codominant model 1; COD2, codominant model 2; COD3, codominant model 3; DM, dominant model; RM, recessive model; OD, overdominant model; OR, odds ratio; CI, confidence interval.

populations. Forest plots of the results of the AM model for the association of *TP73 G4C14-A4T14* with cancer development in different ethnic populations are shown in Figure 3.

Subgroup analysis based on cancer types

All the genetic models were applied to analyze the correlation between the *TP73 G4C14-A4T14* variant and each cancer type (Table 3). The AM and DM models demonstrated significantly increased susceptibility to gynecological cancers (OVC, CC and EM) in carriers of the *TP73 G4C14-A4T14* variant. Five of the genetic models, including AM, COD2, COD3, DM, and RM indicated significant a significant association of the variant with susceptibility to CRC. The *G4C14-A4T14* variant was only associated with oral cancer (OC) risk in the COD2 model. Four genetic models implied significant risk susceptibility for HNC, including AM, COD1, DM, and OD model. Cancers in 'others' category (HCC + NHL + NB) also showed significant risk association with *TP73 G4C14-A4T14* variant in four genetic models-

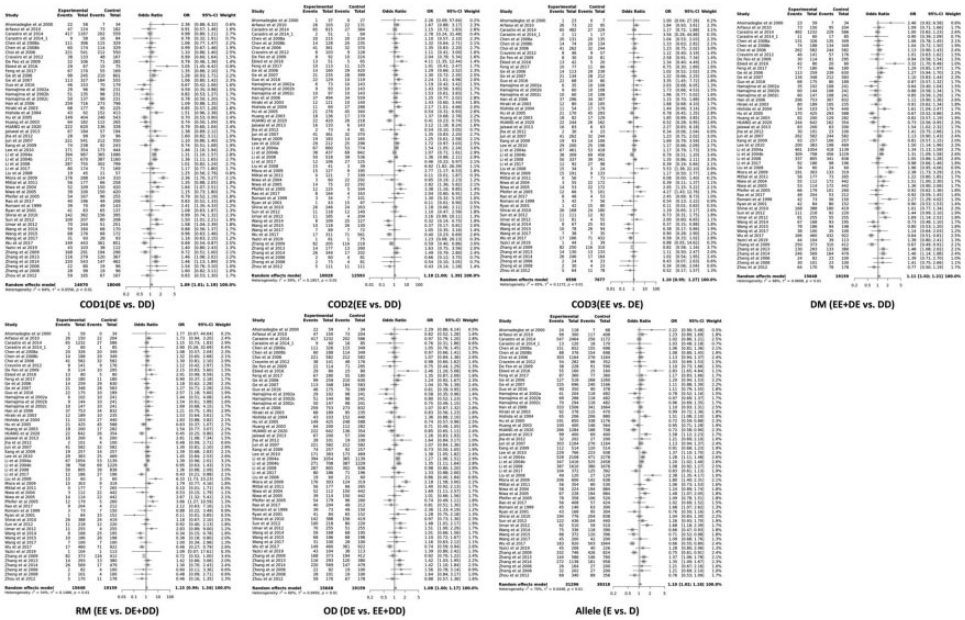


Figure 2. Forest plots of results of different genetic models for the association between *TP73 G4C14-A4T14* polymorphism and cancer development.
AM, allele model; COD1, codominant model 1; COD2, codominant model 2; COD3, codominant model 3; DM, dominant model; RM, recessive model; OD, overdominant model; OR, odds ratio; CI, confidence interval.

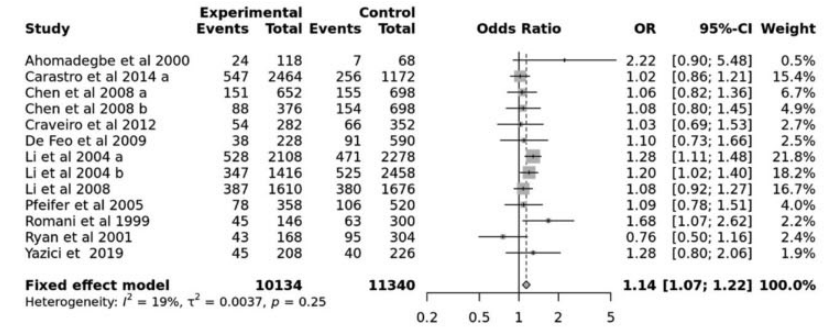
AM, COD1, DM, and OD model. No connection of this polymorphism was found with the risk of LC, EC, GC, BC, UBC + PC, and SC development. Forest plots presenting AM on the cancer type-based association of *TP73 G4C14-A4T14* variant with cancer development are presented in Figure 4.

Subgroup analysis based on control sources

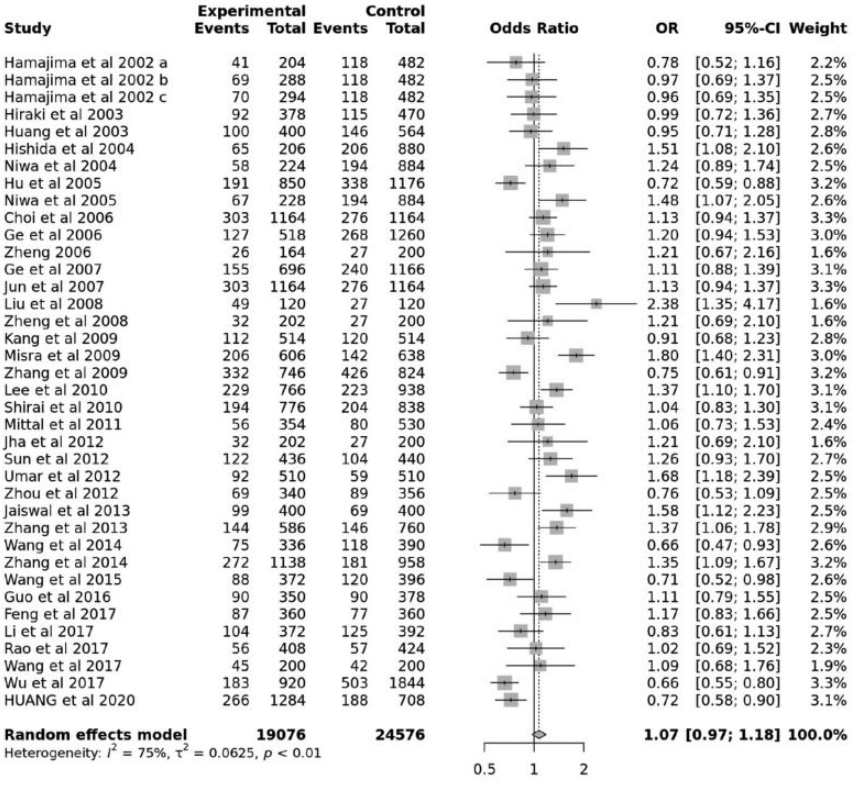
Among the two types of controls, only studies with HB controls revealed a significant risk susceptibility of the *TP73 G4C14-A4T14* variant for cancer development. Five genetic models supported this association namely, the AM, COD1, COD2, DM, and RM models. Studies with PB controls did not reveal any significant risk susceptibility for cancer in relation to the *TP73 G4C14-A4T14* variant (Table 4).

