Association of NAT2 phenotype with risk of head and neck carcinoma: A meta-analysis

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Received August 18, 2011; Accepted November 17, 2011

DOI: 10.3892/ol.2011.493

Abstract. N-acetyltransferase 2 (NAT2) is a key enzyme involved in the metabolism of xenobiotics and plays a significant role in the detoxification of numerous potential carcinogens. According to its acetylation status, NAT2 acetylator may be classified into two phenotypes, rapid and slow. Numerous studies have demonstrated that the polymorphisms of *NAT2* were correlated with individual susceptibility to several malignant neoplasms, including head and neck carcinomas (HNC). However, the associations between the acetylator phenotypes and HNC risk in each study were not entirely consistent. To assess these associations more comprehensively, we performed a meta-analysis. In this meta-analysis, 16 eligible studies including 2,965 cases with HNC and 3,919 controls were identified by searching the databases of PubMed, Medline and the ISI Web of Knowledge. Odds ratios (ORs) with 95% confidence intervals (95% CIs) were used to evaluate the association. No significant associations between the rapid acetylator phenotype in NAT2 and HNC risk were found either in the overall analysis (OR=0.98; 95% CI 0.83, 1.15; I^2=57%; $P_{heterogeneity}$=0.003) or in the subgroup analysis by ethnicity (for the Caucasian population, OR=1.03, 95% CI 0.85, 1.24, I^2=63%, $P_{heterogeneity}$=0.002; for other mixed populations, OR=0.78, 95% CI=0.61, 1.00, I^2=0%, $P_{heterogeneity}$=0.47). In conclusion, this meta-analysis suggested that there is no association between the NAT2 phenotype and the risk of HNC.

Introduction

Head and neck carcinoma (HNC), arising from the sites of the oral cavity, oropharynx, hypopharynx and larynx, is the sixth most common type of cancer worldwide (1). It is characterized by a moderately low survival rate, a high recurrence rate, and a high rate of second primary malignancy (2). In 2009, approximately 49,260 new cases (35,530 males and 13,730 females) of HNC were diagnosed in the USA, and 11,480 deaths occurred (8,300 males and 3,180 females) (1). Present evidence has proven that numerous factors contribute to the risk of squamous cell carcinoma of the head and neck, including tobacco use, alcohol consumption (3), viral infection (4) and genetic polymorphisms (5). In particular, tobacco smoking and alcohol consumption account for approximately 80% of HNC cases (6,7). However, it is worth noting that only a fraction of smokers and alcohol consumers develop HNC. This phenomenon suggests that host factors, including genetic variation, contribute to the inter-individual variation in the susceptibility to HNC.

Numerous procarcinogens are known to exist in tobacco, including polycyclic aromatic hydrocarbons (PAHs), aromatic and heterocyclic amines; nitroso-compounds in smoking tobacco; and nitrosamines, aromatic and heterocyclic amines in smokeless tobacco. Most of these carcinogens generally undergo bioactivation and inactivation by phase I and II enzymes, respectively. The phase II enzymes, including Glutathione S-transferases (GSTs) and N-acetyltransferase (NAT), contribute to the detoxification metabolism. Human NAT comprises the isoenzymes, NAT1 and NAT2. In contrast to the wide tissue distribution of NAT1, NAT2 is expressed predominantly in liver (8), although it is also found in numerous human tissues (9). NAT2 is a key phase II enzyme that participates in the bioconversion of aromatic and heterocyclic amines (10,11). According to the activity and stability that arise from its DNA sequence variations, the *NAT2* gene may be classified into two allele types; slow and rapid (12). Previous studies demonstrated that either slow or rapid acetylation may be associated with various tobacco-associated cancers. Cascorbi *et al* reported that rapid acetylation status was a highly significant risk factor in lung cancer development (13). Inversely, Hein *et al* found that NAT2 slow acetylation increased the risk of bladder cancer (14). In other relevant studies, no significant association between *NAT2* polymorphisms and cancer was found, including colon (15), gastric (16), breast (17) and liver (18). These findings indicated that the activities of the NAT2 enzyme may be associated with the type of cancer, and its

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Abbreviations: NAT2, N-acetyltransferase 2; HNC, head and neck carcinoma; OR, odds ratio; 95% CI, 95% confidence interval

Key words: N-acetyltransferase 2, phenotype, head and neck carcinoma

variance may be due to inter-individual variation of genetic susceptibility to cancers in the general population.

