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Original Article

N-Acetyltransferase 2 (*NAT2*) genetic variation and the susceptibility to noncardiac gastric adenocarcinoma in Taiwan

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Abstract

Background: *N*-Acetyltransferase (NAT) is an important enzyme with the capacity to metabolize carcinogenic aromatic amines. However, it remains controversial whether the encoded functional *NAT2* genetic polymorphism is related to the risk of gastric adenocarcinoma (GA). The aim of this study was to evaluate the association between *NAT2* genetic variation and gastric adenocarcinoma (GA), with special reference to the gastric noncardiac adenocarcinoma (GNA).
Methods: Peripheral white blood cell DNA from 368 GA patients and 368 age- and sex-matched controls were genotyped for *NAT2* by a polymerase chain reaction method. The lifestyle habits of the participants were assessed using a semiquantitative food−frequency questionnaire. *NAT2* genotype, interaction with lifestyle habits, and the risk of GA and GNA were analyzed by logistic regression.
Results: GA patients were more likely to have a smoking habit, ate more salted foods, and consumed more well-done meat than the controls. There was no association between the *NAT2* genotypes and susceptibility to GA. However, if patients with gastric cardiac adenocarcinoma (GCA; $n = 42$) were excluded, the *NAT2* slow acetylators (without rapid acetylator allele) had a higher risk of GA than intermediate and rapid acetylators (odds ratio = 1.53; 95% confidence interval, 1.05−2.23, $p = 0.027$). In addition, there was a synergic effect of *NAT2* slow acetylator and well-done meat intake to the development of GNA (odds ratio = 3.83; 95% confidence interval, 1.68−8.76, $p = 0.001$).
Conclusion: *NAT2* slow acetylators have a higher risk of GNA than intermediate and rapid acetylators have in a Taiwanese population. The intake of well-done meat, an additive to the acetylator status, may contribute to the incidence of gastric carcinogenesis.

Keywords: arylamine *N*-acetyltransferase; gastric adenocarcinoma; gastric cancer; stomach neoplasms

1. Introduction

Aromatic amines (including heterocyclic amines and arylamines) formed from cigarette smoking and food cooked well-done are potent precarcinogens or carcinogens.[1] Aromatic amines are principally disposed of by *N*-acetyltransferase (NAT), in cooperation with a few phase 1or 2 enzymes.[2−5] The NAT enzymes are mainly encoded by the *NAT2* gene, which has many functional single nucleotide polymorphisms (SNP). The number of wild-type *NAT2*4* allele is divided in humans into rapid (2 alleles), intermediate (1 allele), and slow acetylators (none).[3,5] These different acetylator statuses may carry different individual susceptibilities to many cancers and diseases.[6−13] Among them, the association of gastric adenocarcinoma (GA) and *NAT2* genotypes has recently garnered much attention.[14−25]

GA is one of the most common cancers in many countries. The stomach is the primary gateway for nourishment, and thus

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

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speculated to be exposed to many precarcinogens and carcinogens. It is also believed that the pathogenesis of GA is multifactorial and interactive with genetic and environmental factors.[26] Although heterogeneity exists in earlier studies, a meta-analysis has shown no association between *NAT2* polymorphism and GA susceptibility.[24] However, a more recent meta-analysis suggested that *NAT2* acetylator status has an effect on the risk of GA among East Asians.[25] In addition, lifestyle habit is a crucial environmental factor, which may interact with genetic factors to promote the development of GA.[17−22] The information of lifestyle habit and other confounding factors was controversial and complex in the *NAT2* gene−GA association studies.[17−22] Furthermore, gastric cardiac adenocarcinoma (GCA) was believed to have different characteristics and risk factors from gastric noncardiac adenocarcinoma (GNA).[27−29] However, all prior relevant literature did not further analyze the subgroups of GCA and GNA.[14−25] The aims of this study were to explore the relationship between *NAT2* genetic variation and GC in a Taiwanese population, with special reference to GNA, and also to investigate the gene-environment interactions with different lifestyle habits to the susceptibility of GA.

