

Susceptibility to Head and Neck Cancers

Subjects: Biology

Submitted by: Masoud Sadeghi

Definition

HNC involves a series of tumors originating in the oropharynx, hypopharynx, oral cavity, lip, larynx, or nasopharynx. Smoking, alcohol consumption, and high-risk human papillomaviruses have been related to HNC. In connection with the role of genetics in HNC, several recent meta-analyses have reported the association of polymorphisms with the risk of HNCs.

1. Introduction

Cellular inflammation and immunity can play a significant role in various stages of carcinogenesis [1] such as head and neck cancers (HNCs). HNC mortality rates are elevating and disproportionately affect people in low- and middle-income countries and areas with restricted resources [2]. Global Burden of Disease Study (GBD) in 2016 estimated 512,492 deaths due to HNC (a minimum of 15,018 deaths in North Africa and the Middle East to a maximum of 199,280 in South Asia) and predicted the death count to reach 705,901 in 2030 [3][4]. HNC involves a series of tumors originating in the oropharynx, hypopharynx, oral cavity, lip, larynx, or nasopharynx [5]. Smoking, alcohol consumption, and high-risk human papillomaviruses have been related to HNC [5][6][7]. In connection with the role of genetics in HNC, several recent meta-analyses have reported the association of polymorphisms with the risk of HNCs [8][9][10][11].

A number of heterocyclic and aromatic amines are the main carcinogenic compounds of tobacco smoke [12][13] that their metabolism in humans is complex and includes acetylation as a main pathway for DNA mutation and the onset of carcinogenesis [14]. In particular, two N-acetyltransferases, NAT1 and NAT2 perform a role in catalyzing the deactivation and activation of several carcinogenic amines through N- and O-acetylation, respectively [14][15]. Both NAT genes (NAT1 and NAT2) have polymorphisms in humans and in accordance with slow and rapid acetylator phenotypes [16]. The NAT2 metabolized gene is located in region 10 of chromosome 8p21, which contains two exons with a long intron of about 8.6 kb [17]. Exon 1 is very short (100 bp) and the entire protein-coding region in Exon 2 is 870 bp [18]. Also, the NAT1 gene is located on the short arm of chromosome 8 (8p21) [19][20]. NAT1 accelerates acetylation specifically for arylamine receptor structures such as p-aminosalicylic and p-aminobenzoic acids [21] and NAT2 acetylates other arylamine-acceptor structures, such as isoniazid, sulfasalazine, procainamide, and caffeine [19].

Evidence from the published articles on the relationship between NAT1 and NAT2 polymorphisms and HNC susceptibility is conflicting [22][23]. The association between the polymorphisms (NAT1 and NAT2) and the HNC risk has been evaluated by one [24] and four [25][26][27][28] meta-analyses, respectively. However, these studies were published several years ago with the most recent one being published in 2015. Therefore, through this meta-analysis, we intend to update the evidence on the association between the polymorphisms and the HNC risk by including more studies. In addition, we aim to conduct trial sequential analysis (TSA) and meta-regression.

2. Analysis on Results

Twenty-eight studies included in the analysis were published between 1998 and 2014 (**Table 1**). Fourteen articles [22][23][29][30][31][32][33][34][35][36][37][38][39][40] reported the results in Caucasians, nine [41][42][43][44][45][46][47][48][49] in Asians, and five [50][51][52][53][54] among participants of mixed ethnicity. The control source in eighteen articles [22][23][41][30][32][33][36][37][38][39][42][43][45][46][47][51][52][54] was hospitals and ten [29][31][34][35][40][44][48][49][50][53] recruited the controls from a general population. In total, the articles included 5154 HNC cases and 6194 controls. Age, gender distribution, sample size, tumor type, genotyping method, and the quality score are shown in **Table 1** .

Table 1. Characteristics of the articles included in the meta-analysis.

The First Author, Publication Year	Country	Ethnicity	Control Source	Number		Mean Year		Male Percentage		Type of Tumor	Genotyping Method	Quality Score
				Case	Control	Case	Control	Case	Control			
Gonzalez, 1998 [34]	Spain	Caucasian	PB	75	200	58.7	45	100	75	Oral, pharyngeal, laryngeal	PCR-RFLP	7
Katoh, 1998 [41]	Japan	Asian	HB	62	122	61.7	62.4	64.5	61.5	Oral	PCR-RFLP	7
Henning, 1999 [23]	Germany	Caucasian	HB	255	510	61.4	NA	90.6	NA	Laryngeal	PCR	7
Jourenkova-Mironova, 1999 [37]	France	Caucasian	HB	250	172	54.4	54.9	96	94.8	Oral, pharyngeal, laryngeal	PCR-RFLP	7