HNC belongs to the tobacco-associated group of cancers; thus, NAT2 plays a key role in the development of these types of cancer. A number of molecular epidemiological studies investigated the correlation between acetylator phenotypes in NAT2 and the risk of HNC. However, until now the results have been inconsistent and even contradictory. Therefore, we performed a meta-analysis of 16 published studies including 2,965 cases and 3,919 controls to obtain a more precise evaluation of the association between the NAT2 acetylator phenotype and HNC risk.

Materials and methods

Literature search strategy. Eligible studies were identified by searching the databases of PubMed, Medline and the ISI Web of Knowledge for relevant literature in English. The latest searches were undertaken on July 5, 2011. The following queries were used: ['N-acetyltransferase 2' or 'NAT 2'], and ['polymorphism' or 'SNP' or 'phenotype'], and ['head and neck cancer' or 'oropharyngeal cancer' or 'hypopharyngeal cancer' or 'oral cancer' or 'laryngeal cancer']. All of the searched studies were retrieved and their references were checked carefully to find additional eligible studies.

Inclusion and exclusion criteria. To identify eligible studies in this meta-analysis, the following criteria were established: i) case-control studies investigating the association of the NAT2 acetylator phenotype with HNC risk; ii) the diagnosis of head and neck cancer, including oral, oropharyngeal, hypopharyngeal and laryngeal cancer was confirmed by pathological examination; iii) controls were confirmed as free from HNC; iv) the sample used in the studies was blood; v) the studies were full-text articles; and vi) the studies were written in English.

The exclusion criteria were: i) non-case-control studies; ii) cases with other types of cancer, including nasopharyngeal and thyroid cancer; iii) case reports, letters, reviews, editorial articles and non-full-text literature; iv) no available phenotype or genotype information; and v) duplication of the previous publications.

Data extraction. The full-texts of the candidate articles were reviewed carefully by two independent investigators. The following variables were extracted from each study if available: the first author's surname, publication year, country of origin and ethnicity of participants, and the number of cases and controls with the studied phenotypes. According to the data from the Louisville University website (http://www.louisville.edu/medschool/pharmacology/NAT.html, updated July 22, 2011), *NAT2*4* is regarded as the most common rapid acetylation allele, and *NAT2*11A*, *NAT2*12A-C*, *NAT2*13A* and *NAT2*18* are also considered as rapid alleles. Other alleles are considered as slow. In our studies, the NAT2 acetylator phenotype was classified into two groups according to its acetylation status, rapid or slow. A rapid acetylator is defined as being a carrier of at least one of the rapid acetylator alleles, whereas the slow acetylator carries two slow acetylator alleles. The different ethnic descents were classified as Caucasian, Asian, Turkish or other. Data were extracted independently by two investigators. If the results were discordant, a third investigator checked the data.

Statistical analysis. The meta-analysis was performed using the Review Manager 5 (version 5.0.18, provided by the Cochrane Collaboration). The strength of the association between the NAT2 acetylator phenotype and individual susceptibility to HNC was estimated using odds ratios (ORs) with 95% confidence intervals (95% CIs). The pooled ORs were evaluated for rapid versus slow acetylator phenotypes. To evaluate the ethnicity-specific effect, subgroup analyses were performed according to ethnic group (Caucasian and other mixed populations). $P \leq 0.05$ was considered to indicate statistical significance.