2. Methods

2.1. Study population

A total of 368 consecutive patients with pathology-confirmed gastric adenocarcinoma were prospectively enrolled in this study from 2001 to 2005. The other 368 sex- and age-matched (±3 years) patients without GC were recruited as controls. These controls were the in- or outpatients of our hospital, who had received pan-endoscopy examination and the results turned out be no GA.

GCA was defined as the tumor located only in the cardiac region of the stomach, or tumors located primarily in the cardiac region with slight involvement of the fundus.[27]

The participants were interviewed after written consent was obtained, and they completed an abbreviated food frequency questionnaire. Those patients who declined to give consent or who failed to answer the questionnaire were excluded. This study protocol was approved by the Institutional Review Board of Taipei Veterans General Hospital, Taipei, Taiwan.

2.2. Lifestyle evaluation

The lifestyle evaluation of this study was mainly focused on dietary habits. These habits were assessed using a semi-quantitative food frequency questionnaire, modified from a previously validated instrument.[10,30] This questionnaire included common food items with specified serving sizes that were described using natural portions of standard weight and volume measures of the servings commonly consumed in this study population. Cue cards were used to help identify serving sizes of individual food. Participants were asked how often, on average over the past year, they consumed that amount of each food. Participants chose one of seven frequency categories, which ranged from “Never” to “Six or more times daily”. The selected frequency categories for most food items were converted to a daily intake. As the average level of alcohol consumption in Taiwan is modest, habitual alcohol drinking was defined as consuming at least 30 g of alcohol, on average, daily for >10 years.

2.3. NAT2 genotyping

DNA was isolated from frozen white blood cells of the participants. The *NAT2* genotype was determined by the SNP-specific polymerase chain reaction (PCR), adopted from the studies by Hein and Doll.[31,32] This method can identify the seven most frequent SNPs: 191G > A (rs1801279), 282C > T (rs1041983), 341T > C (rs1801280), 481C > T (rs1799929), 590G > A (rs1799930), 803A > G (rs1208), and 857G > A (rs1799931). The wild-type allele detected was *NAT2*4*. Both *NAT2*4* and *NAT2*13* were regarded as rapid acetylator alleles, with other genotypes noted as slow acetylator alleles.[1,2] The presence of any two slow acetylator mutant alleles defines the slow acetylator genotype, whereas intermediate and rapid acetylators have one and zero slow acetylator alleles, respectively. Laboratory personnel were blinded to the case−control status.

2.4. Statistical analysis

Expected gene frequencies were calculated from respective single allele frequencies using the Hardy−Weinberg equation, wherein the observed and expected gene frequencies were compared using the chi-square goodness-of-fit test. Chi-square test was used for categorical data. The odds ratio (OR) with a 95% confidence interval (CI) of the possible risk factors for GA was calculated by logistic regression. The effect of modifying the relationship between the *NAT2* acetylator status and GA by lifestyle habit was assessed using a multivariate logistic regression analysis. This was done to compare the goodness of fit of the model containing an interaction term (*NAT2* acetylator status × lifestyle habit) with a reduced model containing indicator variables of the main effects of acetylator status and lifestyle habit.[10] Overall survival (OS) was estimated from survival curve based on the Kaplan−Meier method, and the log−rank test was used to compare the OS between different *NAT2* acetylator statuses. Statistical tests were based on a two-tailed probability. A p value < 0.05 was considered significant. All of the above-mentioned analyses were performed using SPSS 17.0 software (SPSS Inc., Chicago, IL, USA). In addition, G*Power 3.1.7 (Heinrich Heine University Düsseldorf, German) was used to estimate the required sample size. Under the assumption of effect size = 0.15, $\alpha = 0.05$, and power = 0.80, the total sample size was 349.

3. Results

Among the lifestyle risk factors, habitual alcohol drinking, vegetable, fruit consumption, and Lauren's histological type were not shown to be associated with GA (Table 1). However,

GA patients had elevated frequencies of smoking habit, salted food, and fried oily meat intake than controls.