The First Author, Publication Year	Country	Ethnicity	Control Source	Number		Mean Year		Male Percentage		Type of Tumor	Genotyping Method	Quality Score
				Case	Control	Case	Control	Case	Control			
Morita, 1999 [48]	Japan	Asian	PB	145	164	59.0	49.8	86.9	62.2	Oral, pharyngeal, laryngeal	PCR	7
Olshan, 2000 [54]	USA	Mixed	HB	171	193	59.5	56.8	81.3	59.1	Oral, pharyngeal, laryngeal	PCR	7
Chen, 2001 [29]	USA	Caucasian	PB	341	552	NA	NA	70.4	71.6	Oral	PCR-RFLP	9
Fronhoffs, 2001 [32]	Germany	Caucasian	HB	291	300	59.8	47.1	80.1	58	Oral, pharyngeal, laryngeal	RT-PCR	6
Hahn, 2002 [35]	Germany	Caucasian	PB	94	92	61.5	45.1	65.9	51.1	Oral	PCR-RFLP	7
Lei, 2002 [45]	China	Asian	HB	62	56	60.2	58.2	NA	NA	Laryngeal	PCR-RFLP	7
Varzim, 2002 [40]	Portugal	Caucasian	PB	88	172	62.8	43.0	94.3	72.7	Laryngeal	PCR-RFLP	7
Cheng, 2003 [43]	Taiwan	Asian	HB	279	325	NA	NA	NA	NA	Pharyngeal	PCR-RFLP	6
Gajecka, 2005 [33]	Poland	Caucasian	HB	289	311	57.9	45.9	100	100	Laryngeal	PCR-RFLP	8
Rydzanicz, 2005 [38]	Poland	Caucasian	HB	266	143	61.6	53.1	95.1	100	Oral, pharyngeal, laryngeal	PCR-RFLP	8
Unal, 2005 [39]	Turkey	Caucasian	HB	45	104	53.5	50.0	93.3	65.4	Laryngeal	PCR-RFLP	7
Marques, 2006 [52]	Brazil	Mixed	HB	231	212	56.6	55.3	83.5	79.2	Oral	PCR-RFLP	8
Gara, 2007 [51]	Tunisia	Mixed	HB	64	160	50.7	53.6	65.6	45	Oral, pharyngeal, laryngeal	PCR-RFLP	7
Majumder, 2007 [47]	India	Asian	HB	297	342	NA	NA	NA	NA	Oral	PCR-RFLP	6
Boccia, 2008 [22]	Italy	Caucasian	HB	210	245	63.6	63.3	71.4	72.2	Oral, pharyngeal, laryngeal	PCR-RFLP	8
Buch, 2008 [50]	USA	Mixed	PB	182	399	58.7	58.7	87.4	75.7	Oral	PCR-RFLP	9
Harth, 2008 [36]	Germany	Caucasian	HB	312	300	59.7	47.2	80.4	58.7	Oral, pharyngeal, laryngeal	PCR-RFLP	6
Chatzimichalis, 2010 [30]	Greece	Caucasian	HB	88	102	66.5	62.5	87.5	74.5	Laryngeal	PCR-RFLP	8
Demokan, 2010 [31]	Turkey	Caucasian	PB	95	93	59.6	53.3	86.3	52.7	Oral, pharyngeal, laryngeal	PCR	8
Hou, 2011 [44]	China	Asian	PB	172	170	49.6	49.6	100	100	Oral, pharyngeal	PCR-RFLP and Taqman	9
Balaji, 2012 [42]	India	Asian	HB	157	132	53.1	55.1	54.8	34.8	Oral	Taqman	7
Majumder, 2012 [46]	India	Asian	HB	299	381	NA	NA	NA	NA	Oral	PCR	6
Tian, 2013 [49]	China	Asian	PB	233	102	60.0	60.0	NA	NA	Laryngeal	PCR	8
Marques, 2014 [53]	Brazil	Mixed	PB	101	141	NA	NA	NA	NA	Oral, pharyngeal, laryngeal	PCR-RFLP	7

Abbreviations: HB, hospital-based; PB, Population-based; PCR, Polymerase Chain Reaction; RT, Real Time; RFLP, Restriction Fragment Length Polymorphism; NA, Not Available. Taqman: The 5' Nuclease Assay.

Table 2 shows the prevalence of slow and rapid acetylators of NAT1 and NAT2 polymorphisms. Eight studies

[23][41][31][32][37][40][46][54] included NAT1 polymorphism with 1509 HNC cases and 1829 controls and twenty-five studies [22][23][41][29][30][31][33][34][35][36][37][38][39][40][42][43][44][45][47][48][49][50][51][52][53] included NAT2 polymorphism with 4393 HNC cases and 5321 controls.

Table 2. Prevalence of the polymorphisms of N-acetyltransferases 1 and 2 (NAT1 and NAT2), (slow vs. rapid acetylators).

