Association of TNF-α -308G>A Polymorphism with Susceptibility to Cervical Cancer and Breast Cancer – a Systematic Review and Meta-analysis

Asociace TNF-α -308G>A polymorfizmu s citlivostí na karcinom děložního čípku a prsu – systematický přehled a metaanalýza

Farbod M.[1], Karimi-Zarchi M.[2,3], Heiranizadeh N.[4], Seifi-Shalamzari N.[5], Akbarian-Bafghi M. J.[6], Jarahzadeh M. H.[7], Neamatzadeh H.[8,9]

[1] Cancer Institute, Imam Khomeini Hospital, Tehran University of Medical Sciences, Tehran, Iran
[2] Abortion Research Center, Yazd Reproductive Sciences Institute, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[3] Department of Obstetrics and Gynecology, Iran University of Medical Sciences, Tehran, Iran
[4] Department of Surgery, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[5] Department of Emergency Medicine, Shahrekord University of Medical Sciences, Shahrekord, Iran
[6] Department of Healthcare Management, Bam University of Medical Sciences, Bam, Iran
[7] Department of Anesthesiology and Critical Care, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[8] Department of Medical Genetics, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[9] Mother and Newborn Health Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

Summary

Background: To date, several studies have been carried out on the association of TNF-α -308G>A with the risk of cervical cancer (CC) and breast cancer (BC). However, their conclusions were not consistent. Thus, we performed a comprehensive meta-analysis to evaluate the association more precisely from all eligible case-control studies. ***Methods:*** We searched the PubMed, Google Scholar and Cochrane Library databases systematically to identify relevant studies up to 1 February 2019. The pooled odds ratio (OR) with 95% confidence interval (CI) was calculated using a fixed- or random-effects model. ***Results:*** A total of 40 case-control studies including 20 studies with 4,780 cases and 4,620 controls on CC and 20 studies with 12,390 cases and 14,910 controls on BC were selected in this meta-analysis. The pooled results showed that the TNF-α -308G>A polymorphism was significantly associated with an increased risk of CC (A vs. G: OR 1.277; 95% CI 1.104–1.477; P = 0.001; AA vs. GG: OR 1.333; 95% CI 1.062–1.674; P = 0.013; AG vs. GG: OR 1.307; 95% CI 1.064–1.605; P = 0.011; and AA + AG vs. GG: OR 1.324; 95% CI 1.104–1.587; P = 0.002) and BC (AA vs. AG + GG: OR 0.094; 95% CI 0.058–0.152; P ≤ 0.001). In the stratified analyses by ethnicity, the TNF-α -308G>A polymorphism was significantly associated with the risk of CC (in Caucasians and Africans) and BC (Caucasians and Asians). ***Conclusion:*** Our findings showed that TNF-α -308G>A polymorphism may be a risk factor for cervical cancer and breast cancer overall and by ethnicity.

Key words

cervical cancer – breast cancer – TNF-α gene – polymorphism – meta-analysis

The authors would like to thank Sahel Khajehnoori from the Mother and Newborn Health Research Center for assisting in the revision of this paper.

Autoři děkují Sahel Khajehnoori z Mother and Newborn Health Research Center za pomoc při revizi článku.

The authors declare they have no potential conflicts of interest concerning drugs, products, or services used in the study.

Autoři deklarují, že v souvislosti s předmětem studie nemají žádné komerční zájmy.

The Editorial Board declares that the manuscript met the ICMJE recommendation for biomedical papers.

Redakční rada potvrzuje, že rukopis práce splnil ICMJE kritéria pro publikace zasílané do biomedicínských časopisů.

Prof. Mojgan Karimi-Zarchi, M.D.
Abortion Research Center
Yazd Reproductive Sciences Institute
Shahid Sadoughi University
of Medical Sciences
Yazd, Iran
e-mail: mk.zarchi55@gmail.com

Submitted/Obdrženo: 10. 2. 2019
Accepted/Přijato: 5. 3. 2019

doi: 10.14735/amko2019170

Souhrn

Východiska: Bylo provedeno několik studií týkajících se souvislosti TNF-α -308G>A s rizikem karcinomu děložního čípku (cervical cancer – CC) a prsu (breast cancer – BC). Nicméně jejich závěry nebyly konzistentní. Proto jsme provedli komplexní metaanalýzu, aby bylo možné souvislost shodněji zhodnotit ze všech příslušných případových kontrolních studiích. ***Metody:*** Do 1. února 2019 jsme systematicky prohledali PubMed, Google Scholar a databázi Cochrane Library. Míra rizika (OR) s 95% intervalem spolehlivosti (CI) byla vypočtena pomocí modelu s pevnými nebo náhodnými efekty. ***Výsledky:*** V této metaanalýze bylo vybráno celkem 40 případových studií zahrnujících 20 studií s 4 780 případy a 4 620 kontrolami na CC a 20 studií s 12 390 případy a 14 910 kontrolami na BC. Souhrnné výsledky ukázaly, že TNF-α -308G>A polymorfizmus byl významně spojen se zvýšeným rizikem CC (A vs. G: OR 1,277; 95% CI 1,104–1,477; p = 0,001; OR 1,333; 95% CI 1,062–1,674; p = 0,013; AG vs. GG: OR 1,307; 95% CI 1,064–1,605; p = 0,011 a AA + AG vs. GG: 95% CI 1,104–1,587; p = 0,002) a BC (AA vs. AG + GG: OR 0,094; 95% CI 0,058–0,152, p ≤ 0,001). Ve stratifikovaných analýzách podle etnicity byl polymorfizmus TNF-α -308G>A významně spojen s rizikem CC (u kavkazské a africké populace) a BC (u bělochů a Asiatů). ***Závěr:*** Naše výsledky ukázaly, že polymorfizmus TNF-α -308G>A může být rizikovým faktorem karcinomu děložního čípku a BC v závislosti na etnicitě.