The heterogeneity among studies was estimated using Chi-square-based Q-tests. We also quantified the effect of heterogeneity by the I^2 test. The % CI ranges from 0 to 100% and represents the proportion of inter-study variability that may be attributed to heterogeneity rather than chance. % CI values of 25, 50 and 75% were defined as low, moderate and high estimates, respectively. When the Q-test P-value was >0.1 or the % CI <50%, ORs were pooled according to the fixed-effects model (Mantel-Haenszel model). Otherwise, the random-effects model (DerSimonian and Laird model) was used. One-way sensitivity analyses were used to assess the stability of the meta-analysis results.

The Begg's funnel plots and Egger's test were conducted to evaluate the possible publication bias using Stata (version 11; StataCorp, College Station, TX, USA). Statistical significance was considered when the P-value of Egger's test was ≤0.05.

P-values were two-sided. Two reviewers analyzed data independently and obtained the same results.

Results

Study characteristics. The process of study selection and exclusion is shown in Fig. 1. A total of 45 abstracts were retrieved through PubMed and Medline, and 2 additional articles were found through the ISI Web of Knowledge. After reviewing all 47 articles carefully, 16 eligible articles including 2,965 cases with HNC and 3,919 controls were identified and included in the final meta-analysis (19-34). The main characteristics of all 16 studies are described in Table I. The studies were case-control studies that evaluated the association between the NAT2 acetylation status and the susceptibility to HNC. The year of publication of the included studies ranged from 1998 to 2010. There were 11 studies of Caucasians (19,21-23,25-28,30,31,34), 3 of Asians (24,32,33), 1 of Turkish (20) and 1 of a mixed population (including Caucasian and other mixed populations) (29). All cases of HNC were pathologically confirmed. All articles were written in English.

Meta-analysis. The pooled ORs were evaluated for rapid versus slow acetylator phenotypes in NAT2. The overall OR was 0.98 and the 95% CI was 0.83, 1.15 (P=0.76). In the subgroup analysis of ethnicity, no increased risks were found either in the Caucasian population (OR=1.03; 95% CI 0.85, 1.24; P=0.37) or in the other mixed populations (OR=0.78; 95% CI 0.61, 1.00; P=0.05) (Table II).

Table I. Main characteristics of all studies included in the meta-analysis.

First author (Refs.)	Publication year	Country of origin	Ethnicity	Cases		Controls	
				Rapid	Slow	Rapid	Slow
Chatzimichalis (19)	2010	Greece	Caucasian	49	39	37	65
Demokan (20)	2010	Turkey	Turkish	45	50	48	45
Buch (21)	2008	USA	Caucasian	98	84	175	224
Harth (22)	2008	Germany	Caucasian	123	189	119	181
Boccia (23)	2008	Italy	Caucasian	101	109	117	128
Majumder (24)	2007	India	Asian	107	190	137	205
Rydzanicz (25)	2005	Poland	Caucasian	93	89	71	72
Gajecka (26)	2005	Poland	Caucasian	162	127	146	165
Hahn (27)	2002	Germany	Caucasian	35	59	35	57
Varzim (28)	2002	Portugal	Caucasian	41	47	96	76
Chen (29)	2001	USA	Caucasian	133	187	226	294
			Others (mixed)	10	11	24	8
Jourenkova -Mironova (30)	1999	France	Caucasian	108	142	81	91
Henning (31)	1999	Germany	Caucasian	117	138	224	286
Morita (32)	1999	Japan	Asian	127	18	147	17
Katoh (33)	1998	Japan	Asian	55	7	115	7
Gonzalez (34)	1998	Spain	Caucasian	47	28	163	37

Rapid, rapid acetylator phenotype; Slow, slow acetylator phenotype.

Table II. Summary of ORs with 95% CIs for rapid acetylator phenotype in NAT2 and head and neck carcinoma risk.