Author, Year	NAT1			
	Case		Control	
	Slow	Rapid	Slow	Rapid
Katoh, 1998 [41]	9	53	46	76
Henning, 1999 [23]	144	109	232	164
Jourenkova-Mironova, 1999 [37]	141	109	98	74
Olshan, 2000 [54]	83	88	108	85
Fronhoffs, 2001 [32]	195	96	206	94
Varzim, 2002 [40]	48	40	107	65
Demokan, 2010 [31]	53	42	42	51
Majumder, 2012 [46]	128	171	168	213
Author, Year	NAT2			
	Case		Control	
	Slow	Rapid	Slow	Rapid
Gonzalez, 1998 [34]	28	47	37	163
Katoh, 1998 [41]	7	55	7	115
Henning, 1999 [23]	138	117	286	224
Jourenkova-Mironova, 1999 [37]	142	108	91	81
Morita, 1999 [48]	18	127	17	147
Chen, 2001 [29]	198	143	302	250
Hahn, 2002 [35]	59	35	57	35
Lei, 2002 [45]	50	12	34	22
Varzim, 2002 [40]	47	41	76	96
Cheng, 2003 [43]	39	240	54	271
Gajecka, 2005 [33]	127	162	165	146
Rydzanicz, 2005 [38]	131	135	72	71
Unal, 2005 [39]	15	30	7	97
Marques, 2006 [52]	29	202	38	174
Gara, 2007 [51]	33	31	59	101
Majumder, 2007 [47]	190	107	205	137
Boccia, 2008 [22]	109	101	128	117
Buch, 2008 [50]	84	98	224	175
Harth, 2008 [36]	189	123	181	119
Chatzimichalis, 2010 [30]	39	49	65	37
Demokan, 2010 [31]	50	45	45	48
Hou, 2011 [44]	46	126	33	137
Balaji, 2012 [42]	100	57	67	65
Tian, 2013 [49]	189	44	56	46
Marques, 2014 [53]	48	53	51	90

When there was one study for a subgroup, we could delete it [55]. Subgroup analyses were performed based on ethnicity, sample size, control source, genotyping method, and tumor type (**Table 3**). With regards to NAT1 polymorphism, no subgroup differences were observed. For NAT2 polymorphism, significant subgroup effects were observed for ethnicity and the control source. Slow acetylators among Asians and also the population-based studies could be effective factors on the pooled result of the association between NAT2 polymorphism and the HNC risk.

Table 3. Subgroup analyses of association between N-acetyltransferases 1 and 2 (NAT1 and NAT2) polymorphisms and the risk of head and neck cancer (slow vs. rapid acetylators).

Polymorphism	Variable (N)	OR	95% CI	p-Value	I ²	P _{heterogeneity}	
NAT1	Overall (8)	0.89	0.77, 1.02	0.09	48%	0.06	
	Ethnicity						
	Caucasian (5)	0.96	0.80, 1.15	0.64	0%	0.45	
	Asian (2)	0.55	0.17, 1.80	0.32	87%	0.005	
	Control source						
	Hospital-based (6)	0.87	0.74, 1.01	0.06	46%	0.10	
	Population-based (2)	1.05	0.51, 2.17	0.90	72%	0.06	
	Sample size						
	≥200 (6)	0.90	0.77, 1.04	0.15	0%	0.87	
	<200 (2)	0.67	0.13, 3.56	0.64	91%	0.0007	
	Genotyping method						
	PCR (4)	0.94	0.79, 1.14	0.54	26%	0.26	
	PCR-RFLP (3)	0.64	0.34, 1.18	0.15	74%	0.02	
	Tumor type						
	Oral (2)	0.55	0.17, 1.80	0.32	87%	0.005	
Laryngeal (2)	0.87	0.67, 1.15	0.33	0%	0.43		
NAT2	Overall (25)	1.22	1.02, 1.46	0.03	74%	<0.00001	
	Ethnicity						
	Caucasian (13)	1.10	0.89, 1.37	0.38	71%	<0.0001	
	Asian (8)	1.60	1.13, 2.26	0.008	69%	0.002	
	Mixed (4)	1.04	0.61, 1.77	0.89	79%	0.003	
	Control source						
	Hospital-based (15)	1.10	0.88, 1.37	0.39	71%	<0.0001	
	Population-based (10)	1.41	1.04, 1.92	0.03	75%	<0.0001	
	Sample size						
	≥200 (20)	1.19	1.00, 1.42	0.05	70%	<0.00001	
	<200 (5)	1.49	0.68, 3.29	0.32	85%	<0.0001	

Polymorphism	Variable (N)	OR	95% CI	p-Value	I	P
	Genotyping method					
	PCR (4)	1.47	0.77, 2.78	0.24	85%	0.0002
	PCR-RFLP (19)	1.14	0.93, 1.39	0.21	72%	<0.00001
	Tumor type					
	Oral (7)	1.05	0.80,1.38	0.72	62%	0.01
	Pharyngeal (2)	0.82	0.54, 1.24	0.35	0%	0.96
	Laryngeal (8)	1.48	0.88, 2.51	0.14	88%	<0.00001

Abbreviations: PCR, Polymerase Chain Reaction; RFLP, Restriction Fragment Length Polymorphism.

The meta-regression analyses assessing the effect of publication year, the sample size, and the mean age and gender distribution of cases and controls on the risk of HNC in NAT1 and NAT2 polymorphisms are shown in **Table 4**. Sample size, the mean age of cases, and the percentage of males in the controls were confounding factors for the pooled result of the association between NAT2 polymorphism and the HNC susceptibility. With an increase in sample size, age of the cases, and percentage of males in the controls, the OR decreased.

Table 4. Meta-regression analysis of association between N-acetyltransferases 1 and 2 (NAT1 and NAT2) polymorphisms and the risk of head and neck cancer (slow vs. rapid acetylators).