Klíčová slova

karcinom děložního čípku – karcinom prsu – gen TNF-α – polymorfizmus – metaanalýza

Introduction

There has been a progressive increase in the incidence and mortality of gynaecological cancers and breast cancer (BC). BC and cervical cancer (CC) are the first and second most common malignancies, respectively, in women [1–3]. Moreover, BC and CC rank as the first (15.0%) and fourth (6.6%) leading causes, respectively, of female cancer deaths worldwide [4,5]. In 2017, 255,180 new BC cases and 41,070 BC deaths were estimated to have occurred in the United States [4,6]. In the same year, 12,820 new CC cases were diagnosed and 4,210 CC deaths were estimated in the US. BC and gynaecological cancers are known to be of multifactorial aetiology. Nulliparity, childbearing age, HPV infection, environment and lifestyle are the most well-established risk factors for BC and gynaecological cancers [7].

Epidemiological and clinical data show that the development of cancer is a multifactorial process [8]. Genetic risks of gynaecological cancers and BC have attracted increasing concern in research on the gene variations involved in immune systems and inflammatory pathways [9]. However, the exact mechanism of BC and/or CC is still largely unexplored. In past decades, apart from genetic variations that have raised major concerns in cancer biology, the role of inflammation factors such as tumour necrosis factor-alpha (TNF-α) has been widely researched in the aetiology of cancer [10,11]. The human TNF-α gene located on chromosome 6p21.3 contains 8 exons and encodes 382 amino acid proteins, in which -308G>A and -238 G>A are the most common polymorphisms [12,13]. TNF-α is a potential pro-inflammatory cytokine, which plays a critical role in a wide range of inflammatory, autoimmune and malignant diseases. To date, more and more studies indicate that TNF-α polymorphisms, especially the -308G>A polymorphism, are associated with gynaecological cancers and BC.

To date, several case-control studies have been performed to investigate the association of TNF-α -308G>A polymorphism with the risk of CC and BC. However, their results are still inconclusive and controversial. These different results may be due to differences in ethnic background, sample size and lifestyle and other factors. Thus, a meta-analysis with a large sample size should be performed to clarify the role of TNF-α -308G>A polymorphism in CC and BC. Therefore, we performed this meta-analysis on all the eligible case-control studies to make a more accurate assessment of the associations.

Materials and methods

Search strategy

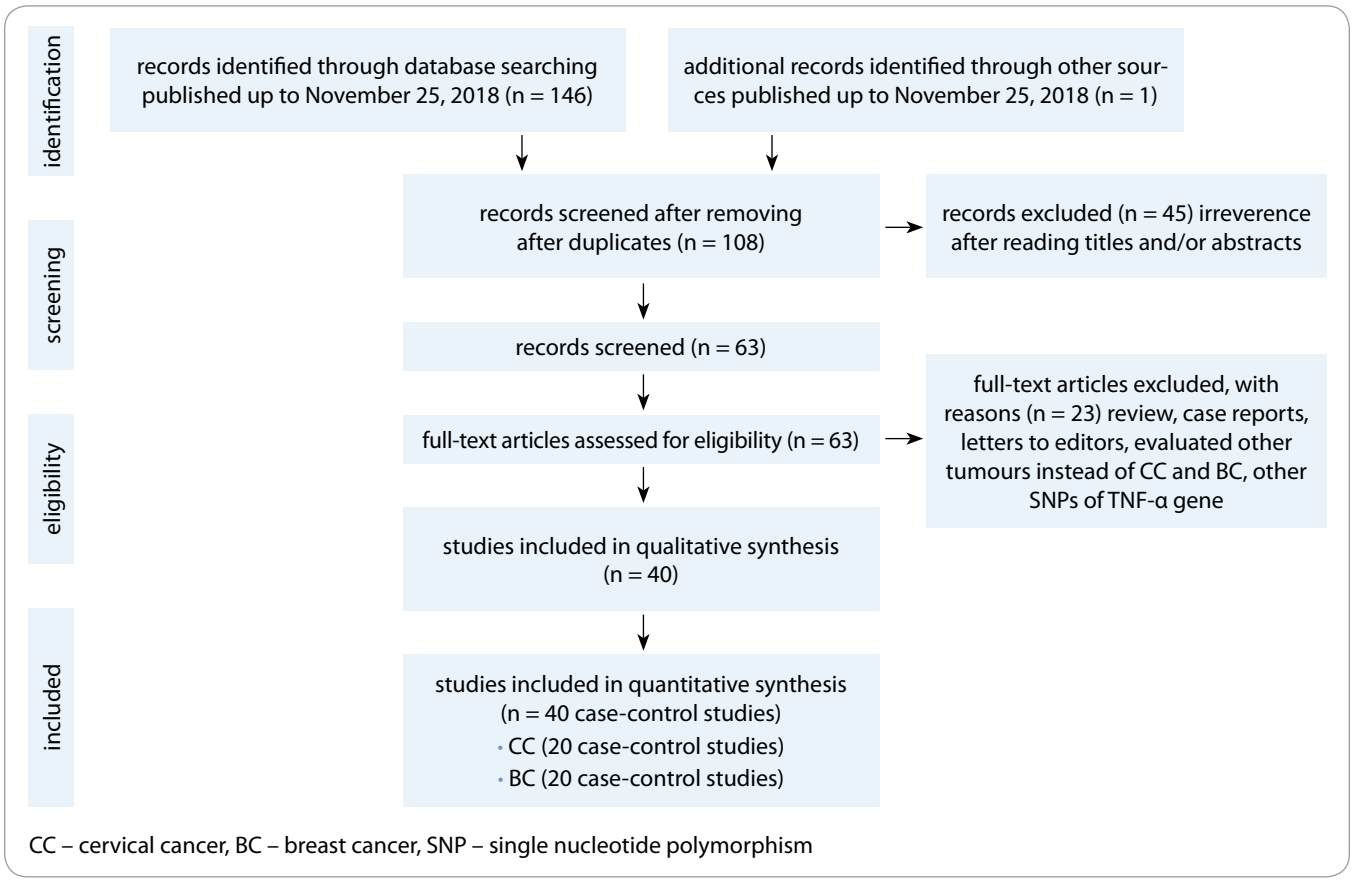
We searched the PubMed, Google Scholar, EBSCO, EMBASE, Web of Science, Islamic World Science Citation Center (ISC), Scientific Information Database (SID), Wanfang, Ovid, Weipu and China National Knowledge Infrastructure (CNKI) databases for all articles on the association of the NF-α-308G>A polymorphism in CC and BC risk up to 1 February 2019. We used the following key words and terms for the research: ('Breast cancer' or 'Breast Carcinoma') and ('Cervical Cancer' or 'Cervical Carcinoma' or 'Cervical tumour' or 'Uterine Cervix Cancer') and ('Tumour Necrosis Factor' or 'TNF-α' or 'Cachexin' or 'Cachectin') and ('TNF -308G>A' OR 'rs1800629' or 'c.-488G>A'). In addition, the reference lists of all eligible studies, reviews and previous meta-analyses were also manually screened for additional or missing potential studies. The search was performed without language limitations.