First author (Refs.)	Ethnicity	OR	95% CI
Chatzimichalis (19)	Caucasian	2.21	1.23, 3.95
Demokan (20)	Turkish	0.84	0.48, 1.50
Buch (21)	Caucasian	1.49	1.05, 2.12
Harth (22)	Caucasian	0.99	0.72, 1.37
Boccia (23)	Caucasian	1.01	0.70, 1.47
Majumder (24)	Asian	0.84	0.61, 1.16
Rydzanicz (25)	Caucasian	1.06	0.68, 1.64
Gajecka (26)	Caucasian	1.44	1.04, 1.99
Hahn (27)	Caucasian	0.97	0.53, 1.75
Varzim (28)	Caucasian	0.69	0.41, 1.16
Chen (29)	Caucasian	0.93	0.70, 1.23
	Mixed	0.3	0.09, 0.98
	Total	0.87	0.66, 1.15
Jourenkova -Mironova (30)	Caucasian	0.85	0.58, 1.26
Henning (31)	Caucasian	1.08	0.80, 1.46
Morita (32)	Asian	0.82	0.40, 1.65
Katoh (33)	Asian	0.48	0.16, 1.43
Gonzalez (34)	Caucasian	0.38	0.21, 0.69
	Total Caucasian	1.03	0.85, 1.24
	Mixed	0.78	0.61, 1.00
	Total	0.98	0.83, 1.15

OR, odds ratio; CI, confidence interval.

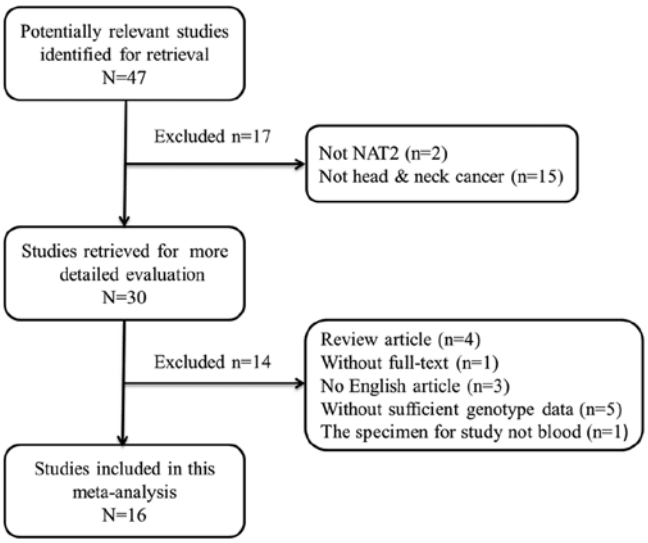

Figure 1. Study flow chart, showing the selection of case-control studies.

Heterogeneity and sensitivity analysis. Heterogeneity among all studies was assessed both in the overall comparisons and in the subgroup analyses. The evidence of significant heterogeneity was found in the overall comparison ($P_{heterogeneity}$=0.003, % CI=57%) and the Caucasian subgroup ($P_{heterogeneity}$=0.002, % CI=63%), whereas no significant heterogeneity was observed in the other mixed population subgroup ($P_{heterogeneity}$=0.47, % CI=0%) (Fig. 2).

In the sensitivity analysis, the effect of each study on the pooled OR was examined by repeating the meta-analysis while