Polymorphism	Variable		Point Estimate	Standard Error	Lower Limit	Upper Limit	Z-Value	p-Value	
NAT1	Publication year	Slope	0.01830	0.01361	-0.00837	0.04497	1.34462	0.17875	
		Intercept	-36.77098	27.26207	-90.20365	16.66169	-1.34880	0.17740	
	Sample size	Slope	0.00027	0.00045	-0.00060	0.00115	0.61240	0.54027	
		Intercept	-0.25993	0.24912	-0.74819	0.22833	-1.04340	0.29676	
	Mean age of cases	Slope	-0.01179	0.03248	-0.07546	0.05186	-0.36300	0.71660	
		Intercept	0.57037	1.93376	-3.21972	4.36047	0.29496	0.76803	
	Mean age of controls	Slope	-0.02263	0.03624	-0.09365	0.04839	-0.62459	0.53224	
		Intercept	1.17938	2.13386	-3.00290	5.36167	0.55270	0.58047	
	Male percentage of cases	Slope	-0.01131	0.01256	-0.03593	0.01331	-0.90074	0.36773	
		Intercept	0.86738	1.11137	-1.31087	3.04562	0.78046	0.43512	
	Male percentage of controls	Slope	-0.00268	0.00617	-0.01478	0.00942	-0.43474	0.066375	
		Intercept	0.03230	0.43459	-0.81948	0.88409	0.07433	0.94074	
	NAT2	Publication year	Slope	0.00944	0.01016	-0.01047	0.02934	0.092942	0.35267
			Intercept	-18.82284	20.36308	-58.73373	21.08806	-0.92436	0.35530
Sample size		Slope	-0.00080	0.00020	-0.00120	-0.00040	-3.91239	0.00009	
		Intercept	0.50882	0.11300	0.28733	0.73030	4.50265	0.00001	
Mean age of cases		Slope	-0.04050	0.01356	-0.06706	-0.01393	-2.098776	0.00281	
		Intercept	2.47888	0.80007	0.91077	4.04699	3.09832	0.00195	
Mean age of controls		Slope	-0.00438	0.00889	-0.02180	0.01305	-0.49203	0.62270	
		Intercept	0.34691	0.47403	-0.58217	1.27600	0.73184	0.46427	
Male percentage of cases		Slope	-0.0629	0.00393	-0.01399	0.00141	-1.60201	0.10915	
		Intercept	0.57366	0.33428	-0.08152	1.22884	1.71610	0.08614	
Male percentage of controls		Slope	-0.00785	0.00289	-0.01351	-0.00219	-2.71989	0.00653	
		Intercept	0.64373	0.22152	0.20956	1.07790	2.90598	0.00366	

3. Current Insights

This meta-analysis showed a significant relationship between NAT2 polymorphisms and the HNC susceptibility with slow acetylators being at higher risk for HNC than rapid acetylators. For NAT2 polymorphism, the ethnicity, the control source, and genotyping methods could modify the association of this polymorphism and the HNC risk. In addition, TSA showed the amount of information for the association between the polymorphisms (NAT1 and NAT2) and the HNC risk was not large enough.

The findings from studies exploring the association of NAT1 polymorphism with other cancers and HNC are different. One meta-analysis [24] found NAT1 polymorphism to be related to the risk of lung, colorectal, head and neck, bladder, and gastric carcinomas, but not with prostate, breast, and pancreatic carcinomas and non-Hodgkin's lymphoma. Varzim et al. [40] checked the association between NAT1 polymorphism and the laryngeal cancer risk and found that the association depends on tumor location. Among the eight studies included in our meta-analyses [23][41][31][32][37][40][46][54] which evaluated the association between NAT1 polymorphism and the HNC risk, just one study [41] reported a protective role of NAT1 slow acetylators in the HNC patients while the rest of the studies did not find any association.

Comparing the individual studies included in the meta-analysis, differences were observed between the studies. For example, five studies [34][39][42][49] found an elevated risk of HNC for NAT2 slow acetylators, one found a protective role of these acetylators in HNC patients, and three did not find any association between NAT2 polymorphism and the HNC risk [23][38][43].

Effective factors on the association between NAT polymorphisms and the risk of HNC were not included in our analysis due to low numbers of studies, including smoking, gene combination, and the linkage disequilibrium. One study [34] found an elevated frequency of the NAT2 slow acetylator genotypes among HNC patients who smoked less than those who smoked more frequently. Another study reported an association in cases with a smoking history ≤ 30 years in duration [41]. These contradictory results [41][34][39] suggest the need to evaluate the effect of NAT polymorphisms independent of the history of smoking. In addition, assessing the frequencies of gene-gene combination (NAT2 with GSTM1, XPD, and CYP1A1) between cases with laryngeal cancer and the controls, the frequency of combinations was superior to cases than in controls where the numbers of combinations had an increased risk of laryngeal cancer and the numbers of other combinations had a protective role [33]. The linkage disequilibrium between the genes of NAT1 and NAT2 has been observed in HNC [23][31][56] and other cancers [57][58][59]. Research [60] showed the highest level of carcinogen-DNA adducts formation in cases with acetylation activity of NAT1 rapid and NAT2 slow. Therefore, future studies should consider the linkage between these polymorphisms.