Eligibility criteria

The inclusion criteria of studies in our meta-analysis were as follows: 1) studies with case-control or cohort design; 2) studies that evaluated the association of the TNF-α -308G>A polymorphism with CC and BC risk; and 3) studies with sufficient data to estimate the odds ratio (OR) with 95% confidence interval (CI). Accordingly, the major exclusion criteria were: 1) studies on male BC; 2) case-only studies or no control group was included; 3) family-based and or linkage studies; 4) studies lacking sufficient published data; 5) case reports, reviews, abstracts, letters to editors and posters; 6) duplicates of previous studies.

Data extraction

Two reviewers extracted the data independently and carefully from the eligible studies using a standard protocol in accordance with inclusion criteria. Any disagreement between the included



Schema 1. Flow diagram of selecting eligible studies for the meta-analysis.

studies and the data was resolved by discussion among the authors and if a conflicting evaluation still existed another author was consulted to resolve the dispute. For each of the eligible case-control studies, we have collected the following data: first authors, year of publication, country, ethnicity (Caucasian, Asian, African and Mixed), source of healthy controls (hospital-based studies and population-based studies), number of cases and controls, the numbers of cases and controls for each genotype, Hardy-Weinberg equilibrium (HWE) in controls and minor allele frequency (MAF).

Statistical analyses

Ethical approval was not required for this study, as it is a systematic review and meta-analysis. The OR and corresponding 95% CI were evaluated to estimate the association of TNF-α -308G>A polymorphism with the risk of CC and BC. The Ztest was used to assess the significance of the pooled OR, in which $P < 0.05$ was considered as statistically significant. In this meta-analysis, the pooled ORs for TNF-α -308G>A polymorphism were performed under all five genetic models, i.e., allele (A vs. G), homozygote (AA vs. GG), heterozygote (AG vs. GG), dominant (AA + AG vs. GG) and recessive (AA vs. AG + GG), respectively. Between-study heterogeneity was analysed by a chi-squared-based Q-statistic test, in which the P-value < 0.05 was considered significant. In addition, we used the Higgins (I2) test to assess the degree of between-study heterogeneity, in which the I2 values of 25%, 50% and 75% were nominally considered low, moderate and high estimates, respectively. Accordingly, the pooled ORs were calculated using a fixed-effects model (Mantel-Haenszel method) (if $P > 0.05$ or $I2 < 50\%$); otherwise, a random-effects model (DerSimonian- Laird method) was chosen (if $P < 0.05$ or $I2 > 50\%$) based on the level of heterogeneity. For each study, the departure of the TNF-α -308G>A polymorphism frequencies in control groups from the HWE was tested using the goodness-of-fit test (i. chi-square test), and deviation was considered when $P < 0.05$. We performed subgroup analysis according to ethnicity, source of controls (population-based or hospital-based), genotyping methods and HWE. The stability and reliability of the results were evaluated using a sensitivity analysis, in which one study was deleted each time and the analyses were repeated. In addition, a sensitivity analysis was performed by excluding those studies departing from the HWE. Publication bias was tested with the funnel plot and Egger's linear regression asymmetry test; $P < 0.05$ suggested statistically significant publication bias. All analyses were performed with the Comprehensive Meta-Analysis (CMA) 2.0 software (Biostat, USA). Two-sided P-values < 0.05 were considered statistically significant.

Results

The selection process of eligible studies is shown in Schema 1. According to our

Tab. 1. Characteristics of the case-control studies included in the meta-analyses.