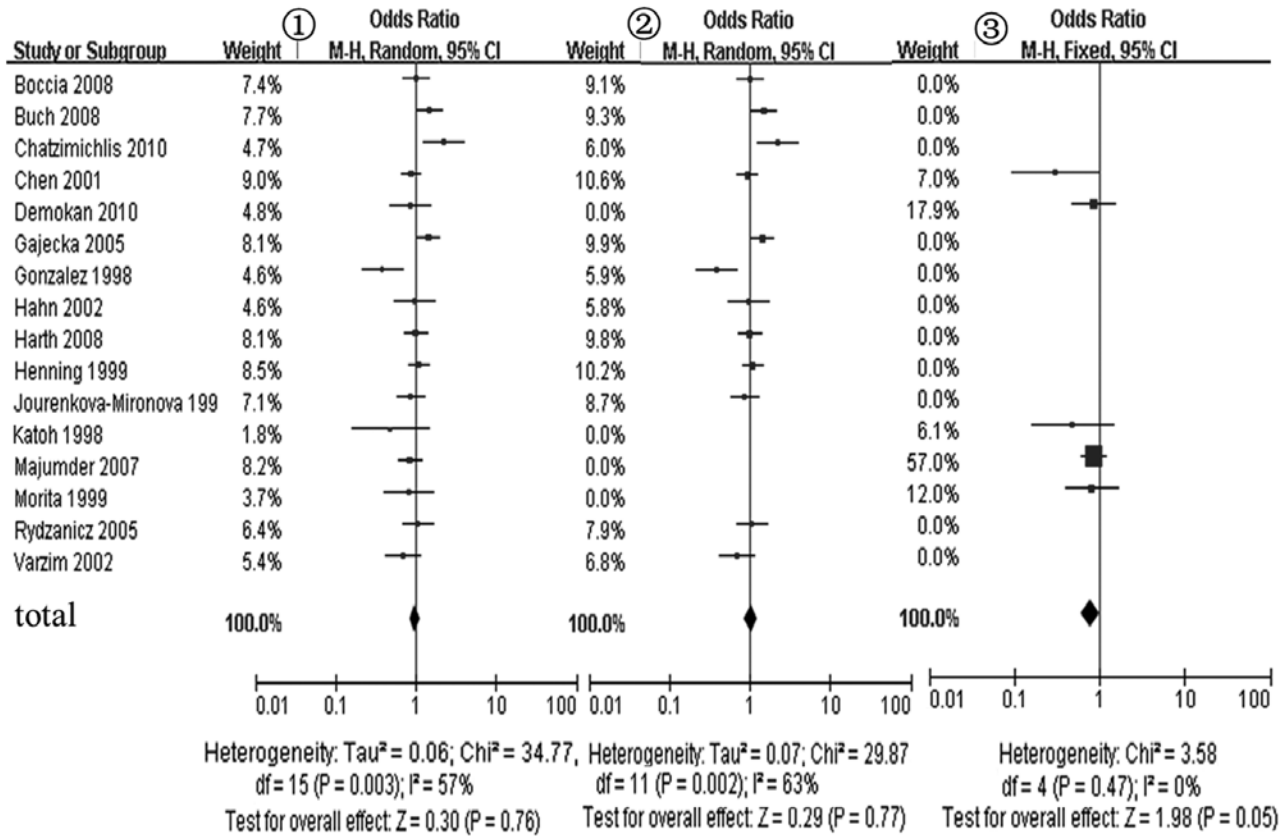

Figure 2. Forest plot showing the association between the rapid acetylator phenotype in NAT2 and risk of head and neck carcinoma. ①, in overall population; ②, in Caucasian population; ③, in other population.

omitting each study, one at a time. This procedure proved that our results were reliable and robust.

Publication bias. Begg's funnel plots and Egger's tests were conducted to graphically estimate the publication bias of the included literature. The shape of funnel plots revealed no obvious asymmetry. In addition, Egger's test also indicated no significant publication bias in this meta-analysis (t=-1.09, P=0.293).