4. Conclusions

There was no association between NAT1 polymorphism and susceptibility to HNC, whereas an association between and NAT2 polymorphism and the HNC risk was found. Slow acetylators of NAT2 polymorphism were at greater risk for HNC than the rapid acetylators. Despite the stability of the results, the presence of high heterogeneity, publication bias, and confounding factors warrant the need for more studies to confirm the results of the present meta-analysis as well as TSA.

References

1. Rezaei, F.; Mohammadi, H.; Heydari, M.; Sadeghi, M.; Mozaffari, H.R.; Khavid, A.; Godiny, M.; Brand, S.; M Dürsteler, K.; Brühl, A.B.; et al. Association between IL-8 (-251T/A) and IL-6 (-174G/C) Polymorphisms and Oral Cancer Susceptibility: A Systematic Review and Meta-Analysis. *Medicina* 2021, 57, 405.
2. Patterson, R.H.; Fischman, V.G.; Wasserman, I.; Siu, J.; Shrimme, M.G.; Fagan, J.J.; Koch, W.; Alkire, B.C. Global burden of head and neck cancer: Economic consequences, health, and the role of surgery. *Otolaryngol.-Head Neck Surg.* 2020, 162, 296-303.
3. Vos, T.; Abajobir, A.A.; Abate, K.H.; Abbafati, C.; Abbas, K.M.; Abd-Allah, F.; Abdulkader, R.S.; Abdulle, A.M.; Abebo, T.A.; Abera, S.F. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: A systematic analysis for the Global Burden of Disease Study 2016. *Lancet* 2017, 390, 1211–1259.
4. Foreman, K.J.; Marquez, N.; Dolgert, A.; Fukutaki, K.; Fullman, N.; McGaughey, M.; Pletcher, M.A.; Smith, A.E.; Tang, K.; Yuan, C.-W. Forecasting life expectancy, years of life lost, and all-cause and cause-specific mortality for 250 causes of death: Reference and alternative scenarios for 2016–40 for 195 countries and territories. *Lancet* 2018, 392, 2052–2090.
5. Nigro, C.L.; Denaro, N.; Merlotti, A.; Merlano, M. Head and neck cancer: Improving outcomes with a multidisciplinary approach. *Cancer Manag. Res.* 2017, 9, 363.
6. Weinberger, P.M.; Yu, Z.; Haffty, B.G.; Kowalski, D.; Harigopal, M.; Brandsma, J.; Sasaki, C.; Joe, J.; Camp, R.L.; Rimm, D.L. Molecular classification identifies a subset of human papillomavirus-associated oropharyngeal cancers with favorable prognosis. *J. Clin. Oncol.* 2006, 24, 736–747.
7. Johnson, D.E.; Burtress, B.; Leemans, C.R.; Lui, V.W.Y.; Bauman, J.E.; Grandis, J.R. Head and neck squamous cell carcinoma. *Nat. Rev. Dis. Primers* 2020, 6, 1–22.
8. Mozaffari, H.R.; Rostamnia, M.; Sharifi, R.; Safaei, M.; Zavattaro, E.; Tadakamadla, S.K.; Imani, M.M.; Sadeghi, M.; Golshah, A.; Moradpoor, H. A PRISMA-compliant meta-analysis on association between X-ray repair cross complementing (XRCC1, XRCC2, and XRCC3) polymorphisms and oral cancer susceptibility. *Gene* 2021, 781, 145524.
9. Rezaei, F.; Doulatparast, D.; Sadeghi, M. Common polymorphisms of Interleukin-10 (-1082A/G, -592A/C, and -819C/T) in oral cancers: An updated meta-analysis. *J. Interferon Cytokine Res.* 2020, 40, 357–369.
10. Xia, S.; Wu, S.; Wang, M. The Association Between the XRCC1 Arg399Gln Polymorphism and the Risk of Head and Neck Cancer: An Updated Meta-Analysis Including 14586 Subjects. *Technol. Cancer Res. Treat.* 2021, 20, 15330338211033060.
11. Wu, T.; Zhang, Z.T.; Li, L.; Liu, R.Y.; Bei, B.T. Correlation between hypoxia-inducible factor-1 α C1772T/G1790A polymorphisms and head and neck cancer risk: A meta-analysis. *World J. Surg. Oncol.* 2021, 19, 210.
12. Vineis, P. Epidemiology of cancer from exposure to arylamines. *Environ. Health Perspect.* 1994, 102, 7–10.
13. Bartsch, H.; Malaveille, C.; Friesen, M.; Kadlubar, F.; Vineis, P. Black (air-cured) and blond (flue-cured) tobacco cancer risk IV: Molecular dosimetry studies implicate aromatic amines as bladder carcinogens. *Eur. J. Cancer* 1993, 29, 1199–1207.
14. Hein, D.W.; Doll, M.A.; Rustan, T.D.; Gray, K.; Feng, Y.; Ferguson, R.J.; Grant, D.M. Metabolic activation and deactivation of arylamine carcinogens by