First Author	Country (ethnicity)	SOC	Genotyping method	Case/ control	Cases					Controls					MAFs	HWE
					Genotype			Allele		Genotype			Allele			
Cervical Cancer					GG	AG	AA	G	A	GG	AG	AA	G	A		
Jang 2001 [14]	Korea (Asian)	PB	PCR-RFLP	51/92	46	3	2	95	7	85	7	0	177	7	0.038	0.704
Calhoun 2002 [15]	USA (Caucasian)	HB	sequencing	127/107	91	27	9	209	45	73	30	4	176	38	0.177	0.678
Stanczuk 2003 [16]	Zimbabwe (African)	PB	ARMS-PCR	103/101	74	28	1	176	30	81	18	2	180	22	0.108	0.410
Gostout 2003 [17]	USA (Caucasian)	HB	sequencing	127/175	91	27	9	209	45	117	53	5	287	63	0.180	0.731
Duarte 2005 [18]	Portugal (Caucasian)	PB	PCR-RFLP	195/244	138	50	7	326	64	200	40	4	440	48	0.098	0.236
Deshpande 2005 [19]	USA (Caucasian)	HB	sequencing	258/411	188	54	16	430	86	297	100	14	694	128	0.155	0.130
Govan 2006 [20]	South Africa (African)	HB	ARMS-PCR	244/228	174	62	8	410	78	172	46	10	390	66	0.144	0.005
Kohaar 2007 [21]	India (Asian)	HB	PCR-RFLP	120/165	94	22	4	210	30	150	15	0	315	15	0.045	0.540
Wang 2009 [22]	China (Asian)	PB	TaqMan	456/800	386	67	3	839	73	666	126	8	1458	142	0.088	0.457
Singh 2009 [23]	India (Asian)	HB	PCR-RFLP	150/162	122	17	11	261	39	147	11	4	305	19	0.058	≤ 0.001
Ivansson 2010 [24]	Sweden (Caucasian)	PB	TaqMan	1263/552	891	340	32	2122	404	396	138	18	930	174	0.157	0.169
Zu 2010 [25]	China (Asian)	HB	PCR	83/91	30	50	3	110	56	66	16	9	148	34	0.186	≤ 0.001
Wang 2011 [26]	China (Asian)	PB	PCR	186/200	149	30	7	328	44	144	46	10	334	66	0.165	0.019
Zuo 2011 [27]	China (Asian)	HB	PCR-RFLP	239/110	158	81	0	397	81	83	25	2	191	29	0.131	0.941
Wang 2012 [28]	China (Asian)	HB	PCR-RFLP	285/318	247	30	8	524	46	274	35	9	583	53	0.083	≤ 0.001
Barbisan 2012 [58]	Argentina (Caucasian)	HB	PCR-RFLP	122/176	87	32	3	206	38	126	46	4	298	54	0.153	0.483
Badano 2012 [30]	Argentina (Caucasian)	HB	sequencing	56/113	44	10	2	98	14	101	12	0	214	12	0.053	0.551
Sousa 2014 [31]	Portugal (Caucasian)	PB	TaqMan	223/205	152	65	6	369	77	164	39	2	367	43	0.104	0.849
Zidi 2014 [32]	Tunisia (African)	HB	ARMS-PCR	130/260	55	33	43	143	117	141	35	84	317	203	0.390	≤ 0.001
Roszak 2015 [33]	Poland (Caucasian)	HB	HMR	362/399	217	123	22	557	167	263	125	11	651	147	0.184	0.397

SOC – source of controls, HB – hospital based, PB – population based, PCR – polymerase chain reaction, RFLP – restriction fragment length polymorphism, ARMS – amplification-refractory mutation system, SNP – single nucleotide polymorphism, HMR – high resolution melting, MAF – minor allele frequency, HWE – Hardy-Weinberg equilibrium

Tab. 1 – continuing. Characteristics of the case-control studies included in the meta-analyses.

First Author	Country (ethnicity)	SOC	Genotyping method	Case/ control	Cases					Controls					MAFs	HWE
					Genotype			Allele		Genotype			Allele			
Breast Cancer																
Mestiri 2001 [34]	Tunisia (African)	PB	PCR-RFLP	243/174	167	53	23	387	99	117	53	4	287	61	0.175	0.480
Park 2002 [35]	Korea (Asian)	PB	PCR-RFLP	95/190	75	20	0	170	20	134	54	2	322	58	0.153	0.173
Giordani 2003 [36]	Italy (Caucasian)	PB	PCR-RFLP	125/100	104	19	2	227	23	84	15	1	183	17	0.085	0.721
Azmy 2004 [37]	UK (Caucasian)	HB	Sequencing	705/498	475	208	22	1158	252	313	167	18	793	203	0.204	0.458
Smith 2004 [38]	UK (Caucasian)	PB	ARMS-PCR	123/214	98	21	4	217	29	146	56	12	348	80	0.187	0.041
Kamali-Sarvestani 2005 [39]	Iran (Asian)	PB	ASO-PCR	223/235	192	31	0	415	31	203	32	0	438	32	0.068	0.262
Scola 2006 [40]	Italy (Caucasian)	PB	PCR-RFLP	84/106	71	12	1	154	14	79	26	1	184	28	0.132	0.471
Gallicchio 2007 [41]	USA (Caucasian)	HB	TaqMan	59/907	44	14	1	102	16	593	273	41	1459	355	0.196	0.186
Gaudet 2007 [42]	USA (Caucasian)	PB	sequencing	3170/2691	2240	832	98	5312	1028	1873	737	81	4483	899	0.167	0.412
Gaudet 2007	Poland (Caucasian)	PB	sequencing	1989/2295	1441	514	34	3396	582	1617	632	46	3866	724	0.158	0.081
Sirotkovic-Skerlev 2007 [43]	Croatia (Caucasian)	HB	sequencing	158/76	136	22	0	294	22	68	8	0	144	8	0.053	0.628
Gonullu 2007 [44]	Turkey (Caucasian)	PB	sequencing	38/24	30	6	2	66	10	15	9	0	39	9	0.188	0.258
Ostashkin 2008 [45]	Russia (Caucasian)	PB	ARMS-PCR	167/139	126	39	2	291	43	108	28	3	244	34	0.122	0.466
Kohaar 2009 [46]	India (Asian)	HB	PCR-RFLP	40/150	21	16	3	58	22	137	13	0	287	13	0.043	0.579
Marie-Genica 2010 [47]	Germany (Caucasian)	PB	PCR-RFLP	3138/5476	2238	822	78	5298	978	3795	1527	154	9117	1835	0.168	0.978
Pooja 2011a [48]	India (Asian)	PB	sequencing	265/237	238	22	5	498	32	225	10	2	460	14	0.030	≤ 0.001
Pooja 2011b	India (Caucasian)	PB	sequencing	200/200	177	21	2	375	25	166	34	0	366	34	0.085	0.188
Karakus 2011 [49]	Turkey (Caucasian)	PB	PCR-RFLP	204/204	167	36	1	370	38	159	45	0	363	45	0.110	0.076
Madeleine 2011 [50]	USA (Caucasian)	PB	SNPlex assay	869/900	603	245	21	1451	287	613	264	23	1490	310	0.172	0.387
Flores-Ramos 2013 [51]	Mexico (Latinos)	PB	PCR-RFLP	495/294	302	302	67	906	436	254	38	2	546	42	0.071	0.660

SOC – source of controls, HB – hospital based, PB – population based, PCR – polymerase chain reaction, RFLP – restriction fragment length polymorphism, ARMS – amplification-refractory mutation system, SNP – single nucleotide polymorphism, MAF – minor allele frequency, HWE – Hardy-Weinberg equilibrium

Tab. 2. Meta-analysis results of association between TNF-α -308G>A polymorphism and cervical cancer risk.