Test of heterogeneity

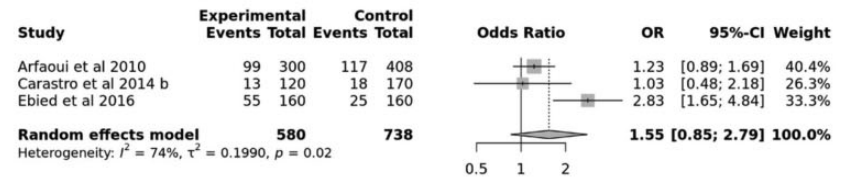
We determined the level of heterogeneity in this meta-analysis by Q-test. The level of significance was determined by P_H and the level of heterogeneity was estimated by I^2 statistics. Heterogeneity was significant in the maximum subgroup analysis models ($P_H<0.1$) and random-effects models were applied, while fixed-effects models were used for analyses with $P_H>0.10$. There was significant heterogeneity in all the genetic models for overall cancer. The results for the heterogeneity test of heterogeneity are displayed in Tables 2–4.



Caucasian: AM (E vs. D)



Asian: AM (E vs. D)



African: AM (E Vs. D)

Figure 3. Forest plots of results of allele model (AM) on association between *TP73 G4C14-A4T14* polymorphism and cancer development in relation to ethnicity.
OR, odds ratio; CI, confidence interval.

Table 3. Associations of *TP73 G4C14-A4T14* polymorphism with risks of different cancer types.

Comparison	Subgroup	N	P_H	I^2	Model	OR	95% CI	P_Z
AM (E vs. D)	LC	11	<0.0001	85.05	Random	0.90	0.76–1.08	0.260
	Gynecological (CC + EM + OVC)	10	0.781	0	Fixed	1.16	1.04–1.31	**0.011**
	CRC	6	0.124	42.12	Fixed	1.26	1.10–1.44	**0.0007**
	GC	5	0.038	60.58	Random	0.98	0.81–1.19	0.872
	EC	4	0.010	73.76	Random	1.04	0.75–1.45	0.819
	BC	4	0.0003	84.3	Random	1.36	0.77–2.42	0.290
	OC	4	0.009	74.25	Random	1.22	0.91–1.63	0.178
	UBC + PC	4	0.169	40.46	Fixed	1.10	0.96–1.26	0.176
	HNC	2	0.367	0	Fixed	1.25	1.10–1.41	**0.0006**
	SC	2	0.865	0	Fixed	1.09	0.97–1.23	0.151
	Other cancers (HCC + NHL + NB)	3	0.404	0	Fixed	1.44	1.14–1.81	**0.002**
COD1 (DE vs. DD)	LC	11	0.0001	72.65	Random	0.97	0.82–1.15	0.764
	Gynecological (CC + EM + OVC)	10	0.031	50.99	Random	1.18	0.95–1.47	0.134
	CRC	6	0.069	51.07	Random	1.06	0.81–1.38	0.684
	GC	5	0.139	42.45	Fixed	0.94	0.80–1.10	0.452
	EC	4	0.033	65.66	Random	1.04	0.72–1.49	0.846
	BC	4	0.002	79.29	Random	1.31	0.69–2.49	0.401
	OC	4	0.0002	84.57	Random	1.21	0.76–1.95	0.421
	UBC + PC	4	0.315	15.37	Fixed	1.08	0.91–1.28	0.374
	HNC	2	0.660	0	Fixed	1.39	1.19–1.63	$\mathbf{3.44\times10^{-5}}$
	SC	2	0.609	0	Fixed	1.05	0.90–1.21	0.536
	Other cancers (HCC + NHL + NB)	3	0.223	33.32	Fixed	1.61	1.18–2.20	**0.003**
COD2 (EE vs. DD)	LC	11	<0.0001	79.36	Random	0.75	0.50–1.11	0.148
	Gynecological (CC + EM + OVC)	10	0.313	14.15	Fixed	1.34	0.98–1.81	0.064
	CRC	6	0.387	4.56	Fixed	1.97	1.39–2.78	**0.0001**
	GC	5	0.035	61.42	Random	1.10	0.68–1.76	0.702
	EC	4	0.054	60.65	Random	1.16	0.49–2.76	0.732
	BC	4	0.042	63.43	Random	1.39	0.52–3.75	0.510
	OC	4	0.361	6.4	Fixed	1.51	1.02–2.25	**0.042**
	UBC + PC	4	0.082	55.26	Random	1.44	0.56–3.67	0.447
	HNC	2	0.384	0	Fixed	1.18	0.84–1.67	0.348
	SC	2	0.797	0	Fixed	1.31	0.95–1.81	0.102
	Other cancers (HCC + NHL + NB)	3	0.535	0	Fixed	1.64	0.92–2.91	0.092
COD3 (EE vs. DE)	LC	11	0.005	60.32	Random	0.78	0.58–1.05	0.102
	Gynecological (CC + EM + OVC)	10	0.016	55.74	Random	1.03	0.62–1.71	0.897
	CRC	6	0.199	31.56	Fixed	1.81	1.27–2.59	**0.001**
	GC	5	0.199	33.3	Fixed	1.02	0.79–1.32	0.864
	EC	4	0.077	56.27	Random	1.16	0.50–2.70	0.726
	BC	4	0.312	15.9	Fixed	1.27	0.74–2.17	0.384
	OC	4	0.700	0	Fixed	1.26	0.83–1.89	0.276
	UBC + PC	4	0.132	46.61	Fixed	1.28	0.84–1.95	0.256
	HNC	2	0.507	0	Fixed	0.85	0.60–1.21	0.374
	SC	2	0.635	0	Fixed	1.25	0.90–1.75	0.182
	Other cancers (HCC + NHL + NB)	3	0.462	0	Fixed	1.08	0.60–1.94	0.801

(continued)

Table 3. Continued.

