

Section/topic	#	R Checklist item #												Reported on page #			
TITLE																	
Title	1	Correlation betwe	en hyp	oxia-indu	cible factor-1	lα polymorph	isms a	and head and	neck c	cancer	risk						
ABSTRACT																	
Structured summary	2	Abstract Objective: We performed a meta-analysis to explore the role of hypoxia-inducible factor-1 $\alpha$ (HIF-1 $\alpha$ ) C1772T/G1790A polymorphisms in the progress of head and neck cancer (HNC). Materials and Methods: PubMed, Embase and Web of Science databases were used to retrieve the eligible published papers. Pooled odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were used to evaluate the correlation strength. Results: Our results demonstrated that HIF-1 $\alpha$ C1772T polymorphism was significantly related to an increased HNC risk (OR=2.27, 95%CI=1.17-4.42 for homozygous model; OR=11.53, 95%CI=1.11-120.4 for recessive model), especially exists in Caucasians (OR=2.16, 95%CI=1.09-4.27 for homozygous model; OR=2.28, 95%CI=1.15-5.51 for recessive model). Similarly, the remarkable correlation was discovered between G1790A polymorphism and HNC risk (OR=72.11, 95%CI=2.08-2502.4 for homozygous model; OR=58.05, 95%CI=1.70-1985.77 for recessive model). Moreover, in the subgroup analysis by source of controls, a statistically significant correlation was discovered in population-based (PB) subgroup, but not in hospital-based (HB) subgroup. Conclusion: Our study demonstrated that both HIF-1 $\alpha$ C1772T and G1790A polymorphisms might be strongly															
INTRODUCTIO	Ν																
Rationale	3	Our study demo risk of HNC, es	onstrate peciall	ed that bo y among	th HIF-1α Caucasion	C1772T and group for C	G17 1772	90A polymor T polymorphi	phism ism.	ns mig	ght be	e stroi	ngly r	elated	l to the hig	gher	
Objectives	4	Participants: head	d and n	eck cance	er												
		Interventions: T(C	C1772T	); A(G179	0A)												
		Comparisons: C(	C1772	T); G(G17	90A)												
		Outcomes:	<b>X</b> 7	<u> </u>	<b>T</b> .1 • •	<u> </u>							1				
		First Author	Year	Country	Ethnicity	Genotyping Method	SC	Case-Control	Case	S		Cont	rols		Cancer Type	HWE	
		C1772T							CC	CT	ΤT	CC	CT	TT			
		Prasad J2018IndiaAsianSequencingHB50/5043704280OSCC0.539															
		Alves LR	2012	Brazil	Brazilian	PCR-RFLP	PB	40/88	0	1	39	0	85	3	OSCC	< 0.001	
		Mera-Menendez	2012	Spain	Caucasion	PCR-RFLP	HB	118/148	85	18	15	113	27	8	Glottic laryngeal	0.001	



		F													cancer	
		Shieh TM	2010	China	Asian	Sequencing	HB	305/96	282	23	0	89	7	0	OSCC	0.711
		Chen MK	2009	China	Asian	PCR-RFLP	PB	174/347	163	10	1	334	13	0	OC	0.722
		Munoz-Guerra MF	2009	Spain	Caucasion	PCR-RFLP	PB	70/148	57	6	7	113	27	8	OSCC	0.001
		Tanimoto K	2003	Japan	Asian	Sequencing	PB	55/110	45	10	0	98	12	0	HNSCC	0.545
		G1790A							AA	AG	GG	AA	AG	GG		
		Alves LR	2012	Brazil	Brazilian	PCR-RFLP	PB	40/88	37	1	2	0	7	81	OSCC	0.698
		Mera-Menendez F	2012	Spain	Caucasion	PCR-RFLP	HB	111/139	0	4	107	0	9	130	Glottic laryngeal cancer	0.693
		Shieh TM	2010	China	Asian	Sequencing	HB	305/96	0	24	281	0	7	89	OSCC	0.711
		Chen MK	2009	China	Asian	PCR-RFLP	PB	174/347	1	20	153	0	14	333	OC	0.701
		Munoz-Guerra MF	2009	Spain	Caucasion	PCR-RFLP	PB	64/139	3	21	40	0	9	130	OSCC	0.693
									0	4	51	Δ	0	101	HNSCC	0.655