- recombinant human NAT1 and polymorphic NAT2 acetyltransferases. *Carcinogenesis* 1993, 14, 1633-1638.
15. Hein, D.W.; Doll, M.A.; Fretland, A.J.; Leff, M.A.; Webb, S.J.; Xiao, G.H.; Devanaboyina, U.-S.; Nangju, N.A.; Feng, Y. Molecular genetics and epidemiology of the NAT1 and NAT2 acetylation polymorphisms. *Cancer Epidemiol. Prev. Biomark.* 2000, 9, 29-42.
 16. Vatsis, K.P.; Weber, W.W. Structural heterogeneity of Caucasian N-acetyltransferase at the NAT1 gene locus. *Arch. Biochem. Biophys.* 1993, 301, 71-76.
 17. Feki-Tounsi, M.; Khelifi, R.; Louati, I.; Fourati, M.; Mhiri, M.-N.; Hamza-Chaffai, A.; Rebai, A. Polymorphisms in XRCC1, ERCC2, and ERCC3 DNA repair genes, CYP1A1 xenobiotic metabolism gene, and tobacco are associated with bladder cancer susceptibility in Tunisian population. *Environ. Sci. Pollut. Res.* 2017, 24, 22476-22484.
 18. Imam, H.; Imam, T.; Abbas, S.Z.; Ismail, M.; Muhammad, S.A. Association study of NAT2 gene polymorphism and risk of oral cancer in Southern Punjab, Pakistan. *J. Pak. Med Assoc.* 2021, 71, 1954-1958.
 19. Sabbagh, N.; Delaporte, E.; Marez, D.; Lo-Guidice, J.-M.; Piette, F.; Broly, F. NAT2 genotyping and efficacy of sulfasalazine in patients with chronic discoid lupus erythematosus. *Pharmacogenetics* 1997, 7, 131-135.
 20. Wang, L.; Minchin, R.F.; Butcher, N.J. Arylamine N-acetyltransferase 1 protects against reactive oxygen species during glucose starvation: Role in the regulation of p53 stability. *PLoS ONE* 2018, 13, e0193560.
 21. Minchin, R.F. Acetylation of p-aminobenzoylglutamate, a folic acid catabolite, by recombinant human arylamine N-acetyltransferase and U937 cells. *Biochem. J.* 1995, 307, 1-3.
 22. Boccia, S.; Cadoni, G.; Sayed-Tabatabaei, F.A.; Volante, M.; Arzani, D.; De Lauretis, A.; Cattell, C.; Almadori, G.; Van Duijn, C.M.; Paludetti, G. CYP1A1, CYP2E1, GSTM1, GSTT1, EPHX1 exons 3 and 4, and NAT2 polymorphisms, smoking, consumption of alcohol and fruit and vegetables and risk of head and neck cancer. *J. Cancer Res. Clin. Oncol.* 2008, 134, 93-100.
 23. Henning, S.; Cascorbi, I.; Münchow, B.; Jahnke, V.; Roots, I. Association of arylamine N-acetyltransferases NAT1 and NAT2 genotypes to laryngeal cancer risk. *Pharmacogenetics* 1999, 9, 103-111.
 24. Zhang, K.; Gao, L.; Wu, Y.; Chen, J.; Lin, C.; Liang, S.; Su, J.; Ye, J.; He, X. NAT1 polymorphisms and cancer risk: A systematic review and meta-analysis. *Int. J. Clin. Exp. Med.* 2015, 8, 9177.
 25. Zheng, Y.; Li, Y.; Teng, Y.; Zhang, Z.; Cao, X. Association of NAT2 phenotype with risk of head and neck carcinoma: A meta-analysis. *Oncol. Lett.* 2012, 3, 429-434.
 26. Zhuo, X.-L.; Ling, J.-J.; Zhou, Y.; Zhao, H.-Y.; Song, Y.-F.; Tan, Y.-H. NAT2 polymorphisms with oral carcinoma susceptibility: A meta-analysis. *Mol. Biol. Rep.* 2012, 39, 8813-8819.
 27. Ying, X.-J.; Dong, P.; Shen, B.; Wang, J.; Wang, S.; Wang, G. Possible association of NAT2 polymorphism with laryngeal cancer risk: An evidence-based meta-analysis. *J. Cancer Res. Clin. Oncol.* 2011, 137, 1661-1667.
 28. Zhang, L.; Xiang, Z.; Hao, R.; Li, R.; Zhu, Y. N-acetyltransferase 2 genetic variants confer the susceptibility to head and neck carcinoma: Evidence from 23 case-control studies. *Tumor Biol.* 2014, 35, 3585-3595.
 29. Chen, C.; Ricks, S.; Doody, D.R.; Fitzgibbons, E.D.; Porter, P.L.; Schwartz, S.M. N-Acetyltransferase 2 polymorphisms, cigarette smoking and alcohol consumption, and oral squamous cell cancer risk. *Carcinogenesis* 2001, 22, 1993-1999.
 30. Chatzimichalis, M.; Xenellis, J.; Tzagaroulakis, A.; Sarof, P.; Banis, K.; Gazouli, M.; Bibas, A. GSTT1, GSTM1, GSTM3 and NAT2 polymorphisms in laryngeal squamous cell carcinoma in a Greek population. *J. Laryngol. Otol.* 2010, 124, 318-323.
 31. Demokan, S.; Suoglu, Y.; Gözeler, M.; Demir, D.; Dalay, N. N-acetyltransferase 1 and 2 gene sequence variants and risk of head and neck cancer. *Mol. Biol. Rep.* 2010, 37, 3217-3226.