The *NAT2* genotype was in Hardy–Weinberg equilibrium in the GA and control groups ($p = 0.87$ and $p = 0.06$, respectively). There was no association between the susceptibility to GA and the *NAT2* genotypes and three acetylators status (Table 2). However, if patients with GCA ($n = 42$) were excluded, the *NAT2* slow acetylators (without rapid acetylator allele) had a higher risk of GA than intermediate and rapid acetylators (odds ratio = 1.53; 95% confidence interval, 1.05–2.23, $p = 0.027$, Table 3). In addition, there was significant interaction between *NAT2* slow acetylator and high intake of well-done meat (odds ratio = 3.83; 95% confidence interval, 1.68–8.76, $p = 0.001$, Table 3).

Table 4 shows that there was no association between Lauren's histological type and *NAT2* acetylator status.

It was found that GNA patients with slow acetylators had a trend of poor OS, compared with those with rapid/intermediate acetylators. However, this finding did not reach a level of statistical difference (Fig. 1).

Table 2
Genotypes of *NAT2* in patients with gastric cardiac adenocarcinoma (GCA), gastric noncardiac adenocarcinoma (GNA) and controls.[a]

Acetylator status	GCA($n = 42$) *n* (%)	GNA ($n = 326$) *n* (%)	Controls ($n = 368$) *n* (%)
Rapid	13 (31.0)	89 (27.3)	108 (29.3)
*NAT2*4/*4*	13	88	106
*NAT2*4/*13*	0	1	2
Intermediate	24 (57.1)	161 (49.4)	199 (54.1)
*NAT2*4/*5B*	2	8	12
*NAT2*4/*6A*	16	94	117
*NAT2*4/*7B*	6	59	69
*NAT2*13/*6A*	0	0	1
Slow	5 (11.9)	76 (23.3)	61 (16.6)
*NAT2*5B/*6A*	0	7	5
*NAT2*5B/*7B*	0	4	3
*NAT2*6A/*6A*	2	21	17
*NAT2*6A/*7B*	2	30	27
*NAT2*7B/*7B*	1	14	9

GCA = gastric cardiac adenocarcinoma; GNA = gastric noncardiac adenocarcinoma; NAT = *N*-acetyltransferase.

[a] No statistical difference of *NAT2* genotype and *NAT2* acetylator status among the three groups.

4. Discussion

The NAT enzyme is crucial to disposing of carcinogenic aromatic amines, which can arise from the extent to which meat is cooked well-done, and cigarette smoking. The present study suggests that *NAT2* slow acetylators had a higher risk of GA than intermediate and rapid acetylators, after excluding the patients with GCA. In addition, well-done meat intake had a synergic effect with *NAT2* slow acetylator status to confer the development of GNA.

As to the GA and *NAT2* genetic variation, the results of the previous studies were inconclusive. A few studies have suggested that slow or rapid acetylator status was related to the GA carcinogenesis.[16,22,23] However, many other studies have disproved this association.[14–21] One previous meta-analysis has shown no association of *NAT2* polymorphism and GA susceptibility.[24] However, considering the heterogeneity of the relevant studies, a more recent meta-analysis suggested that *NAT2* acetylator status has an effect on the risk of GA among

Table 1
Characteristics and risk factors of patients with gastric cardiac adenocarcinoma (GCA), gastric noncardiac adenocarcinoma (GNA) and controls.

		GCA ($n = 42$) *n* (%)	GNA ($n = 326$) *n* (%)	Controls ($n = 368$) *n* (%)	*p*
Sex	M	31 (73.8)	215 (66.0)	246 (66.8)	0.60
	F	11 (26.2)	111 (34.0)	122 (33.2)	
Age (y)	≥60	29 (69.0)	231 (70.9)	257 (69.8)	0.94
	<60	13 (31.0)	95 (29.1)	111 (30.2)	
Smoking	Yes	15 (35.7)	118 (36.2)	80 (21.7)	<0.001*
	No	27 (64.3)	208 (63.8)	288 (78.3)	
Alcohol drinking	Yes	7 (16.7)	51 (15.6)	42 (11.4)	0.22
	No	35 (83.3)	275 (84.4)	326 (88.6)	
Vegetable consumption (serving/d)	Low (≤1)	12 (28.6)	99 (30.4)	103 (28.0)	0.79
	High (>1)	30 (71.4)	227 (69.6)	265 (72.0)	
Fruit intake (serving/d)	Low (≤1)	9 (21.4)	80 (24.5)	73 (19.8)	0.33
	High (>1)	33 (78.6)	246 (75.5)	295 (80.2)	
Salted food intake (serving/wk)	Low (≤2)	32 (76.2)	253 (77.6)	312 (84.8)	0.04*
	High (>2)	10 (23.8)	73 (22.4)	56 (15.2)	
Well-done meat intake (serving/wk)	Low (≤2)	30 (71.4)	188 (57.7)	273 (74.2)	<0.001*
	High (>2)	12 (28.6)	138 (42.3)	95 (25.8)	
Lauren's histological type[a]	Intestinal	17 (51.5)	142 (47.8)	—	0.82
	Diffuse	13 (39.4)	133 (44.8)	—	
	Mixed	3 (9.1)	22 (7.4)	—	