		Tanimoto K	2003	Japan	Asian	Sequencing	PB	55/110	0	4	51	0	9	101	IINSCC	0.055
		Tanimoto K Study design: cas	2003 se-cont	Japan rol study.	Asian	Sequencing	PB	55/110	0	4	51	0	9	101	mosee	0.000
METHODS		Tanimoto K Study design: cas	2003 se-cont	Japan rol study.	Asian	Sequencing	PB	55/110	0	4	51	0	9	101	IINSCC	
METHODS Protocol and registration	5	Tanimoto K Study design: cas Indicate if a revie information include	2003 se-cont w proto ding reg	Japan rol study. ocol exists gistration r	Asian , if and wher number.	Sequencing re it can be ad	PB	55/110 ed (e.g., Web a	addres	s), an	d, if a	vailab	9 le, pro	ovide i	registration	
<b>METHODS</b> Protocol and registration Eligibility criteria	5	Tanimoto K Study design: cas Indicate if a revie information incluo First Author	2003 se-cont w proto ding reg Year	Japan rol study. pocol exists gistration r Country	Asian , if and when number. Ethnicity	Sequencing re it can be ad Genotyping Method	PB cccesso SC	55/110 ed (e.g., Web a Case-Control	addres Case	4 s), an	d, if a	vailab Cont	le, pro	ovide i	registration Cancer Type	HWE
<b>METHODS</b> Protocol and registration Eligibility criteria	5	Tanimoto K Study design: cas Indicate if a revie information includ First Author C1772T	2003 se-cont w proto ding reg Year	Japan rol study. pcol exists gistration r Country	Asian , if and wher number. Ethnicity	Sequencing re it can be ac Genotyping Method	PB cccesso SC	55/110 ed (e.g., Web a Case-Control	addres Case	s), an	d, if a	vailab Cont	le, pro rols	Dvide I	registration Cancer Type	HWE
METHODS Protocol and registration Eligibility criteria	5	Tanimoto K Study design: cas Indicate if a revie information includ First Author C1772T Prasad J	2003 se-cont w proto ding reg Year 2018	Japan rol study. ocol exists gistration r Country India	Asian , if and when number. Ethnicity Asian	Sequencing re it can be ad Genotyping Method Sequencing	PB cccesso SC HB	55/110 ed (e.g., Web a Case-Control 50/50	addres Case CC 43	s), an s CT 7	d, if a	vailab Cont CC 42	le, pro rols CT 8	Dvide I TT 0	registration Cancer Type OSCC	0.539
<b>METHODS</b> Protocol and registration Eligibility criteria	5	Tanimoto K Study design: cas Indicate if a revie information includ First Author C1772T Prasad J Alves LR	2003 se-cont w proto ding reg Year 2018 2012	Japan rol study. ocol exists gistration r Country India Brazil	Asian , if and wher number. Ethnicity Asian Brazilian	Sequencing re it can be ac Genotyping Method Sequencing PCR-RFLP	PB ccesso SC HB PB	55/110 ed (e.g., Web a Case-Control 50/50 40/88	addres Case CC 43 0	4 s), an s CT 7 1	31 d, if a TT 0 39	vailab Cont CC 42 0	le, pro rols CT 8 85	TT 0 3	registration Cancer Type OSCC OSCC	0.539 <0.001
<b>METHODS</b> Protocol and registration Eligibility criteria	5	Tanimoto K Study design: cas Indicate if a revie information includ First Author C1772T Prasad J Alves LR Mera-Menendez F	2003 se-cont w proto ding reg Year 2018 2012 2012	Japan rol study. ocol exists gistration r Country India Brazil Spain	Asian , if and when number. Ethnicity Asian Brazilian Caucasion	Sequencing re it can be ad Genotyping Method Sequencing PCR-RFLP PCR-RFLP	PB ccesso SC HB PB HB	55/110 ed (e.g., Web a Case-Control 50/50 40/88 118/148	addres Case CC 43 0 85	s), an s CT 7 1 18	TT 0 39 15	vailab Cont CC 42 0 113	le, pro rols CT 8 85 27	TT 0 3 8	registration Cancer Type OSCC OSCC Glottic laryngeal cancer	HWE 0.539 <0.001 0.001