Comparison	Subgroup	N	P_H	I^2	Model	OR	95% CI	P_Z
DM(EE + DE vs. DD)	LC	11	<0.0001	80.92	Random	0.93	0.77–1.13	0.454
	Gynecological (CC + EM + OVC)	10	0.287	16.99	Fixed	1.18	1.02–1.36	**0.022**
	CRC	6	0.102	45.62	Fixed	1.20	1.02–1.42	**0.027**
	GC	5	0.063	55.14	Random	0.94	0.75–1.18	0.606
	EC	4	0.020	69.4	Random	1.04	0.72–1.51	0.824
	BC	4	0.001	83.18	Random	1.39	0.71–2.72	0.333
	OC	4	0.0003	84.09	Random	1.26	0.81–1.97	0.305
	UBC + PC	4	0.274	22.87	Fixed	1.10	0.95–1.30	0.250
	HNC	2	0.499	0	Fixed	1.36	1.17–1.59	$\mathbf{5.2\times-10^{-5}}$
	SC	2	0.708	0	Fixed	1.08	0.94–1.24	0.302
	Other cancers (HCC + NHL + NB)	3	0.246	28.63	Fixed	1.61	1.20–2.16	**0.002**
RM (EE vs. DE + DD)	LC	11	<0.0001	74.92	Random	0.76	0.53–1.08	0.124
	Gynecological (CC + EM + OVC)	10	0.130	34.78	Fixed	1.31	0.97–1.77	0.081
	CRC	6	0.309	16.24	Fixed	1.89	1.35–2.65	**0.0002**
	GC	5	0.105	47.75	Fixed	0.95	0.75–1.21	0.683
	EC	4	0.060	59.41	Random	1.18	0.51–2.74	0.698
	BC	4	0.115	49.39	Fixed	1.36	0.82–2.26	0.231
	OC	4	0.693	0	Fixed	1.37	0.93–2.03	0.112
	UBC + PC	4	0.098	52.37	Random	1.40	0.57–3.42	0.460
	HNC	2	0.413	0	Fixed	1.05	0.74–1.47	0.795
	SC	2	0.732	0	Fixed	1.29	0.94–1.78	0.118
	Other cancers (HCC + NHL + NB)	3	0.518	0	Fixed	1.38	0.79–2.42	0.254
OD (DE vs. EE + DD)	LC	11	0.002	63.76	Random	1.01	0.87–1.16	0.914
	Gynecological (CC + EM + OVC)	10	0.007	60.39	Random	1.16	0.91–1.48	0.222
	CRC	6	0.045	55.95	Random	0.97	0.74–1.27	0.816
	GC	5	0.370	6.47	Fixed	0.97	0.83–1.13	0.723
	EC	4	0.031	66.35	Random	1.05	0.73–1.51	0.788
	BC	4	0.007	74.96	Random	1.23	0.70–2.18	0.478
	OC	4	0.001	83.05	Random	1.18	0.75–1.83	0.477
	UBC + PC	4	0.323	13.79	Fixed	1.06	0.90–1.26	0.474
	HNC	2	0.744	0	Fixed	1.38	1.18–1.61	$\mathbf{5.29\times10^{-5}}$
	SC	2	0.553	0	Fixed	1.03	0.89–1.19	0.729
	Other cancers (HCC + NHL + NB)	3	0.190	39.8	Fixed	1.52	1.13–2.06	**0.006**

AM, allele model; COD1, codominant model 1; COD2, codominant model 2; COD3, codominant model 3; DM, dominant model; RM, recessive model; OD, overdominant model; BC, breast cancer; EC, esophageal cancer; GC, gastric cancer; SC, skin cancer; CRC, colorectal cancer; LC, lung cancer; HNC, head and neck cancer; EM, endometrial cancer; OC, oral cancer; PC, prostate cancer; CC, cervical cancer; OVC, ovarian cancer; UBC, bladder cancer; OR, odds ratio; CI, confidence interval.

Publication bias and sensitivity analysis

Publication bias was determined using Egger's and Begg–Mazumdar's tests (Table 5). The funnel plots are shown in Figure 5. We conducted the bias study on the overall analysis with 55 studies using seven genetic models. There was no noticeable visual asymmetry signifying the presence of publication bias. Moreover, the pooled outcomes of this study were

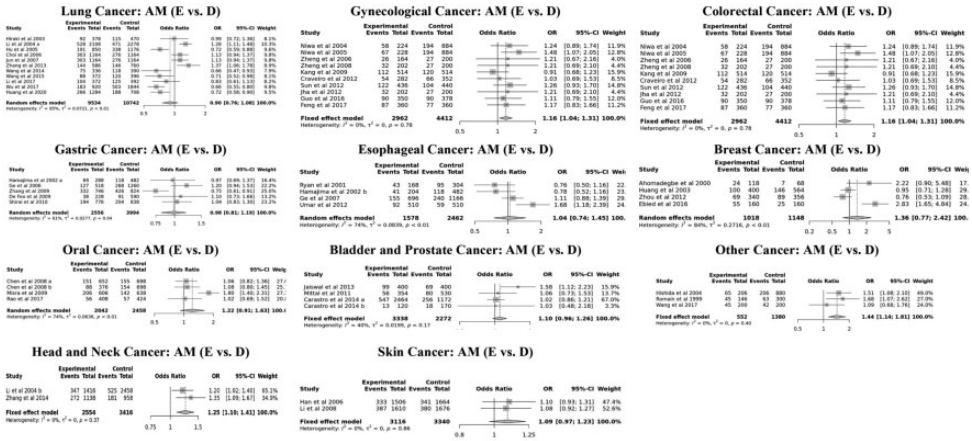


Figure 4. Forest plots of results of allele model (AM) on association between *TP73 G4C14-A4T14* polymorphism and cancer development in relation to cancer type.
OR, odds ratio; CI, confidence interval.

Table 4. Associations of *TP73 G4C14-A4T14* polymorphism with cancer risk based on control source.

Comparison	Subgroup	N	P_H	I^2	Model	OR	95% CI	P_Z
AM (E vs. D)	PB	24	<0.0001	66.33	Random	1.05	0.95–1.17	0.343
	HB	31	<0.0001	72.17	Random	1.13	1.03–1.24	**0.010**
COD1 (DE vs. DD)	PB	24	<0.0001	62.95	Random	1.07	0.94–1.22	0.312
	HB	31	<0.0001	65.03	Random	1.11	1.00–1.24	**0.053**
COD2 (EE vs. DD)	PB	24	0.0005	55.96	Random	1.04	0.80–1.35	0.789
	HB	31	<0.0001	60.08	Random	1.29	1.05–1.59	**0.017**
COD3 (EE vs. DE)	PB	24	0.0174	41.81	Random	1.02	0.81–1.29	0.848
	HB	31	0.002	48.76	Random	1.15	0.95–1.39	0.148
DM (EE + DE vs. DD)	PB	24	<0.0001	65.83	Random	1.07	0.94–1.22	0.310
	HB	31	<0.0001	69.51	Random	1.14	1.02–1.27	**0.019**
RM (EE vs. DE + DD)	PB	24	0.004	48.93	Random	1.04	0.82–1.32	0.750
	HB	31	0.0001	56.27	Random	1.23	1.01–1.50	**0.037**
OD (DE vs. EE + DD)	PB	24	0.0002	58.32	Random	1.08	0.95–1.22	0.245
	HB	31	<0.0001	61.82	Random	1.09	0.98–1.21	0.098

HB, hospital-based; PB, population-based; OR, odds ratio; CI, confidence interval.

considered to be free from publication bias because the *p*-values were not significant in any of the seven genetic models.

To confirm the authenticity of the final findings, we conducted a sensitivity analysis of the studies by sequential elimination of the studies. The impact of each study on the final pooled ORs was checked, and none of the studies affected the pooled ORs. The sensitivity analysis thus confirmed the credibility and robustness of this meta-analysis (Table 6).

