Susceptibility to Head and Neck Cancers

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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.

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

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	Qual Scor
				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
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

The First Author, Publication Year	Country	Ethnicity	Control Source	Number		Mean Year		Male Percentage		Type of Tumor	Genotyping Method	Qual Scor
				Case	Control	Case	Control	Case	Control			
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

Author, Year	*NAT1*			
	Case		Control	
	Slow	Rapid	Slow	Rapid
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

Polymorphism	Variable (N)	OR	95% CI	*p*-Value	I^2	$P_{heterogeneity}$
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**
	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**

Polymorphism	Variable		Point Estimate	Standard Error	Lower Limit	Upper Limit	Z-Value	*p*-Value
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.

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