<b>METHODS</b> Protocol and registration Eligibility criteria	5	Tanimoto K Study design: cas Indicate if a revie information includ First Author C1772T Prasad J Alves LR Mera-Menendez F Shieh TM	2003 se-cont w proto ding rec Year 2018 2012 2012 2010	Japan rol study. ocol exists gistration r Country India Brazil Spain China	Asian , if and when number. Ethnicity Asian Brazilian Caucasion Asian	Sequencing re it can be ac Genotyping Method Sequencing PCR-RFLP PCR-RFLP Sequencing	PB CCCESSO SC HB PB HB HB	55/110 ed (e.g., Web a Case-Control 50/50 40/88 118/148 305/96	addres Case CC 43 0 85 282	4 s), an s CT 7 1 18 23	31 d, if a TT 0 39 15 0	vailab Cont CC 42 0 113 89	9 le, pro rols CT 8 85 27 7	TT 0 3 8 0	Cancer Type OSCC OSCC Glottic laryngeal cancer OSCC	0.539 <0.001 0.711
<b>METHODS</b> Protocol and registration Eligibility criteria	5	Tanimoto K Study design: cas Indicate if a revie information includ First Author C1772T Prasad J Alves LR Mera-Menendez F Shieh TM Chen MK	2003 se-cont w proto ding reg Year 2018 2012 2012 2010 2009	Japan rol study. ocol exists gistration r Country India Brazil Spain China China	Asian , if and when number. Ethnicity Asian Brazilian Caucasion Asian Asian	Sequencing re it can be ad Genotyping Method Sequencing PCR-RFLP PCR-RFLP Sequencing PCR-RFLP	PB ccesso SC HB PB HB HB PB	55/110 ed (e.g., Web a Case-Control 50/50 40/88 118/148 305/96 174/347	0 addres Case CC 43 0 85 282 163	4 s), an cT 7 1 18 23 10	31 d, if a TT 0 39 15 0 1	vailab Cont CC 42 0 113 89 334	9 le, pro rols CT 8 85 27 7 13	TT 0 3 8 0 0	registration Cancer Type OSCC OSCC Glottic laryngeal cancer OSCC OSCC	HWE 0.539 <0.001 0.001 0.711 0.722
<b>METHODS</b> Protocol and registration Eligibility criteria	5	Tanimoto K Study design: cas Indicate if a revie information includ First Author C1772T Prasad J Alves LR Mera-Menendez F Shieh TM Chen MK Munoz-Guerra MF	2003 se-cont w proto ding rec Year 2018 2012 2012 2010 2009 2009	Japan rol study. cool exists gistration r Country India Brazil Spain China China Spain	Asian , if and when number. Ethnicity Asian Brazilian Caucasion Asian Asian Caucasion	Sequencing re it can be ac Genotyping Method Sequencing PCR-RFLP PCR-RFLP Sequencing PCR-RFLP PCR-RFLP	PB CCCESSO SC HB PB HB HB PB PB	55/110 ed (e.g., Web a Case-Control 50/50 40/88 118/148 305/96 174/347 70/148	0 addres Case CC 43 0 85 282 163 57	4 s), an s CT 7 1 18 23 10 6	31 rd, if a TT 0 39 15 0 1 7	vailab Cont CC 42 0 113 89 334 113	9 le, pro rols CT 8 85 27 7 13 27	TT 0 3 8 0 0 8	registration Cancer Type OSCC OSCC Glottic laryngeal cancer OSCC OC OSCC	HWE 0.539 <0.001 0.711 0.722 0.001
<b>METHODS</b> Protocol and registration Eligibility criteria	5 6	Tanimoto K Study design: cas Indicate if a revie information includ First Author C1772T Prasad J Alves LR Mera-Menendez F Shieh TM Chen MK Munoz-Guerra MF Tanimoto K	2003 se-cont w proto ding reg Year 2018 2012 2012 2010 2009 2009 2009	Japan rol study. ocol exists gistration r Country India Brazil Spain China China Spain Japan	Asian , if and wher number. Ethnicity Asian Brazilian Caucasion Asian Caucasion Asian	Sequencing Te it can be ac Genotyping Method Sequencing PCR-RFLP PCR-RFLP PCR-RFLP PCR-RFLP PCR-RFLP PCR-RFLP Sequencing	PB CCCESSO SC HB PB HB PB PB PB PB	55/110 ed (e.g., Web a Case-Control 50/50 40/88 118/148 305/96 174/347 70/148 55/110	0 addres Case CC 43 0 85 282 163 57 45	4 s), an s CT 7 1 18 23 10 6 10	31 d, if a TT 0 39 15 0 1 7 0	vailab Cont CC 42 0 113 89 334 113 98	9 le, pro rols CT 8 85 27 7 13 27 12	TT 0 3 8 0 0 8 0	registration Cancer Type OSCC OSCC Glottic laryngeal cancer OSCC OC OSCC OC OSCC	HWE 0.539 <0.001 0.001 0.711 0.722 0.001 0.545