Poly-morphism	Genetic model	Type of model	Heterogeneity		Odds ratio				Publication bias	
			I^2 (%)	P_H	OR	95% CI	Z_{test}	P_{OR}	P_{Beggs}	P_{Eggers}
Overall	A vs. G	random	61.94	≤ 0.001	1.277	1.104–1.477	3.291	0.001	0.029	0.025
	AA vs. GG	fixed	27.43	0.125	1.333	1.062–1.674	2.481	0.013	0.314	0.366
	AG vs. GG	random	70.89	≤ 0.001	1.307	1.064–1.605	2.552	0.011	0.183	0.141
	AA + AG vs. GG	random	67.34	≤ 0.001	1.324	1.104–1.587	3.030	0.002	0.097	0.056
	AA vs. AG + GG	fixed	35.98	0.056	1.221	0.977–1.525	1.758	0.079	0.537	0.336
Asian	A vs. G	random	78.48	≤ 0.001	1.403	0.970–2.029	1.798	0.072	0.035	0.062
	AA vs. GG	fixed	43.54	0.088	1.089	0.670–1.770	0.343	0.731	1.000	0.540
	AG vs. GG	random	82.21	≤ 0.001	1.469	0.895–2.411	1.521	0.128	0.173	0.267
	AA + AG vs. GG	random	81.63	≤ 0.001	1.500	0.954–2.359	1.756	0.079	0.173	0.121
	AA vs. AG + GG	random	50.71	0.048	1.040	0.487–2.217	0.100	0.920	0.901	0.647
African	A vs. G	fixed	0.00	0.786	1.234	0.996–1.529	1.925	0.054	1.000	0.739
	AA vs. GG	fixed	0.00	0.537	1.156	0.757–1.766	0.672	0.502	1.000	0.289
	AG vs. GG	fixed	24.821	0.264	1.670	1.228–2.270	3.268	0.001	1.000	0.564
	AA + AG vs. GG	fixed	0.00	0.585	1.453	1.111–1.902	2.725	0.006	1.000	0.766
	AA vs. AG + GG	fixed	0.00	0.702	0.955	0.640–1.425	–0.225	0.822	1.000	0.185
Caucasian	A vs. G	random	52.45	0.032	1.242	1.043–1.478	2.438	0.015	0.754	0.203
	AA vs. GG	fixed	22.58	0.242	1.586	1.147–2.193	2.791	0.005	0.175	0.072
	AG vs. GG	random	54.87	0.023	1.123	0.905–1.395	1.056	0.291	0.754	0.906
	AA + AG vs. GG	random	52.80	0.031	1.201	0.982–1.469	1.787	0.074	0.916	0.501
	AA vs. AG + GG	fixed	22.15	0.246	1.569	1.137–2.165	2.744	0.006	0.348	0.079

OR – odds ratio, CI – confidence interval

search strategy, 147 articles were screened initially. From these, we excluded 107 articles because these articles did not provide detailed data, were reviews, case reports and previous meta-analyses, and/or had overlapped data. Finally, a total of 40 case-control studies were included in this meta-analysis. The characteristics of the included studies are shown in Tab. 1. Among the 40 studies, there were 20 studies with 4,780 cases and 4,620 controls on CC [14–33] and 20 studies with 12,390 cases and 14,910 controls on BC [34–51]. All of the selected papers were written in English or Chinese. The selected studies included 12 groups of Asians (8 on CC and 4 on BC), 23 groups of Caucasians (9 on CC and 14 on BC) and 4 groups of Africans (3 on CC and one on BC). The TNF-α -308G>A polymorphism frequency in each study, the results of the HWE test in control groups and MAFs are shown in Tab. 1. The distribution of genotypes in all studies was consistent with HWE except for six studies on CC and two studies for BC (Tab. 1).

Quantitative synthesis

Cervical cancer

Tab. 2 listed the main results of the meta-analysis of TNF-α -308G>A polymorphism and CC risk. The pooled data showed that there was a significant association between TNF-α -308G>A polymorphism and CC risk under four genetic models i.e., allele (A vs. G: OR 1.277; 95% CI 1.104–1.477; P = 0.001, Graph 1A), homozygote (AA vs. GG: OR 1.333; 95% CI 1.062–1.674; P = 0.013), heterozygote (AG vs. GG: OR 1.307; 95% CI 1.064–1.605; P = 0.011) and dominant (AA + AG vs. GG: OR 1.324; 95% CI 1.104–1.587; P = 0.002, Graph 1A). When stratified by ethnicity, there was a significant association between TNF-α -308G>A polymorphism and CC risk in Caucasians (allelic model A vs. G, OR 1.242; 95% CI 1.043–1.478; P = 0.015; homozygote model AA vs. GG, OR 1.586; 95% CI 1.147–2.193; P = 0.005; recessive model: AA vs. AG + GG, OR 1.569; 95% CI 1.137–2.165; P = 0.006) and Africans (heterozygote model AG vs. GG, OR 1.670; 95% CI 1.228–2.270; P = 0.001 and dominant model AA + AG vs. GG, OR 1.453; 95% CI 1.111–1.902; P = 0.006). However, there was no significant association in Asians.

Breast cancer

Tab. 3 summarised the main results of the meta-analysis for TNF-α -308G>A

Tab. 3. Meta-analysis results of association between TNF-α -308G>A polymorphism and breast cancer risk.