TSA outcomes

The TSA plots (Figure 6) indicated that the Z-curves exceeded the required information size in the overall population and in Whites

Table 5. Publication bias analysis.

	Genetic model						
Test	AM	COD1	COD2	COD3	DM	RM	OD
Egger's test	0.277	0.630	0.524	0.882	0.434	0.563	0.676
Begg–Mazumdar's test	0.364	0.437	0.913	0.948	0.446	0.404	0.557

AM, allele model; COD1, codominant model 1; COD2, codominant model 2; COD3, codominant model 3; DM, dominant model; RM, recessive model; OD, overdominant model.

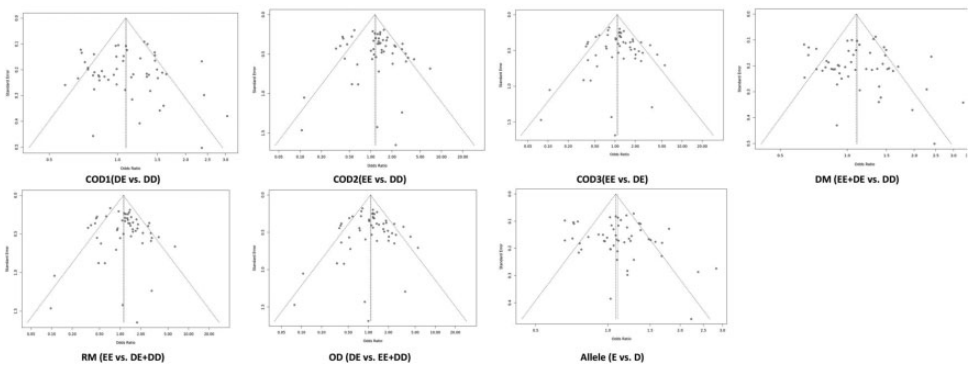


Figure 5. Funnel plots indicating publication bias of included studies for different models.
AM, allele model; COD1, codominant model 1; COD2, codominant model 2; COD3, codominant model 3; DM, dominant model; RM, recessive model; OD, overdominant model; OR, odds ratio; CI, confidence interval.

and Asians, indicating that the total cases and controls were sufficient to confirm the outcomes, and no further studies were required. However, the Z-curve did not exceed the required information size in Africans, and further studies are therefore required to confirm the outcome.

Discussion

The *TP73* gene encodes multiple protein isoforms with similar or opposite functions. The protein shows almost 63% homology with the tumor suppressor protein p53 in terms of its DNA-binding capability, oligomerization of the domains, and gene transactivation.[21] The protein isoforms of p73 arise from the utilization of different promoter sites and alternative mRNA splicing. Two common isoforms of p73 are TAp73 (TA domain present) and ΔNp73 (TA domain absent). Of these, TAp73 mimics the tumor suppression activities of p53 by inducing apoptosis, arresting G1 cell cycle checkpoint, and regulating the transcription of p53-related genes, while ΔNp73 exerts opposing functions by promoting oncogenic activities due to the lack of TA domain. ΔNp73 acts as an inhibitor of both p53 and p73 proteins.[10,22,81,82] The *TP73 G4C14-A4T14* variant of exon 2 potentially influences the translation of p73 by forming a stem-loop structure.[21] A recent study identified a significant association between the *TP73 G4C14-A4T14* variant and ΔNp73 tumoral immunostaining in

Table 6. Sensitivity analysis of the included studies.