Discussion

As a well-known environmental risk factor, tobacco contains numerous potential carcinogens, including PAHs, which require bioactivation or inactivation via a series of enzymes. To the best of our knowledge, N-acetylation is a crucial step during the activation of tobacco-related carcinogens (35), therefore tobacco-associated cancers may be associated with the NAT enzyme. Human N-acetyltransferase has two subtypes, NAT1 and NAT2. The *NAT2* gene is located on the chromosome 8p21.3-23.1 and 8p22, and it encodes a 290-amino-acid protein (35,36). As an essential phase II enzyme, NAT2 is key in the process of cancer development. However, the carcinogenesis of tobacco is relatively complex and the role of NAT2 described in different studies is not entirely consistent. In the studies concerning the association of *NAT2* polymorphisms with the increased risk of gastric cancer, Shen *et al* (37) indicated that the rapid acetylator was the protective factor for the development of gastric cancer, whereas Ladero *et al* (38) suggested that it was regarded as a risk factor. However, results in other relevant studies demonstrated that no significant association between *NAT2* polymorphisms and gastric cancer was found (37,39,40). This discrepancy has also existed in the studies of other tobacco-associated cancers, including lung cancer (41-43) and prostate cancer (44-46). Similar results were also found in the studies of HNC, which is strongly associated with tobacco smoking (6). In their study, Gara *et al* indicated that the T341C mutation of the *NAT2* gene (slow allele) was associated with an elevated risk of HNC in the Tunisian population (47). Unal *et al* (48) and Lei *et al* (49) also found that the NAT2 slow acetylator phenotype may increase the risk of susceptibility to laryngeal carcinoma. Among the 16 studies included in this meta-analysis, 2 studies suggested that the NAT2 rapid phenotype was associated with the risk of HNC (19,20), whereas 1 study suggested that it acted as a protective factor for HNC (34). In the remaining 13 studies, no significant association was found between NAT2 phenotypes and cancer risk. These results may be attributable to inter-individual variation (including ethnicity, and the status and level of smoking and alcohol consumption), and may also be due to the limitation of the sample size of these studies. Our meta-analysis included 2,965 cases with HNC and 3,919 controls, and we found no significant association between the NAT2 phenotype and HNC risk. The findings indicated that variations of NAT2 acetylator phenotype may not affect the development of HNC.

The *NAT2* gene has several polymorphisms; at present, 66 alleles have been described (http://www.louisville.edu/

medschool/pharmacology/NAT.html, updated on July 22, 2011). The distributive proportion of NAT2 acetylator phenotypes varies in populations according to ethnicity and geographic origin. The percentage of slow acetylators is 40-70% in Europe, approximately 10% in Japan, 5% in Eskimos and 87% in Egyptians (9). This suggested that NAT2 play different roles in the development of various types of cancer among different ethnic groups. However, in our meta-analysis, we found no significant association between the NAT2 rapid acetylator phenotype and the risk of HNC in either the Caucasian or other mixed population.

Although our meta-analysis pooled 16 relevant studies and the combined results may be more precise than each study individually, several limitations of this meta-analysis should be addressed. Firstly, although 16 studies were included with 2,965 cases and 3,919 controls, the number of studies remained insufficient and the sample size was relatively small, particularly for stratified analysis. This may have limited our ability to detect a certain degree of association. Secondly, in the subgroup analysis of ethnicity, the included studies involved only Caucasian, Asian and Turkish populations. For Asians, only 525 cases and 660 controls were used and for Turkish, only 1 study (involving 95 cases and 93 controls) was conducted. These numbers do not provide sufficient statistical power to evaluate the effect of the NAT2 phenotype on HNC risk in different ethnicities. Thirdly, heterogeneity was found among studies. We applied a random-effect model, but this did not exclude the effect of heterogeneity between studies, even though its effect may have been limited. Finally, although the selection of cases and controls in each study was well defined with the same inclusion and exclusion criteria, the potential confounding factors that affected our results may not have been taken into account. In spite of these limitations, our meta-analysis pooled the number of cases and controls from different studies and significantly increased the statistical power of the analysis.

In conclusion, this meta-analysis, including 16 case-control studies, suggests that there is no significant association between the NAT2 phenotype and the increased risk of HNC. Since few studies are available in this field, the results of this study should be further confirmed by single large sample case-control studies with well-designed, well-matched controls, particularly in populations other than Caucasian. In addition, the correlation between the NAT2 phenotype and HPV-associated HNC should be investigated.

Acknowledgements

We are indebted to the authors of the primary studies.

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