## PRISMA 2009 Checklist

		Alves LR	2012	Brazil	Brazilian	PCR-RFLP	PB	40/88	37	1	2	0	7	81	OSCC	0.698	
		Mera-Menendez F	2012	Spain	Caucasion	PCR-RFLP	HB	111/139	0	4	107	0	9	130	Glottic laryngeal cancer	0.693	
		Shieh TM	2010	China	Asian	Sequencing	HB	305/96	0	24	281	0	7	89	OSCC	0.711	
		Chen MK	2009	China	Asian	PCR-RFLP	PB	174/347	1	20	153	0	14	333	OC	0.701	
		Munoz-Guerra MF	2009	Spain	Caucasion	PCR-RFLP	PB	64/139	3	21	40	0	9	130	OSCC	0.693	
		Tanimoto K	2003	Japan	Asian	Sequencing	PB	55/110	0	4	51	0	9	101	HNSCC	0.655	
Information sources	7	PubMed, Emba	se and	Web of	Science data	abases were	used	to retrieve	the elig	ible j	oublis	hed p	papers				
Search	8	A computeri identifying the 'hypoxia-induci 'polymorphisms 'HNC' or 'ora 'nasopharyngea studies.	zed li quali ible f s' Anc al' or l' or '	terature fied stud actor-1' 1 'carcin 'oral c orophary	search was dies with t And 'mu oma' or 'n avity' or ' 'ngeal'. Fin	conducted the followin tation' or eoplasm' of pharyngeal ally, we sca	by te 'mut 'tur ' or nned	the databa rms: 'hif-' ations' or nor' or 'ca 'laryngeal references	ses of la' or r 'varia ancer' c ' or 'l cited b	PubM 'hypo ants' or 'ca aryng y all	fed, f oxia-in or arcino gophan the in	Emba nduc 'varia gene rynge nclud	ase an ible f ant' sis' A eal' c led stu	nd We cactor- or 'p and 'h or 'hy adies t	eb of Sci ·1α' or '1 polymorph nead and /popharyn to identify	ence for nif-1' or ism' or neck' or geal' or v eligible	
Study selection	9	PRISMA 200	09 Flow Dia	gram													
		Included Eighblity Screening Identification	Records in datab () Records after Full-text fo Studi qualit (mi	dentified through ase searching = 150 ) r duplicates removed (n = 94) rds screened (n = 94 ) articles assessed religibility (n = 33 ) e included in attive synthesis (n = 7 ) e included in attive synthesis ta-analysis) (n = 7 )	Titles and abstracts exc (n = 61) Full-text articles exclude with reasons (n = 26) 1. Review (n = 9) 2. Review (n = 9) 2. No comparison need (n = 11) 3. Unable to extr. enough information (n= 4. Others (n= 4)	luded cl. i: ied act 2)											



## PRISMA 2009 Checklist

Data collection process	10	Three authors are responsible for extracting data and two authors are responsible for verifying the correctness of the data.	
Data items	11	Data have already been shown in the article.	
Risk of bias in individual studies	12	OHAT risk of bias rating tool was applied to evaluate the bias risk of the included articles. Publication bias analysis and sensitivity analysis have been performed in our study.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Results have already been shown in the article.	

Page 1 of 2									
Section/topic	#	Checklist item							
Risk of bias across studies	15	No publication bias was found.							
Additional analyses	16	Sensitivity and subgroup analyses were performed in our study.							