Study	COD1 (DE vs. DD)	COD2 (EE vs. DD)	COD3 (EE vs. DE)	DM (EE + DE vs. DD)	RM (EE vs. DE + DD)	OD (DE vs. EE + DE)	AM (E vs. D)
Overall	1.09 (1.01–1.19)	1.18 (1.00–1.39)	1.1 (0.95–1.27)	1.11 (1.02–1.21)	1.15 (0.99–1.34)	1.08 (1.00–1.17)	1.1 (1.02–1.18)
Ahomadegbe et al.[37]	1.09 (1.00–1.18)	1.18 (1.00–1.39)	1.1 (0.95–1.27)	1.1 (1.02–1.20)	1.15 (0.99–1.34)	1.08 (1.00–1.16)	1.09 (1.02–1.17)
Arfaoui et al.[42]	1.1 (1.01–1.19)	1.17 (0.99–1.39)	1.08 (0.94–1.26)	1.11 (1.02–1.21)	1.14 (0.98–1.33)	1.09 (1.01–1.18)	1.1 (1.02–1.18)
Carastro et al.[39]	1.1 (1.01–1.20)	1.18 (1.00–1.40)	1.1 (0.94–1.27)	1.11 (1.02–1.21)	1.15 (0.99–1.35)	1.09 (1.00–1.18)	1.1 (1.02–1.18)
Carastro et al.[39]	1.1 (1.01–1.19)	1.18 (1.00–1.39)	1.09 (0.94–1.27)	1.11 (1.02–1.21)	1.15 (0.99–1.34)	1.08 (1.00–1.17)	1.1 (1.02–1.18)
Chen et al.[51]	1.09 (1.01–1.19)	1.19 (1.00–1.40)	1.1 (0.95–1.28)	1.11 (1.02–1.21)	1.15 (0.99–1.35)	1.08 (1.00–1.17)	1.1 (1.02–1.18)
Chen et al.[69]	1.1 (1.01–1.19)	1.18 (1.00–1.40)	1.09 (0.94–1.27)	1.11 (1.02–1.21)	1.15 (0.98–1.34)	1.09 (1.00–1.17)	1.1 (1.02–1.18)
Choi et al.[47]	1.09 (1.00–1.19)	1.18 (1.00–1.40)	1.09 (0.94–1.27)	1.11 (1.02–1.21)	1.15 (0.98–1.34)	1.08 (1.00–1.17)	1.1 (1.02–1.18)
Craveiro et al.[26]	1.1 (1.01–1.19)	1.18 (1.00–1.40)	1.1 (0.95–1.27)	1.11 (1.02–1.21)	1.15 (0.99–1.34)	1.08 (1.00–1.17)	1.1 (1.02–1.18)
De Feo et al.[36]	1.1 (1.01–1.19)	1.17 (0.99–1.38)	1.08 (0.94–1.25)	1.11 (1.02–1.21)	1.14 (0.98–1.33)	1.09 (1.01–1.18)	1.1 (1.02–1.18)
Ebeid et al.[66]	1.08 (1.00–1.18)	1.16 (0.99–1.37)	1.1 (0.94–1.27)	1.1 (1.01–1.19)	1.14 (0.98–1.32)	1.07 (1.00–1.16)	1.09 (1.01–1.16)
Feng et al.[38]	1.09 (1.00–1.19)	1.19 (1.00–1.40)	1.1 (0.95–1.28)	1.11 (1.02–1.21)	1.16 (0.99–1.35)	1.08 (1.00–1.17)	1.1 (1.02–1.18)
Ge et al.[67]	1.09 (1.00–1.19)	1.18 (1.00–1.40)	1.1 (0.95–1.28)	1.11 (1.02–1.21)	1.15 (0.99–1.34)	1.08 (1.00–1.17)	1.1 (1.02–1.18)
Ge et al.[49]	1.09 (1.01–1.19)	1.18 (1.00–1.40)	1.09 (0.94–1.27)	1.11 (1.02–1.21)	1.15 (0.98–1.34)	1.08 (1.00–1.17)	1.1 (1.02–1.18)
Guo et al.[52]	1.1 (1.01–1.20)	1.17 (0.99–1.38)	1.07 (0.93–1.24)	1.11 (1.02–1.21)	1.13 (0.97–1.32)	1.09 (1.01–1.18)	1.1 (1.02–1.18)
Hamajima et al.[31]	1.1 (1.02–1.20)	1.18 (1.00–1.40)	1.09 (0.94–1.26)	1.12 (1.03–1.22)	1.15 (0.98–1.34)	1.09 (1.01–1.18)	1.1 (1.03–1.18)
Hamajima et al.[31]	1.1 (1.01–1.20)	1.18 (1.00–1.39)	1.09 (0.94–1.26)	1.11 (1.02–1.21)	1.15 (0.98–1.34)	1.09 (1.01–1.18)	1.1 (1.02–1.18)
Hamajima et al.[31]	1.1 (1.01–1.20)	1.18 (1.00–1.39)	1.09 (0.94–1.26)	1.12 (1.02–1.21)	1.14 (0.98–1.33)	1.09 (1.01–1.18)	1.1 (1.02–1.18)
Han et al.[63]	1.09 (1.00–1.19)	1.18 (1.00–1.40)	1.1 (0.94–1.27)	1.11 (1.02–1.21)	1.15 (0.98–1.34)	1.08 (1.00–1.17)	1.1 (1.02–1.18)
Hiraki et al.[43]	1.1 (1.01–1.20)	1.18 (1.00–1.39)	1.09 (0.94–1.26)	1.11 (1.02–1.21)	1.15 (0.98–1.34)	1.09 (1.01–1.18)	1.1 (1.02–1.18)
Hishida et al.[65]	1.09 (1.00–1.18)	1.17 (0.99–1.38)	1.09 (0.94–1.27)	1.1 (1.01–1.20)	1.14 (0.98–1.33)	1.08 (1.00–1.17)	1.09 (1.02–1.17)
Hu et al.[60]	1.11 (1.02–1.20)	1.21 (1.02–1.42)	1.11 (0.96–1.29)	1.12 (1.03–1.22)	1.17 (1.01–1.36)	1.09 (1.01–1.18)	1.11 (1.03–1.19)
Huang et al.[62]	1.1 (1.01–1.20)	1.18 (1.00–1.39)	1.08 (0.94–1.26)	1.12 (1.03–1.22)	1.14 (0.98–1.33)	1.09 (1.01–1.18)	1.1 (1.02–1.18)
Huang et al.[54]	1.1 (1.01–1.20)	1.21 (1.03–1.43)	1.12 (0.97–1.29)	1.12 (1.03–1.22)	1.18 (1.02–1.37)	1.09 (1.01–1.18)	1.11 (1.03–1.19)
Jaiswal et al.[56]	1.09 (1.00–1.18)	1.16 (0.99–1.37)	1.09 (0.94–1.26)	1.1 (1.01–1.20)	1.14 (0.98–1.32)	1.08 (1.00–1.17)	1.09 (1.02–1.17)
Jha et al.[28]	1.09 (1.00–1.18)	1.19 (1.01–1.40)	1.1 (0.96–1.28)	1.11 (1.02–1.20)	1.16 (0.99–1.35)	1.08 (1.00–1.17)	1.1 (1.02–1.18)
Jun et al.[55]	1.09 (1.00–1.19)	1.18 (1.00–1.40)	1.09 (0.94–1.27)	1.11 (1.02–1.21)	1.15 (0.98–1.34)	1.08 (1.00–1.17)	1.1 (1.02–1.18)
Kang et al.[48]	1.1 (1.01–1.20)	1.18 (1.00–1.40)	1.09 (0.94–1.26)	1.12 (1.03–1.22)	1.15 (0.98–1.34)	1.09 (1.01–1.18)	1.1 (1.03–1.18)
Lee et al.[35]	1.09 (1.00–1.18)	1.17 (0.99–1.39)	1.1 (0.94–1.27)	1.1 (1.01–1.20)	1.14 (0.98–1.34)	1.08 (1.00–1.16)	1.09 (1.02–1.17)
Li et al.[32]	1.09 (1.00–1.18)	1.17 (0.99–1.39)	1.1 (0.94–1.27)	1.1 (1.01–1.20)	1.14 (0.98–1.34)	1.08 (1.00–1.17)	1.09 (1.02–1.18)

(continued)

Table 6. Continued.