*$p < 0.05$.

F = female; GCA = gastric cardiac adenocarcinoma; GNA = gastric noncardiac adenocarcinoma; M = male.

[a] Lauren's histological type was available in 297 (91.1%) of GNA patients and 33 (78.6%) of GCA patients.

Table 3
Odds ratio of risk factors and interaction with *NAT2* slow acetylator for gastric noncardiac adenocarcinoma.

Risk factors	Odds ratio	95% CI	*p*
NAT2 slow acetylator	1.53	1.05−2.23	0.027*
Smoking	2.04	1.46−2.86	<0.001*
Salted food	1.61	1.09−2.36	0.016*
Well-done meat	2.11	1.53−2.91	<0.001*
NAT2 slow acetylator × smoking	1.07	0.47−2.41	0.872
NAT2 slow acetylator × salted food	4.39	0.51−37.51	0.177
NAT2 slow acetylator × well-done meat	3.83	1.68−8.76	0.001*

*$p < 0.05$.
CI = confidence interval; NAT = *N*-acetyltransferase.

East Asians.[25] Therefore, the real association of GA and *NAT2* genetic polymorphism is still debatable.

Consistent with most of the previous studies,[14−21] we could not prove the association of GA and *NAT2* acetylator status in the present study. However, we found the existence of this association in the patients with GNA. Although GCA is usually categorized into the scope of GA anatomically, many studies have regarded GCA as a different disease entity from GNA.[27−29] This viewpoint is further supported from the fact that the rapid increase in the incidence of GCA worldwide in the past two decades, by contrast to the decline of GNA.[28,29] Compared with GNA, GCA seems to have a higher incidence of salted food intake and well-done meat intake.[27−29] All the previous *NAT2*-GA association studies have not specified the percentage of GCA in their GA patients.[14−25] It is possible that GCA patients were enrolled into their statistical analysis, which made the different results from ours.

Besides including GCA or not into the study, case number is another important factor that affects the results. Of the studies, the Chinese cohort had the largest case number ($n = 503$), which has shown the association of *NAT2* slow acetylators with GA.[22] This finding is compatible with ours, although the statistical significance only existed when GCS patients were excluded in our study. It is probable that the Chinese and Taiwanese share the similar *NAT2* genetic distribution and dietary habits, therefore they confer to the same *NAT2*−GA association. Furthermore, the small sample size of most of the previous studies may easily lead to a Type II error, compared with the Chinese study.[22]

Table 4
The association of *NAT2* acetylator status and Lauren's histological type in patients with gastric adenocarcinoma.

Acetylator status	Intestinal ($n = 159$) *n* (%)	Diffuse ($n = 146$) *n* (%)	Mixed ($n = 25$) *n* (%)	*p*
Rapid	40 (25.2)	41 (28.1)	8 (32.0)	0.75
Intermediate	86 (54.0)	73 (50.0)	10 (40.0)	
Slow	33 (20.8)	32 (21.9)	7 (28.0)	
Rapid/intermediate	126 (79.2)	114 (78.1)	18 (72.0)	0.72
Slow	33 (20.8)	32 (21.9)	7 (28.0)	

NAT = *N*-acetyltransferase.