## RESULTS





## PRISMA 2009 Checklist

Study characteristics	18					Table 1	letaile	d information of	incluc	led arti	icles									
		First Author	Year	Country	Ethnicity	Genotyping Method	SC	Case-Control	Case	s		Cont	trols		Cancer Type	Н				
		C1772T							CC	CT	TT	CC	СТ	TT						
		Prasad J	2018	India	Asian	Sequencing	HB	50/50	43	7	0	42	8	0	OSCC	0.				
		Alves LR	2012	Brazil	Brazilian	PCR-RFLP	PB	40/88	0	1	39	0	85	3	OSCC	<				
		Mera-Menendez F	2012	Spain	Caucasion	PCR-RFLP	HB	118/148	85	18	15	113	27	8	Glottic laryngeal cancer	0.				
		Shieh TM	2010	China	Asian	Sequencing	HB	305/96	282	23	0	89	7	0	OSCC	0.				
		Chen MK	2009	China	Asian	PCR-RFLP	PB	174/347	163	10	1	334	13	0	OC	0.				
		Munoz-Guerra MF	2009	Spain	Caucasion	PCR-RFLP	PB	70/148	57	6	7	113	27	8	OSCC	0.				
		Tanimoto K	2003	Japan	Asian	Sequencing	PB	55/110	45	10	0	98	12	0	HNSCC	0.				
		G1790A							AA	AG	GG	AA	AG	GG						
		Alves LR	2012	Brazil	Brazilian	PCR-RFLP	PB	40/88	37	1	2	0	7	81	OSCC	0.				
		Mera-Menendez F	2012	Spain	Caucasion	PCR-RFLP	HB	111/139	0	4	107	0	9	130	Glottic laryngeal cancer	0.				
		Shieh TM	2010	China	Asian	Sequencing	HB	305/96	0	24	281	0	7	89	OSCC	0.				
		Chen MK	2009	China	Asian	PCR-RFLP	PB	174/347	1	20	153	0	14	333	OC	0.				
		Munoz-Guerra MF	2009	Spain	Caucasion	PCR-RFLP	PB	64/139	3	21	40	0	9	130	OSCC	0.				
		Tanimoto K	2003	Japan	Asian	Sequencing	PB	55/110	0	4	51	0	9	101	HNSCC	0.				
		<ul> <li>HWE: Hardy Weinberg equilibrium; PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism; PCR: polymerase chain reaction</li> <li>[28] Munoz-Guerra, M. F., Fernandez-Contreras, M. E., Moreno, A. L., Martin, I. D., Herraez, B., &amp; Gamallo, C. (2009). Polymorphypoxia inducible factor 1-alpha and the impact on the prognosis of early stages of oral cancer. Ann Surg Oncol, 16(8), 2351 10.1245/s10434-009-0503-8</li> <li>[30] Tanimoto, K., Yoshiga, K., Eguchi, H., Kaneyasu, M., Ukon, K., Kumazaki, T., Nishiyama, M. (2003). Hypoxia-inducible factor polymorphisms associated with enhanced transactivation capacity, implying clinical significance. Carcinogenesis, 24(11), 1779 10.1093/carcin/bgg132</li> </ul>													nisr  -23 acto  -17					
		[32] Prasad, J., Go (HIF-1alpha) C1 47(7), 660-664. c [33] Shieh, T. M., exon 12 of hypo 10.1016/j.oralon	oswam 772T doi: 10 , Char xia-inc cology	ii, B., Go polymorp ).1111/jop ig, K. W. ducible fa 7.2010.04	wda, S. H., phism pred p.12718 , Tu, H. F., actor-1alpha .009	, Gupta, N., Kumar lict short-term prog , Shih, Y. H., Ko, S a and the clinicopat	, S., 2 nosis S. Y., tholog	Agarwal, K., in patients v , Chen, Y. C. gical features	C with o , & L of or	'hauha oral so iu, C al squ	an, A quam . J. (2 uamo	(202 ious c 2010). us cel	18). E cell ca . Asso ll caro	Does H arcino ociatio cinom	Hypoxia-Inducible Fac ma (OSCC)? J Oral I on between the polym a. Oral Oncol, 46(9),	tor Patl orp e47				
		[34] Mera-Menen Polymorphisms	dez, F in HIF	., Hinojar ?-1alpha a	-Gutierrez, affect prese	, A., Guijarro Rojas ence of lymph node	, M., e met	de Gregorio, astasis and ca	J. G., in inf	, Mera luenc	a-Me e tun	nende nor si	ez, E. ze in	, Sanc squar	hez, J. J., Gamallo nous-cell carcinoma o	o, C of tl				



		larynx. Clin Transl Oncol, 15(5), 358-363. doi: 10.1007/s12094-012-0930-z [35] Chen, M. K., Chiou, H. L., Su, S. C., Chung, T. T., Tseng, H. C., Tsai, H. T., & Yang, S. F. (2009). The association between															
														ion between			
		inducible factor-1alpha gene polymorphisms and increased susceptibility to oral cancer. Oral Oncol, 45(12), e222-													2), e222-22		
		10.1016/j.o	oralo	ncolog	gy.2009.07.0	)15											
	[36] Alves, L. R., Fraga, C. A. C., Oliveira, M. V. M., Sousa, A. A., Jorge, A. S. B., Marques-Silva, L., Santos, S. H. S., Gu											. Guimarães,					
		(2012). Hi	gh H	IF-1α	expression g	genotyp	es incre	ease odds rat	io of or	al can	cer. Head N	eck On	col 4: 2	2–7			
Risk of bias within studies	19	9 Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).															