 32. Fronhoffs, S.; Brüning, T.; Ortiz-Pallardo, E.; Bröde, P.; Koch, B.; Harth, V.; Sachinidis, A.; Bolt, H.M.; Herberhold, C.; Vetter, H. Real-time PCR analysis of the N-acetyltransferase NAT1 allele* 3,* 4,* 10,* 11,* 14 and* 17 polymorphism in squamous cell cancer of head and neck. *Carcinogenesis* 2001, 22, 1405-1412.
 33. Gajęcka, M.; Rydzanicz, M.; Jaskula-Sztul, R.; Kujawski, M.; Szyfter, W.; Szyfter, K. CYP1A1, CYP2D6, CYP2E1, NAT2, GSTM1 and GSTT1 polymorphisms or their combinations are associated with the increased risk of the laryngeal squamous cell carcinoma. *Mutat. Res. Fundam. Mol. Mech. Mutagenesis* 2005, 574, 112-123.
 34. Gonzalez, M.; Alvarez, V.; Pello, M.; Menendez, M.; Suarez, C.; Coto, E. Genetic polymorphism of N-acetyltransferase-2, glutathione S-transferase-M1, and cytochromes P450IIE1 and P450IID6 in the susceptibility to head and neck cancer. *J. Clin. Pathol.* 1998, 51, 294-298.
 35. Hahn, M.; Hagedorn, G.; Kuhlisch, E.; Schackert, H.K.; Eckelt, U. Genetic polymorphisms of drug-metabolizing enzymes and susceptibility to oral cavity cancer. *Oral Oncol.* 2002, 38, 486-490.
 36. Harth, V.; Schäfer, M.; Abel, J.; Maintz, L.; Neuhaus, T.; Besuden, M.; Primke, R.; Wilkesmann, A.; Thier, R.; Vetter, H. Head and neck squamous-cell cancer and its association with polymorphic enzymes of xenobiotic metabolism and repair. *J. Toxicol. Environ. Health Part A* 2008, 71, 887-897.
 37. Jourenkova-Mironova, N.; Wikman, H.; Bouchardy, C.; Mitrunen, K.; Dayer, P.; Benhamou, S.; Hirvonen, A. Role of arylamine N-acetyltransferase 1 and 2 (NAT1 and NAT2) genotypes in susceptibility to oral/pharyngeal and laryngeal cancers. *Pharm. Genom.* 1999, 9, 533-537.
 38. Rydzanicz, M.; Wierzbička, M.; Gajęcka, M.; Szyfter, W.; Szyfter, K. The impact of genetic factors on the incidence of multiple primary tumors (MPT) of the head and neck. *Cancer Lett.* 2005, 224, 263-278.
 39. Ünal, M.; Tamer, L.; Akbaş, Y.; Pata, Y.S.; Vayisoğlu, Y.; Değirmenci, U.; Çamdeviren, H. Genetic polymorphism of N-acetyltransferase 2 in the susceptibility to laryngeal squamous cell carcinoma. *Head Neck J. Sci. Spec. Head Neck* 2005, 27, 1056-1060.
 40. Varzim, G.; Monteiro, E.; Silva, R.; Pinheiro, C.; Lopes, C. Polymorphisms of arylamine N-acetyltransferase (NAT1 and NAT2) and larynx cancer susceptibility. *ORL* 2002, 64, 206-212.
 41. Katoh, T.; Kaneko, S.; Boissy, R.; Watson, M.; Ikemura, K.; Bell, D.A. A pilot study testing the association between N-acetyltransferases 1 and 2 and risk of oral squamous cell carcinoma in Japanese people. *Carcinogenesis* 1998, 19, 1803-1807.
 42. Balaji, L.; Krishna, B.S.; Bhaskar, L. An unlikely role for the NAT2 genotypes and haplotypes in the oral cancer of south Indians. *Arch. Oral Biol.* 2012, 57, 513-518.
 43. Cheng, Y.-J.; Chien, Y.-C.; Hildesheim, A.; Hsu, M.-M.; Chen, I.-H.; Chuang, J.; Chang, J.; Ma, Y.D.; Luo, C.-T.; Hsu, W.-L. No association between genetic polymorphisms of CYP1A1, GSTM1, GSTT1, GSTP1, NAT2, and nasopharyngeal carcinoma in Taiwan. *Cancer Epidemiol. Prev. Biomark.* 2003, 12, 179-180.
 44. Hou, Y.-Y.; Ou, H.-L.; Chu, S.-T.; Wu, P.-C.; Lu, P.-J.; Chi, C.-C.; Leung, K.-W.; Lee, C.-Y.; Wu, P.-H.; Hsiao, M. NAT2 slow acetylation haplotypes are associated with the increased risk of betel quid-related oral and pharyngeal squamous cell carcinoma. *Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endodontology.* 2011, 112, 484-492.
 45. Lei, D.; Pan, X.; Guo, C.; Xu, F.; Zhang, L.; Liu, D.; Luan, X. Relationship between polymorphism of N-acetyltransferase 2 and genetic susceptibility to laryngeal carcinoma. *Zhonghua Zhong Liu Za Zhi* 2002, 24, 154-156.
 46. Majumder, M.; Ghosh, S.; Roy, B. Association between polymorphisms at N-acetyltransferase 1 (NAT1) & risk of oral leukoplakia & cancer. *Indian J. Med Res.* 2012, 136, 605.
 47. Majumder, M.; Sikdar, N.; Ghosh, S.; Roy, B. Polymorphisms at XPD and XRCC1 DNA repair loci and increased risk of oral leukoplakia and cancer among NAT2 slow acetylators. *Int. J. Cancer* 2007, 120, 2148-2156.