Subgroup	Genetic model	Type of model	Heterogeneity		Odds ratio				Publication bias	
			I^2 (%)	P_H	OR	95% CI	Z_{test}	P_{OR}	P_{Beggs}	P_{Eggers}
Overall	A vs. G	random	92.22	≤ 0.001	1.126	0.911–1.390	1.099	0.272	0.381	0.351
	AA vs. GG	random	59.96	0.001	1.233	0.854–1.782	1.118	0.263	0.197	0.101
	AG vs. GG	random	98.57	≤ 0.001	0.887	0.489–1.611	–0.394	0.694	0.314	0.799
	AA+AG vs. GG	random	93.08	≤ 0.001	1.172	0.870–1.435	0.866	0.386	0.314	0.427
	AA vs. AG+GG	random	90.30	≤ 0.001	0.094	0.058–0.152	–9.641	≤ 0.001	0.721	0.879
Ethnicity										
Caucasian	A vs. G	random	93.09	≤ 0.001	1.025	0.814–1.291	0.208	0.835	0.766	0.679
	AA vs. GG	random	53.47	0.009	1.023	0.728–1.436	0.129	0.897	0.100	0.320
	AG vs. GG	random	98.92	≤ 0.001	0.750	0.369–1.525	–0.795	0.427	0.047	0.980
	AA+AG vs. GG	random	94.16	≤ 0.001	1.025	0.775–1.356	0.174	0.862	0.921	0.695
	AA vs. AG+GG	random	91.21	≤ 0.001	0.076	0.045–0.128	–9.634	≤ 0.001	1.000	0.859
Asian	A vs. G	random	90.89	≤ 0.001	1.806	0.669–4.872	1.167	0.243	0.308	0.068
	AA vs. GG	fixed	60.60	0.079	3.222	0.317–32.77	0.989	0.323	1.000	0.898
	AG vs. GG	random	82.98	0.001	2.008	0.904–4.460	1.713	0.087	0.089	0.069
	AA+AG vs. GG	random	89.86	≤ 0.001	1.838	0.662–5.099	1.168	0.243	0.308	0.093
	AA vs. AG+GG	random	75.59	0.006	0.142	0.024–0.849	–2.139	0.032	0.734	0.075
SOC										
PB	A vs. G	random	92.76	≤ 0.001	1.078	0.858–1.365	0.646	0.518	0.964	0.523
	AA vs. GG	random	59.64	0.002	1.269	0.861–1.869	1.208	0.229	0.276	0.130
	AG vs. GG	random	98.84	≤ 0.001	0.775	0.384–1.563	–0.713	0.476	0.064	0.969
	AA+AG vs. GG	random	93.80	≤ 0.001	1.060	0.805–1.397	0.416	0.678	0.821	0.607
	AA vs. AG+GG	random	91.70	≤ 0.001	0.091	0.053–0.155	–8.722	≤ 0.001	0.752	0.929
HB	A vs. G	random	91.85	≤ 0.001	1.515	0.606–3.788	0.888	0.374	0.308	0.420
	AA vs. GG	random	73.67	0.022	1.526	0.203–11.467	0.411	0.681	1.000	0.658
	AG vs. GG	random	88.67	≤ 0.001	1.489	0.616–3.602	0.884	0.377	0.089	0.354
	AA+AG vs. GG	random	90.79	≤ 0.001	1.539	0.591–4.005	0.884	0.377	0.308	0.382
	AA vs. AG+GG	random	79.46	0.002	0.103	0.022–0.485	–2.875	0.004	1.000	0.761

SOC – source of controls, HB – hospital based, PB – population based, OR – odds ratio, CI – confidence interval

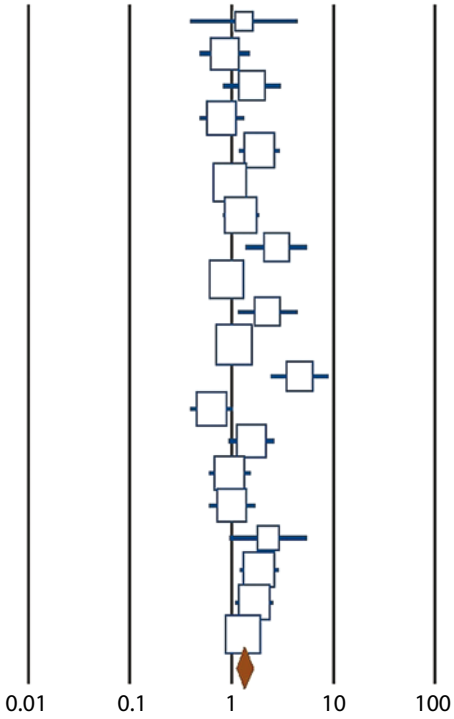
polymorphism and BC. When all eligible studies were pooled together a significant association between TNF-α -308G>A polymorphism and BC risk was found under recessive model (AA vs. AG + GG: OR 0.094; 95% CI 0.058–0.152; P ≤ 0.001, Graph 1B). Similarly, the subgroup analysis results showed a significant association between TNF-α -308G>A polymorphism and increased risk of BC in Asians (AA vs. AG + GG: OR 0.076; 95% CI 0.045–0.128, P ≤ 0.001) and Caucasians (AA vs. AG + GG: OR 0.142; 95% CI 0.024–0.849; P = 0.032) under a recessive model. Furthermore, stratified analyses by source of controls showed that TNF-α -308G>A polymorphism was significantly associated with increased risk of population-based (PB) (AA vs. AG + GG: OR 0.091; 95% CI 0.053–0.155, P ≤ 0.001) and hospital-based (HB) (AA vs. AG + GG: OR 0.103; 95% CI 0.022–0.485; P = 0.004).