Results of individual	20	Table 2 Results of overall and subgroups analyses for C1772T and G1790A polymorphisms															
studies		C1772T	No	T vers	sus C		TT ver	sus CC		TC ve	ersus CC		TT + T	FC versus CC		TT ver	sus TC + CC
				OR	95%CI	$\mathbf{P}^{(Z)}$	OR	(95%CI)	$\mathbf{P}^{(z)}$	OR	(95%CI)	$\mathbf{P}^{(z)}$	OR	(95%CI)	$P^{(z)}$	OR	(95%CI)
		Overall	7	1.66	0.92-2.99	0.095	2.27	1.17-4.42	0.016	0.98	0.70-1.38	0.914	1.16	0.85-1.59	0.355	11.53	1.11-120.4
		PCR-RFLP	4	2.44	0.90-6.64	0.081	2.27	1.17-4.42	0.016	0.86	0.55-1.34	0.506	1.14	0.78-1.67	0.503	11.53	1.11-120.4
		Sequencing	3	1.20	0.70-2.03	0.506				1.20	0.69-2.09	0.514	1.20	0.69-2.09	0.514		
		Caucasian	2	1.26	0.84-1.90	0.270	2.16	1.09-4.27	0.028	0.69	0.40-1.17	0.168	1.02	0.66-1.57	0.926	2.28	1.15-5.51
		Asian	4	1.37	0.88-2.13	0.159				1.30	0.82-2.07	0.269	1.34	0.85-2.12	0.213	_	
		HB	3	1.31	0.90-1.90	0.162				0.92	0.57-1.48	0.736	1.13	0.73-1.74	0.582		
		PB	4	2.87	0.82-10.0	0.099	2.01	0.75-5.41	0.168	1.05	0.64-1.73	0.843	1.20	0.76-1.89	0.442	22.82	0.28-1887.8
		OC	5	1.95	0.70-5.43	0.201	2.01	0.75-5.41	0.168	0.89	0.57-1.40	0.612	1.01	0.66-1.54	0.957	22.82	0.28-1887.8
		G1790A	No	A ver	sus G		AA ve	rsus GG		AG v	ersus GG		AA+	AG versus GC	č	AA vei	rsus AG + GG
				OR	95%CI	$\mathbf{P}^{(Z)}$	OR	(95%CI)	P <sup>(z)</sup>	OR	(95%CI)	$\mathbf{P}^{(z)}$	OR	(95%CI)	$\mathbf{P}^{(z)}$	OR	(95%CI)
		Overall	6	4.11	0.84-20.15	0.081	72.11	2.08-2502.4	0.018	1.94	0.83-4.55	0.128	3.57	0.97-13.14	0.055	58.05	1.70-1985.8
		PCR-RFLP	4	8.39	0.98-72.1	0.053	72.11	2.08-2502.4	0.018	2.81	0.91-8.72	0.074	7.00	1.18-41.68	0.032	58.05	1.70-1985.8
		Sequencing	2	1.01	0.50-2.03	0.975				1.01	0.50-2.06	0.975	1.01	0.50-2.06	0.975		
		Caucasian	2	2.18	0.16-30.19	0.562				2.10	0.16-28.19	0.577	2.24	0.15-34.32	0.563		_
		Asian	3	1.59	0.67-3.78	0.294				1.57	0.69-3.58	0.283	1.59	0.67-3.76	0.290		
		HB	2	0.86	0.43-1.72	0.667				0.85	0.42-1.73	0.660	0.85	0.42-1.73	0.660	_	
		PB	4	9.43	1.20-73.9	0.033	72.11	2.08-2502.4	0.018	3.22	1.28-8.08	0.013	7.83	1.48-41.37	0.015	58.05	1.70-1985.8
		oc	4	9.66	1.31-71.15	0.026	72.11	2.08-2502.4	0.018	3.17	1.26-7.92	0.014	7.92	1.58-39.64	0.012	58.05	1.70-1985.8
		Eorest plots y	were	shown	in the article												