Study	COD1 (DE vs. DD)	COD2 (EE vs. DD)	COD3 (EE vs. DE)	DM (EE + DE vs. DD)	RM (EE vs. DE + DD)	OD (DE vs. EE + DE)	AM (E vs. D)
Li et al.[54]	1.09 (1.00–1.18)	1.19 (1.00–1.41)	1.11 (0.96–1.29)	1.11 (1.01–1.20)	1.16 (0.99–1.35)	1.08 (0.99–1.16)	1.1 (1.02–1.18)
Li et al.[61]	1.1 (1.01–1.19)	1.18 (0.99–1.40)	1.09 (0.94–1.27)	1.11 (1.02–1.21)	1.15 (0.98–1.34)	1.09 (1.00–1.18)	1.1 (1.02–1.18)
Li et al.[71]	1.09 (1.00–1.19)	1.21 (1.02–1.42)	1.12 (0.97–1.29)	1.11 (1.02–1.21)	1.18 (1.01–1.36)	1.08 (1.00–1.17)	1.1 (1.03–1.19)
Liu et al.[44]	1.09 (1.00–1.19)	1.16 (0.99–1.36)	1.08 (0.94–1.25)	1.1 (1.01–1.20)	1.13 (0.98–1.31)	1.08 (1.00–1.17)	1.09 (1.01–1.17)
Misra et al.[74]	1.07 (0.99–1.16)	1.16 (0.99–1.37)	1.1 (0.95–1.27)	1.09 (1.01–1.18)	1.14 (0.98–1.33)	1.06 (0.99–1.15)	1.08 (1.01–1.16)
Mittal et al.[50]	1.09 (1.00–1.19)	1.19 (1.01–1.40)	1.1 (0.96–1.28)	1.11 (1.02–1.21)	1.16 (1.00–1.35)	1.08 (1.00–1.17)	1.1 (1.02–1.18)
Niwa et al.[41]	1.09 (1.00–1.18)	1.19 (1.01–1.41)	1.11 (0.96–1.28)	1.1 (1.01–1.20)	1.16 (1.00–1.35)	1.07 (0.99–1.16)	1.1 (1.02–1.18)
Niwa et al.[27]	1.09 (1.00–1.19)	1.16 (0.98–1.37)	1.08 (0.93–1.25)	1.11 (1.02–1.20)	1.13 (0.97–1.31)	1.08 (1.00–1.17)	1.09 (1.02–1.17)
Pfeifer et al.[57]	1.1 (1.01–1.20)	1.16 (0.99–1.37)	1.08 (0.93–1.24)	1.11 (1.02–1.21)	1.13 (0.98–1.32)	1.09 (1.01–1.18)	1.1 (1.02–1.18)
Rao et al.[33]	1.1 (1.01–1.19)	1.17 (0.99–1.39)	1.09 (0.94–1.26)	1.11 (1.02–1.21)	1.14 (0.98–1.33)	1.09 (1.01–1.18)	1.1 (1.02–1.18)
Romani et al.[24]	1.08 (1.00–1.17)	1.18 (1.00–1.40)	1.1 (0.95–1.28)	1.1 (1.01–1.19)	1.15 (0.99–1.34)	1.07 (0.99–1.16)	1.09 (1.02–1.17)
Ryan et al.[46]	1.09 (1.01–1.19)	1.2 (1.02–1.41)	1.11 (0.96–1.28)	1.11 (1.02–1.21)	1.16 (1.00–1.35)	1.08 (1.00–1.17)	1.1 (1.03–1.18)
Shirai et al.[70]	1.1 (1.01–1.19)	1.18 (1.00–1.40)	1.1 (0.94–1.27)	1.11 (1.02–1.21)	1.15 (0.99–1.34)	1.09 (1.00–1.17)	1.1 (1.02–1.18)
Sun et al.[84]	1.09 (1.00–1.18)	1.18 (1.00–1.40)	1.11 (0.95–1.28)	1.1 (1.01–1.20)	1.16 (0.99–1.35)	1.08 (1.00–1.16)	1.09 (1.02–1.18)
Umar et al.[72]	1.09 (1.00–1.18)	1.17 (0.99–1.38)	1.09 (0.94–1.26)	1.1 (1.01–1.20)	1.14 (0.98–1.32)	1.08 (1.00–1.16)	1.09 (1.01–1.17)
Wang et al.[59]	1.1 (1.01–1.19)	1.21 (1.03–1.42)	1.12 (0.97–1.29)	1.12 (1.03–1.22)	1.18 (1.01–1.36)	1.08 (1.00–1.17)	1.11 (1.03–1.19)
Wang et al.[64]	1.1 (1.01–1.19)	1.21 (1.03–1.42)	1.12 (0.97–1.29)	1.12 (1.03–1.21)	1.18 (1.01–1.37)	1.08 (1.00–1.17)	1.11 (1.03–1.19)
Wang et al.[73]	1.09 (1.00–1.19)	1.18 (1.00–1.40)	1.1 (0.95–1.27)	1.11 (1.02–1.21)	1.15 (0.99–1.34)	1.08 (1.00–1.17)	1.1 (1.02–1.18)
Wu et al.[45]	1.11 (1.02–1.20)	1.22 (1.04–1.43)	1.12 (0.97–1.29)	1.12 (1.04–1.22)	1.18 (1.02–1.37)	1.09 (1.01–1.18)	1.11 (1.04–1.19)
Yazici et al.[30]	1.09 (1.00–1.19)	1.18 (1.00–1.40)	1.1 (0.95–1.27)	1.11 (1.02–1.20)	1.15 (0.99–1.34)	1.08 (1.00–1.17)	1.1 (1.02–1.18)
Zhang et al.[40]	1.1 (1.02–1.20)	1.21 (1.03–1.42)	1.11 (0.96–1.29)	1.12 (1.03–1.22)	1.17 (1.00–1.36)	1.09 (1.00–1.18)	1.11 (1.03–1.19)
Zhang et al.[68]	1.09 (1.00–1.18)	1.18 (0.99–1.39)	1.1 (0.95–1.27)	1.1 (1.01–1.20)	1.15 (0.98–1.34)	1.08 (1.00–1.16)	1.09 (1.02–1.17)
Zhang et al.[25]	1.09 (1.00–1.18)	1.18 (0.99–1.39)	1.1 (0.95–1.28)	1.1 (1.01–1.20)	1.15 (0.98–1.34)	1.07 (0.99–1.16)	1.09 (1.02–1.17)
Zheng[34]	1.09 (1.00–1.18)	1.19 (1.01–1.40)	1.1 (0.95–1.28)	1.11 (1.02–1.20)	1.16 (0.99–1.35)	1.08 (1.00–1.17)	1.1 (1.02–1.18)
Zheng et al.[29]	1.09 (1.00–1.18)	1.19 (1.01–1.40)	1.1 (0.96–1.28)	1.11 (1.02–1.20)	1.16 (0.99–1.35)	1.08 (1.00–1.17)	1.1 (1.02–1.18)
Zhou & Wu[2]	1.1 (1.01–1.19)	1.2 (1.02–1.41)	1.11 (0.96–1.28)	1.12 (1.03–1.22)	1.17 (1.00–1.36)	1.09 (1.00–1.17)	1.1 (1.03–1.19)

All values presented represent odds ratios with 95% confidence intervals; AM, allele model; COD1, codominant model 1; COD2, codominant model 2; COD3, codominant model 3; DM, dominant model; RM, recessive model; OD, overdominant model.

91% of cancer patients.[83] High expression of ΔNp73 in carriers of the *G4C14-A4T14* variant demonstrates the potential role of this polymorphism in carcinogenesis. Numerous studies have evaluated this association, but most of the findings have been inconclusive. We carried out the current meta-analysis to address these