Sensitivity analyses and heterogeneity test

There was a significant heterogeneity for CC (under three genetic models) and BC (under five genetic models) in the overall analysis. Thus subgroup analysis was performed to explore the source of the

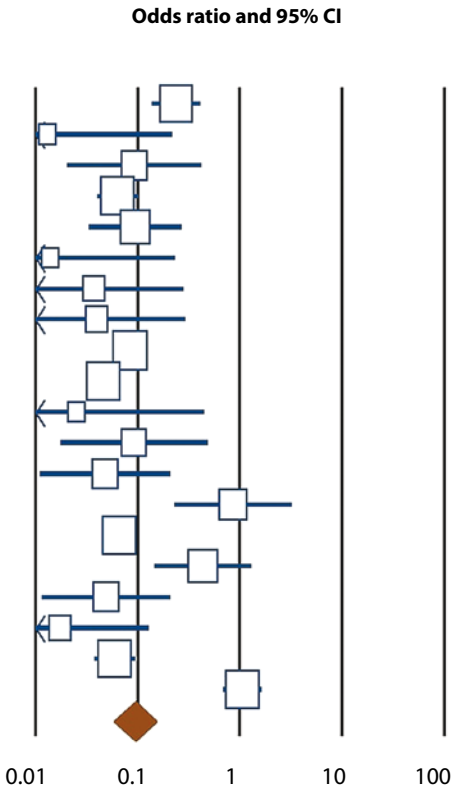
A

Study name	odds ratio	lower limit	upper limit	Z-value	P-value	relative weight
Jang 2001	1.320	0.397	4.393	0.452	0.651	1.78
Calhoun 2002	0.849	0.458	1.488	−0.570	0.568	4.61
Stanczuk 2003	1.587	0.828	3.043	1.391	0.164	4.00
Gostout 2003	0.798	0.485	1.313	−0.888	0.375	5.08
Duarte 2005	1.877	1.198	2.942	2.749	0.006	5.47
Deshpande 2005	0.970	0.684	1.375	−0.171	0.864	6.31
Govan 2006	1.236	0.820	1.861	1.012	0.311	5.80
Kohaar 2007	2.766	1.393	5.491	2.908	0.004	3.78
Wang 2009	0.901	0.658	1.235	−0.646	0.518	6.59
Singh 2009	2.249	1.149	4.402	2.366	0.018	3.87
Ivansson 2010	1.060	0.849	1.322	0.515	0.607	7.33
Zu 2010	4.664	2.454	8.864	4.700	0.000	4.05
Wang 2011	0.639	0.397	1.026	−1.854	0.064	5.27
Zuo 2011	1.576	0.964	2.625	1.747	0.081	4.99
Wang 2012	0.958	0.601	1.528	−0.180	0.857	5.33
Barbisan 2012	1.014	0.608	1.690	0.053	0.958	4.98
Badano 2012	2.295	0.957	5.506	1.861	0.063	2.83
Sousa 2014	1.868	1.199	2.911	2.764	0.006	5.52
Zidi 2014	1.668	1.089	2.552	2.355	0.019	5.66
Roszak 2015	1.292	0.962	1.736	1.703	0.089	6.76
	1.324	1.104	1.587	3.030	0.002	



B

Study name	odds ratio	lower limit	upper limit	Z-value	P-value	relative weight
Mestiri 2001	0.239	0.139	0.408	−5.226	0.000	6.94
Park 2002	0.013	0.001	0.215	−3.037	0.002	2.13
Giordani 2003	0.092	0.021	0.413	−3.113	0.002	4.36
Azmy 2004	0.064	0.040	0.101	−11.634	0.000	7.09
Smith 2004	0.095	0.033	0.269	−4.431	0.000	5.60
Kamali-Sarvestani 2005	0.014	0.001	0.230	−2.988	0.003	2.12
Scola 2006	0.037	0.005	0.280	−3.196	0.001	3.24
Gallicchio 2007	0.040	0.006	0.291	−3.182	0.001	3.32
Gaudet 2007a	0.085	0.068	0.105	−22.183	0.000	7.48
Gaudet 2007b	0.046	0.032	0.065	−17.213	0.000	7.30
Sirotkovic-Skerlev 2007	0.025	0.001	0.447	−2.511	0.012	2.05
Gonullu 2007	0.093	0.018	0.480	−2.833	0.005	4.02
Ostashkin 2008	0.048	0.011	0.206	−4.090	0.000	4.48
Kohaar 2009	0.854	0.231	3.157	−0.236	0.814	4.86
Marie-Genica 2010	0.066	0.052	0.083	−22.937	0.000	7.46
Pooja 2011a	0.437	0.147	1.296	−1.493	0.135	5.47
Pooja 2011b	0.049	0.012	0.208	−4.094	0.000	4.51
Karakus 2011	0.017	0.002	0.128	−3.985	0.000	3.30
Madeleine 2011	0.060	0.038	0.094	−12.114	0.000	7.11
Flores-Ramos 2013	1.055	0.688	1.616	0.244	0.807	7.16
	0.094	0.058	0.152	−9.641	0.000	