Synthesis of	21		were	3110 WH		Table 2	Results	of overall and s	subgroup	s analy	ses for C1772	T and G1	790A p	olymorphisms			
results	C1772T     No     T versus C     TT versus CC     TC versus CC     TT + TC versus CC								TT versus TC + CC								



				OR	95%CI	$\mathbf{P}^{(Z)}$	OR	(95%CI)	P <sup>(z)</sup>	OR	(95%CI)	$\mathbf{P}^{(z)}$	OR	(95%CI)	$\mathbf{P}^{(z)}$	OR	(95%CI)
		Overall	7	1.66	0.92-2.99	0.095	2.27	1.17-4.42	0.016	0.98	0.70-1.38	0.914	1.16	0.85-1.59	0.355	11.53	1.11-120.4
		PCR-RFLP	4	2.44	0.90-6.64	0.081	2.27	1.17-4.42	0.016	0.86	0.55-1.34	0.506	1.14	0.78-1.67	0.503	11.53	1.11-120.4
		Sequencing	3	1.20	0.70-2.03	0.506		—		1.20	0.69-2.09	0.514	1.20	0.69-2.09	0.514	—	
		Caucasian	2	1.26	0.84-1.90	0.270	2.16	1.09-4.27	0.028	0.69	0.40-1.17	0.168	1.02	0.66-1.57	0.926	2.28	1.15-5.51
		Asian	4	1.37	0.88-2.13	0.159		—		1.30	0.82-2.07	0.269	1.34	0.85-2.12	0.213	—	—
		HB	3	1.31	0.90-1.90	0.162		—		0.92	0.57-1.48	0.736	1.13	0.73-1.74	0.582	—	—
		PB	4	2.87	0.82-10.0	0.099	2.01	0.75-5.41	0.168	1.05	0.64-1.73	0.843	1.20	0.76-1.89	0.442	22.82	0.28-1887.8
		OC	5	1.95	0.70-5.43	0.201	2.01	0.75-5.41	0.168	0.89	0.57-1.40	0.612	1.01	0.66-1.54	0.957	22.82	0.28-1887.8
		G1790A	No	A ver	sus G		AA ve	rsus GG		AG v	ersus GG		AA + A	AG versus GG	ì	AA vei	rsus AG + GG
				OR	95%CI	$\mathbf{P}^{(Z)}$	OR	(95%CI)	$\mathbf{P}^{(z)}$	OR	(95%CI)	$\mathbf{P}^{(z)}$	OR	(95%CI)	$\mathbf{P}^{(z)}$	OR	(95%CI)
		Overall	6	4.11	0.84-20.15	0.081	72.11	2.08-2502.4	0.018	1.94	0.83-4.55	0.128	3.57	0.97-13.14	0.055	58.05	1.70-1985.8
		PCR-RFLP	4	8.39	0.98-72.1	0.053	72.11	2.08-2502.4	0.018	2.81	0.91-8.72	0.074	7.00	1.18-41.68	0.032	58.05	1.70-1985.8
		Sequencing	2	1.01	0.50-2.03	0.975		—		1.01	0.50-2.06	0.975	1.01	0.50-2.06	0.975	—	—
		Caucasian	2	2.18	0.16-30.19	0.562				2.10	0.16-28.19	0.577	2.24	0.15-34.32	0.563	—	
		Asian	3	1.59	0.67-3.78	0.294		—		1.57	0.69-3.58	0.283	1.59	0.67-3.76	0.290	—	—
		HB	2	0.86	0.43-1.72	0.667				0.85	0.42-1.73	0.660	0.85	0.42-1.73	0.660	—	
		PB	4	9.43	1.20-73.9	0.033	72.11	2.08-2502.4	0.018	3.22	1.28-8.08	0.013	7.83	1.48-41.37	0.015	58.05	1.70-1985.8
		OC	4	9.66	1.31-71.15	0.026	72.11	2.08-2502.4	0.018	3.17	1.26-7.92	0.014	7.92	1.58-39.64	0.012	58.05	1.70-1985.8
Risk of bias across studies	22	Present resu	Ilts of	any as	sessment of	risk of b	ias acro	ess studies (se	e Item 1	15).							