48. Morita, S.; Yano, M.; Tsujinaka, T.; Akiyama, Y.; Taniguchi, M.; Kaneko, K.; Miki, H.; Fujii, T.; Yoshino, K.; Kusuoka, H. Genetic polymorphisms of drug-metabolizing enzymes and susceptibility to head-and-neck squamous-cell carcinoma. *Int. J. Cancer* 1999, 80, 685-688.
49. Tian, S.; Zhang, J.; Yuan, X.; Huang, M.; Guo, Z.; Chen, F.; Li, Q.; Guan, Z. The association between genetic polymorphisms of NAT1, NAT2 and susceptibility to laryngeal squamous carcinoma (LSCC) in Han population in Guangdong China. *J. Modern Oncol.* 2013, 6, 1213-1218.
50. Buch, S.C.; Nazar-Stewart, V.; Weissfeld, J.L.; Romkes, M. Case-control study of oral and oropharyngeal cancer in whites and genetic variation in eight metabolic enzymes. *Head Neck J. Sci. Spec. Head Neck* 2008, 30, 1139-1147.
51. Gara, S.; Abdennebi, M.; Chatti, S.; Touati, S.; Ladgham, A.; Guemira, F. Association of NAT2 gene substitution mutation T341C with increased risk for head and neck cancer in Tunisia. *Acta Oncol.* 2007, 46, 834-837.
52. Marques, C.F.; Koifman, S.; Koifman, R.J.; Boffetta, P.; Brennan, P.; Hatagima, A. Influence of CYP1A1, CYP2E1, GSTM3 and NAT2 genetic polymorphisms in oral cancer susceptibility: Results from a case-control study in Rio de Janeiro. *Oral Oncol.* 2006, 42, 632-637.
53. Marques, C.R.; Da Silva, T.M.; De Albuquerque, D.M.; Chaves, M.S.; Marques Filho, M.F.; Oliveira, J.S.; Di Pietro, G.; Sousa, S.M.B.; Simoes, A.L.; Rios-Santos, F. NAT2, XRCC1 and hOGG1 polymorphisms, cigarette smoking, alcohol consumption and risk of upper aerodigestive tract cancer. *Anticancer. Res.* 2014, 34, 3217-3224.
54. Olshan, A.F.; Weissler, M.C.; Watson, M.A.; Bell, D.A. GSTM1, GSTT1, GSTP1, CYP1A1, and NAT1 polymorphisms, tobacco use, and the risk of head and neck cancer. *Cancer Epidemiol. Prev. Biomark.* 2000, 9, 185-191.
55. Richardson, M.; Garner, P.; Donegan, S. Interpretation of subgroup analyses in systematic reviews: A tutorial. *Clin. Epidemiol. Glob. Health* 2019, 7, 192-198.
56. Hickman, D.; Risch, A.; Buckle, V.; Spurr, N.; Jeremiah, S.; McCarthy, A.; Sim, E. Chromosomal localization of human genes for arylamine N-acetyltransferase. *Biochem. J.* 1994, 297, 441-445.
57. Moslehi, R.; Chatterjee, N.; Church, T.R.; Chen, J.; Yeager, M.; Weissfeld, J.; Hein, D.W.; Hayes, R.B. Cigarette smoking, N-acetyltransferase genes and the risk of advanced colorectal adenoma. *Future Med.* 2006, 7, 819-829.
58. Cascorbi, I.; Roots, I.; Brockmüller, J. Association of NAT1 and NAT2 polymorphisms to urinary bladder cancer: Significantly reduced risk in subjects with NAT1* 10. *Cancer Res.* 2001, 61, 5051-5056.
59. Chen, J.; Stampfer, M.J.; Hough, H.L.; Garcia-Closas, M.; Willett, W.C.; Hennekens, C.H.; Kelsey, K.T.; Hunter, D.J. A prospective study of N-acetyltransferase genotype, red meat intake, and risk of colorectal cancer. *Cancer Res.* 1998, 58, 3307-3311.
60. Badawi, A.F.; Hirvonen, A.; Bell, D.A.; Lang, N.P.; Kadlubar, F.F. Role of aromatic amine acetyltransferases, NAT1 and NAT2, in carcinogen-DNA adduct formation in the human urinary bladder. *Cancer Res.* 1995, 55, 5230-5237.

Keywords

head and neck carcinoma;oral carcinoma;polymorphism;N-acetyltransferases;meta-analysis