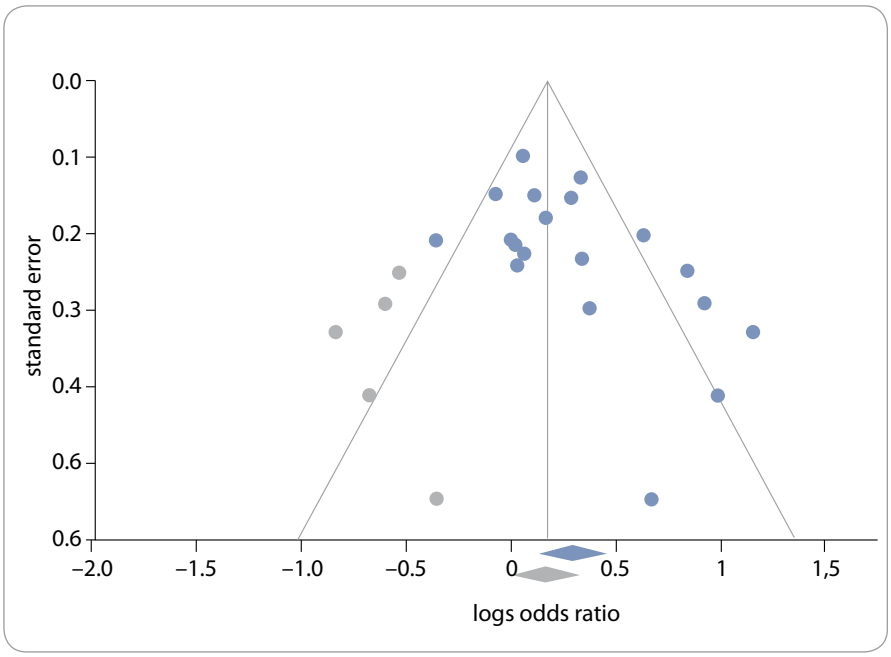


Graph 1. Forest plot of TNF-α -308G>A polymorphism with cervical cancer and breast cancer.
A. Cervical cancer (recessive model AA + AG vs. GG).
B. Breast cancer (dominant model AA vs. AG + GG).
CI – confidence interval

heterogeneity. However, the result indicated that ethnicity, source of controls and publication year were not the main factors responsible for the heterogeneity in this meta-analysis. We performed a sensitivity analysis to assess the influence of the individual study to the pooled ORs by sequentially excluding individual studies. However, the sensitivity analysis showed that the initial results were not considerably adjusted by omitting any individual study (data not shown). In this meta-analysis, we included those HWE-violating studies. However, after those studies were excluded, the TNF-α -308G>A polymorphism association with CC and BC risk was not adjusted.

Publication bias

Begg's funnel plot and Egger's test were utilised to evaluate the publication bias of the literature. Neither Begg's funnel nor Egger's test showed publication bias for BC under all five genetic models. However, publication bias in the included studies for CC showed evidence of remarkable asymmetry under the allele model and supported by Egger's test ($P_{Begg's}$ = 0.029 and $P_{Egger's}$ = 0.025). Thus, we used the Duval and Tweedie non-parametric 'trim and fill' method in testing and adjusting the publication bias in meta-analysis. However, the results did not adjust, indicating that the results were statistically robust and reliable (Fig. 3).



Graph 2. Funnel plot for publication bias in the meta-analysis of TNF-α -308G>A polymorphism and cervical cancer risk under the allele model (A vs. G). "Blue" without and "Grey" with trim and fill method.

Discussion

TNF-α plays a pivotal role in the regulation of immune cells. Genetic variations in the TNF-α gene are thought to modify DNA repair capacity and are suggested to be related to different cancer risks [52]. The human TNF-α gene, encoding an important protein in the regulation of immune cells, plays multiple roles in cell signalling in systemic inflammation, acute phase reaction and disease states [53,54]. In the last decade, epidemiological studies of gynaecological cancers and BC in different ethnicities have showed a significant association between the TNF-α -308G>A polymorphism and the risk of CC and BC [55,56]. However, subsequent replication studies on the association of TNF-α -308G>A polymorphism with CC and BC susceptibility was not consistent. Therefore, to derive a more precise estimation of the associations, we performed a systematic meta-analysis based on 40 case-control studies. The current meta-analysis, which included a total of 20 studies (with 4,780 cases and 4,620 controls) on CC and 20 studies (with 12,390 cases and 14,910 controls) on BC, investigated the association of TNF-α -308G>A polymorphism with susceptibility to CC and BC.

Our pooled data indicated that the AA genotype of TNF-α -308G>A polymorphism may be a risk factor for CC and BC in overall population and by ethnicity. Our results are inconsistent with the most previous meta-analysis on BC. In 2014, Jin et al in meta-analysis reported that the TNF-α -308G>A polymorphism was not associated with BC risk in the overall population. In addition, they have not found a significant association between TNF-α -308G>A polymorphism and BC by ethnicity, control source, genotyping method or HWE status. However, they have found an increased risk of BC in the menopausal status subgroup [56]. Similar to our results, Cai et al in a meta-analysis of 19 studies found that the TNF-α 308G>A polymorphism was significantly associated with CC risk [57]. Furthermore, in another meta-analysis Jin et al have found that -308 G>A and -238 G>A polymorphisms of TNF-α gene may confer susceptibility to CC in an ethnic-specific fashion [55]. However, their meta-analyses did not include all eligible and published studies. Thus, the current study is the most comprehensive meta-analysis on the association of TNF-α -308G>A polymorphism with the risk of CC.

This meta-analysis has several advantages. First, this meta-analysis has pooled the available data from the eligible studies, which has significantly increased the statistical power. In addition, we have concerned the pooled results regarding the source of healthy controls. Second, there was no language or ethnicity limitation in this meta-analysis, thus more original articles that met the criteria were included. However, several limitations of this meta-analysis should be acknowledged. First, we have included only the data of published studies in this meta-analysis. Unpublished studies tend to show more negative results; therefore publication bias may be present at first. Second, the number of studies in-

cluded in the current meta-analysis for Asians was relatively small and might not have enough statistical power. Third, the numbers of studies as well as sample sizes for other ethnicities such as Africans and Latinos were limited, which might be caused the Type-II error in this meta-analysis. Therefore, data on other ethnicities must be evaluated to determine the potential effects of ethnic variation on CC and BC susceptibility. Fourth, there was high heterogeneity under most genetic models and the ethnicity, genotyping methods and source of controls were not the potential source of the heterogeneity. However, because of limited data, we could not explore other potential sources of heterogeneity such as age, nulliparity, childbearing age, HPV infection, environment, background and lifestyle in the current meta-analysis. Finally, the aetiology of BC and CC is complex and multifactorial; gene-gene or gene-environment interactions contribute to the risk of these malignancies. However, in this meta-analysis we have not addressed these interactions due to the lack of data.

In summary, the present meta-analysis results have indicated that the TNF-α -308G>A polymorphism may be associated with an increased risk of CC and BC in the overall population and in an ethnic-specific fashion. However, taking the limitations into consideration, further well-designed studies with larger sample sizes and more ethnic groups are warranted to verify our findings.

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