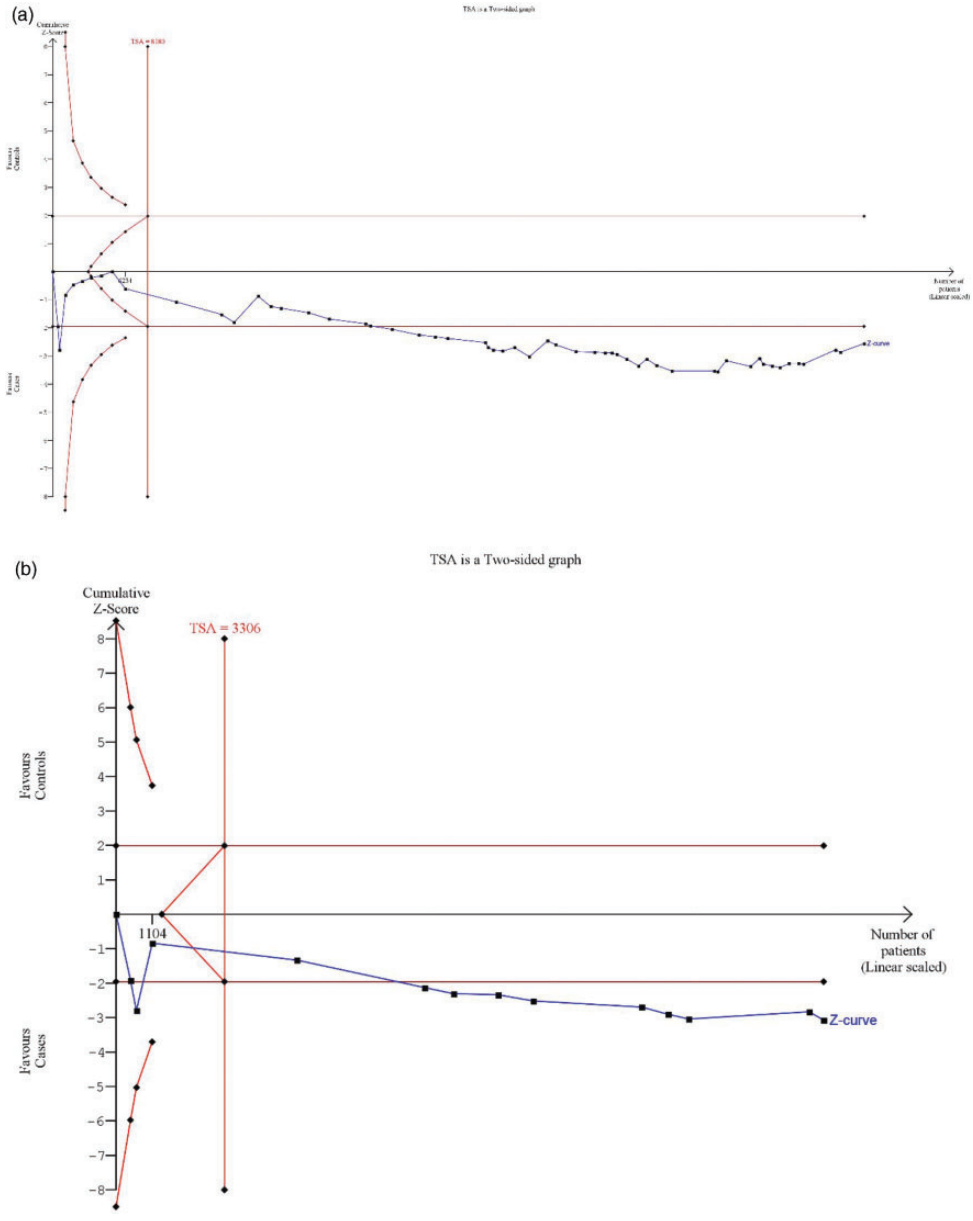


Figure 6. Trial sequential analysis (TSA) of association between *TP73 G4C14-A4T14* polymorphism and cancer risk in allele model. (a) Overall population; (b) Whites; (c) Asians; and (d) Africans.

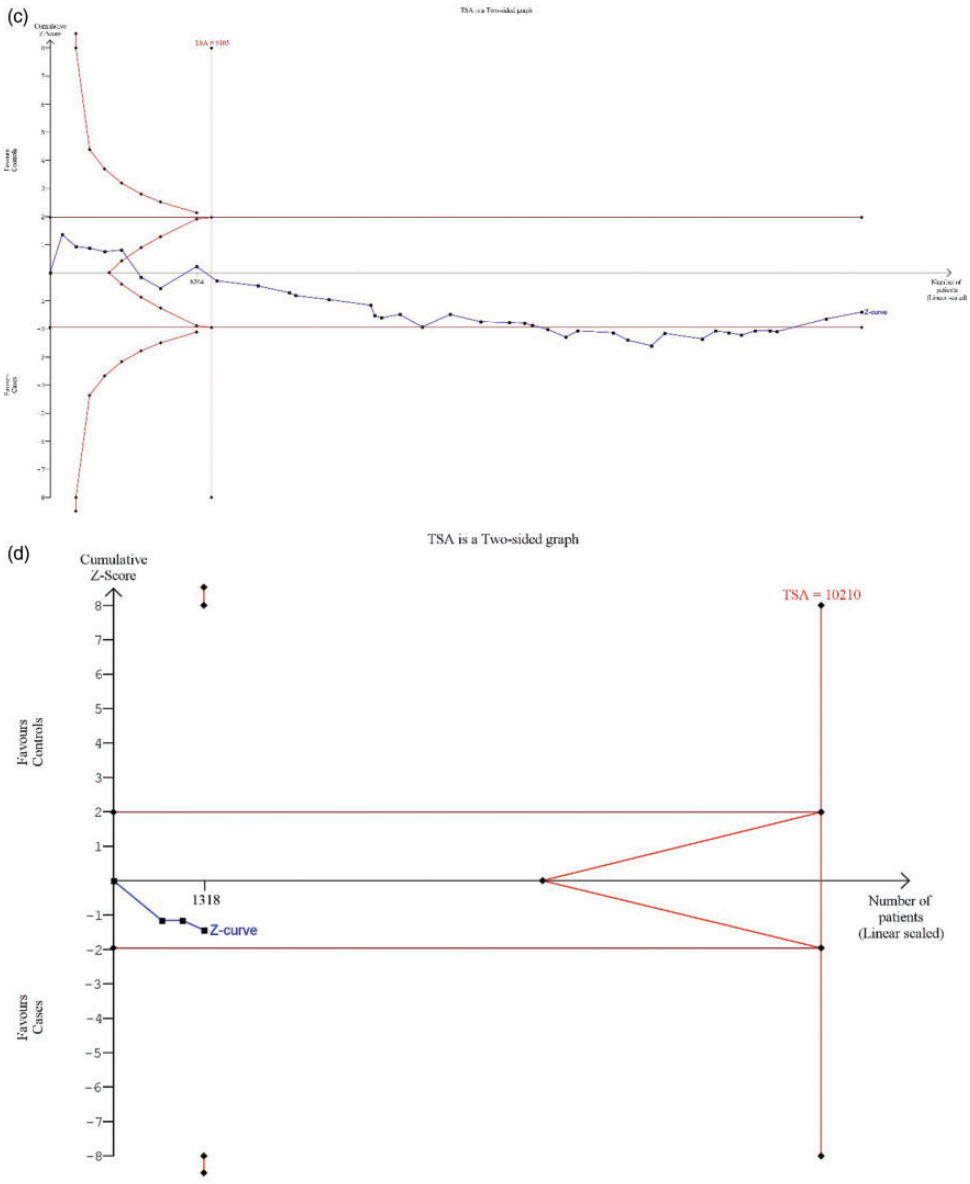


Figure 6. Continued.

inconsistencies, and showed that the *TP73 G4C14-A4T14* variant could significantly elevate the risk of cancer.