Additional	23	In the sensi	tivity	analy	sis, no rema	rkable o	change	was observe	d in the	poole	d ORs after	omittii	ng one	article at a t	ime.		
anaiysis		In the subgr chain reacti homozygou C1772T po 1.15-5.51 fc In the strati 2.08-2502.4 model), pop homozygou 95% CI = 1	roup a on-real is mo lymo or rec fied a for l foulati is mo .70-1	analys estricti del; O rphism essive analys homoz on-ba del; O 985.8	tes of C1772 on fragment PR = 11.53, 9 n and an ince e model). es of G1790 zygous mode sed study su PR = 3.22, 99 for recessiv	2T polyr t length 95% CI reased H A, a sub el; OR = bgroup 5% CI = re mode	norphis polymo = $1.11$ - INC ris stantia = $7.00, 9$ (OR = = $1.28$ -8 l) and C	sm, we found orphism (PCI- -120.4 for red sk for Caucas I relationship 95% CI = 1.7 9.43, 95% C 8.08 for heter DC (P < 0.05	I C1772 R-RFLI cessive sians (C p was of 18-41.6 I = 1.20 ozygou under a	CT poly ) generation model $DR = 2bserve8 for controls0-73.9s modelall generation$	ymorphism otyping met 1). Moreove 2.16, 95% C 2.2 d for PCR-1 lominant me for allelic n lel; OR = 7.3 letic models	could in hod sul r, a sigr I = 1.09 RFLP g odel; O nodel, F 83, 95% ).	herease by proup hificant p-4.27 f enotyp R = 58 Figure 3 p CI =	the HNC r ( $OR = 2.27$ ) relationship for homozyg ing method .05, 95% CI 3; $OR = 72.1$ 1.48-41.37	isk sigr , 95% ( p could gous ma subgro z = 1.70 11, 95% for dom	nificant CI = 1. be disc odel; O pup (OF 0-1985. % CI = 2 ninant r	ly in the pol 17-4.42 for covered betw R = 2.28, 93 R = 72.11, 9 8 for recessi 2.08-2502.4 nodel; OR =
DISCUSSION																	



Summary of evidence	24	The study discovered that HIF-1a C1772T and G1790A polymorphisms were significantly related to the susceptibility to HNC. Moreover, found that C1772T polymorphism could statistically increase the HNC risk among Caucasions at the first time. In addition, HIF-1a G1790 polymorphism was remarkably related to a higher risk of HNC, especially with OC.
Limitations	25	Some inevitable limitations existed in the meta-analysis. Firstly, the sample size in some subgroup was small, so the results from certain analysis could not have sufficient power to confirm the relationship. Secondly, publication bias might exist because several eligible art have not published were not enrolled in our study. Thirdly, the subgroup analyses by age, gender, alcohol, smoking, or other variables performed because of information limitation. Therefore, it is necessary to study the role of HIF-1a C1772T and G1790A polymorphisms risk with more data and larger sample size.
Conclusions	26	In conclusion, the study discovered that HIF-1 $\alpha$ C1772T and G1790A polymorphisms were significantly related to the susceptibility Moreover, we found that C1772T polymorphism could statistically increase the HNC risk among Caucasions at the first time. In addition G1790A polymorphism was remarkably related to a higher risk of HNC, especially with OC. However, further well-designed papers we sample size are required to confirm our results.
FUNDING		
Funding	27	No funding in our paper.

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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