Recent studies have examined the association between the *G4C14-A4T14* variant and lung cancer risk in patients with non-small cell lung cancer (NSCLC). Most of these studies reported no significant risk association, and no significant difference in the frequency of the variant between patients and controls. However, some studies found that this variant was associated

with a reduced risk of NSCLC in AT/AT carriers compared with GC/GC carriers.[43,45,47,59,60,64,71] In contrast, other studies showed that this polymorphism could significantly increase the risk of NSCLC among the variant GC/AT and AT/AT genotype carriers, and a high GC content increased the risk. *TP73* and *MDM2* variants jointly increase the risk of lung cancer, depending on the number of variant alleles.[32,54,55,68] The *G4C14-A4T14* variant also increased the risk of gynecological cancers, with a two-fold increase in susceptibility to high-grade squamous intraepithelial lesion in women carrying the *TP73* AT allele.[26] The risks of CC and EM cancers were also increased among carriers of the *TP73* polymorphism who were passive smokers.[27,28,41,58] However, some association studies failed to detect any significant association between *TP73* genotype and tumor stage, histological type, or lymph node metastasis in patients with gynecological cancers.[29,48,52] Regarding CRC, AT/AT homozygous genotype of *TP73* was associated with an increased risk of CRC and a poor prognosis, whereas AT allele carriers had a better prognosis. However, another study failed to observe any significant association between the *TP73* GC/AT variant genotype and allele distribution and clinical parameters of CRC.[30,35,42,44,57] Some previous studies identified the AC/GT genotype of *G4C14-A4T14* as a significant risk factor for GCs, although other studies found no such association.[31,36,40,67,70]

Decreased expression of p73 mRNA was identified in both inflammatory and non-inflammatory BC cells compared with normal breast epithelial cells, indicating that this variant might increase the risk of BC by reducing the expression of p73. A recent study postulated that the *TP73* GC/AT and AT/AT genotypes could increase the susceptibility to BC, while another study found that the GC/GC genotype was associated with an increased risk of triple-negative BC,[2,37,66] and yet another study found no significant association between this polymorphism and BC.[62] Similar findings were observed in EC studies with contradictory conclusions.[31,46,67,72] *TP73 G4C14-A4T14* was recently identified as a risk factor for OC development.[33,51,74] Although the risk variant was associated with an increased risk of UBC, it showed a significant inverse relationship with PC.[39,50,56] Among other studies of the association between this variant and OC, SC, HNC, and other cancers (HCC + NHL + NB), most identified *G4C14-A4T14* polymorphism as a risk variant for cancer.[24,25,49,53,61,65,69,73]

The current meta-analysis of 55 case–control studies found that the *TP73 G4C14-A4T14* variant was linked to an increased risk of overall cancer development. Five of the tested genetic models (AM, COD1, COD2, DM, and OD) showed a significantly increased risk of overall cancer (1.10, 1.09, 1.18, 1.11, and 1.08-fold, respectively). Subgroup analysis based on ethnicity also showed a significant association between the variant and cancer risk in Africans in two genetic models (COD2, 2.12-fold; RM, 2.00-fold), while four genetic models reported significantly elevated cancer risks among *TP73 G4C14-A4T14* variant carriers in White populations (AM, 1.14-fold; COD2, 1.30-fold; DM, 1.15-fold; RM, 1.24-fold). In terms of specific cancers, sub-group analysis identified significant associations between the *TP73 G4C14-A4T14* variant and the risks of gynecological cancer (OVC, CC and EM), CRC, OC, HNC, and other cancers (HCC + NHL + NB). An increased susceptibility to gynecological cancers was reported in two genetic models (AM, OR = 1.16; DM, OR = 1.18), an increased risk of CRC in five genetic models (AM, OR = 1.26; COD2, OR = 1.97; COD3, OR = 1.81; DM, OR = 1.20; RM, OR = 1.89). The *G4C14-A4T14* variant

was only associated with OC according to the COD2 model (OR = 1.51) and with HNC according to the AM (OR = 1.25), COD1 (OR = 1.39), DM (OR = 1.36), and OD models (OR = 1.38). The variant was significantly associated with 'other cancers' according to the AM (1.57-fold), COD1 (1.80-fold), DM (1.82-fold), and OD (1.67-fold) genetic association models. Moreover, studies with HB controls revealed significant susceptibility of *G4C14-A4T14* variant carriers to cancer according to the AM (OR = 1.13), COD1 (OR = 1.11), COD2 (OR = 1.27), DM (OR = 1.14), and RM models (OR = 1.22).

Some previous systematic meta-analyses examined the relationship between various cancer types and the *TP73 G4C14-A4T14* variant. Yu and colleagues performed a meta-analysis of 23 case–control studies and reported that this polymorphism might be significantly associated with cancer risk in Asian and White populations.[75] Another meta-analysis of 27 case–control studies concluded that carriers of the AT/AT genotype might be at high-risk of developing cancer among Asians and Whites.[76] A further meta-analysis of five case–control studies in 2017 confirmed that the polymorphism was associated with CC risk, but the number of included studies was small.[77] Meng et al. performed a recent meta-analysis of 36 case–control studies and found that the *TP73 G4C14-A4T14* variant was associated with an increased cancer risk, especially among Whites.[78] In contrast to these previous meta-analyses, the current meta-analysis included a large number of studies (55 case–control studies) that provided more consistent outcomes than previous studies. Moreover, we validated the stability and consistency of our findings by carrying out heterogeneity, publication bias, and sensitivity analyses, as well as TSA. The results of this study provide strong evidence for an association between the *TP73 G4C14-A4T14* variant and cancer development, by successfully avoiding publication bias. The quality of the included studies was also evaluated by NOS scoring, and low-quality studies were excluded to maintain the robustness of the final findings.

Although the present meta-analysis was conducted carefully, some limitations could not be avoided. The number of studies included in some of the subgroups was small, due to the lack of available information. In addition, some basic information on both the patients and controls was lacking, such as age, sex, medication, and body mass index, which could have further enriched the analysis. Further analyses should therefore be conducted, including more studies, to confirm the relationship between *TP73 G4C14-A4T14* and cancer risk.

Conclusion

This updated meta-analysis provides strong evidence indicating that the *TP73 G4C14-A4T14* variant may elevate the overall cancer risk, especially in White and African populations. Carriers of the *G4C14-A4T14* variant have increased risks of developing gynecological cancers, such as cervical, ovarian, and endometrial cancer, as well as colorectal, head and neck, and oral cancers, non-Hodgkin's lymphoma, and neuroblastoma. Moreover, studies recruiting HB controls revealed a significant association between the *G4C14-A4T14* variant and cancer risk.

Acknowledgments

The authors are thankful to the Department of Pharmacy, Noakhali Science and Technology University, for supporting the authors during the study.

Availability of data and material

All relevant data that support the study's results are accessible upon request from the corresponding author.

Author contributions

Mohammad Safiqul Islam: conceptualization, supervision, data analysis, software; Sarah Jafrin and Md. Abdul Aziz: literature search; Sarah Jafrin: writing- original draft preparation, methodology; Md. Abdul Aziz: writing – original draft preparation, methodology; writing – reviewing and editing; Mohammad Safiqul Islam: writing – reviewing and editing.

Declaration of conflicting interests

The authors declared no potential conflicts of interest

Funding

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

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