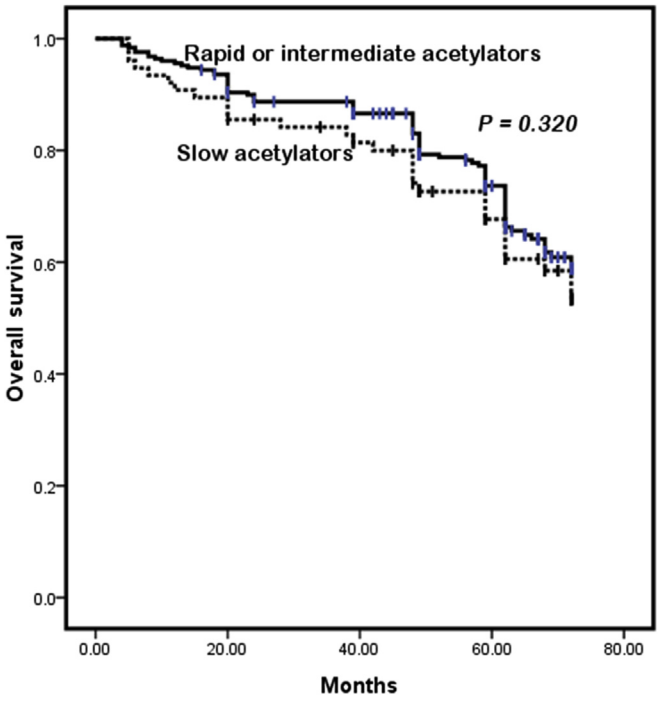

Fig. 1. Overall survival in patients with noncardiac gastric adenocarcinoma. There was no statistical difference between rapid/intermediate acetylators and slow acetylators.

Dietary habits are believed to be crucial environmental factors that may modify the risk of many cancers, such as GA and colorectal cancer.[5,6,10,17−22] Aromatic amines or heterocyclic amines, derived from cooked meat, are the principal carcinogens metabolized by the NAT enzyme.[1] The traditional Chinese method of cooking meat is to chop the meat into pieces and then fry it over a raging fire with plenty of animal oil. This culinary method of meat preparation is equivalent to cooking steak well done in Western cuisine, and may induce a high level of heterocyclic amines. Therefore, we specified the item of well-done meat consumption in our study and we found the synergic interaction of high intake of well-done meat and slow acetylator status in the development of GNA. The OR of GNA was 1.53 for slow acetylators, which was increased to 3.83 after interaction analysis. The result further supports the idea that genetic factors may interact with environmental factors to confer different susceptibility to cancers.

The other two significant lifestyle risk factors found in this study were smoking habit and salted food intake, both of which were believed to produce many carcinogens and precarcinogens.[1,26] However, both of them were found to have no additive effect on the *NAT2* slow acetylators to the GNA (Table 3). It is possible that well-done meat intake can produce more aromatic amines than smoking and salted food can. Therefore, only the well-done meat can present the augmentative effect with slow acetylators to GNA.

One recent study from Korea, which included patients with similar genetic background and dietary habits to China, did not demonstrate the association of *NAT2* genotype alone with

GA.[21] However, they found that slow/intermediate acetylators have a higher risk of GA, after interaction with elevated intake of well-done meat, kimchi, and soybean pastes. This finding is consistent with our result. However, the limitation of this comparison is that the Korean study gathered the slow and intermediate acetylators into one group, whereas most of the previous studies, including ours, categorized the intermediate and rapid acetylators into one group.[24,25] Furthermore, we do not know if the patients with GNA were enrolled into the Korean study or not, which may affect the results as earlier referenced.

Genetic variation of NAT2 may alter enzymatic activity and affect the susceptibility to many other cancers and diseases.[5,6] The previous studies have shown that slow acetylators have a higher risk of bladder cancer and hepatocellular carcinoma (HCC),[6,7,11] which is compatible with the finding of the present study. However, rapid acetylators have been suggested to increase the susceptibility of colorectal cancer and HCC in other studies.[6,8,10] It seems complicated and confusing that the *NAT2* acetylator statuses have different impacts on the various cancers. This may in part be explained by the differences in the carcinogenesis of cancers, environmental factors, and *NAT2* genetic distributions in varied ethnic populations. Furthermore, human acetylation polymorphism influences both the metabolic activation (*O*-acetylation) and deactivation (*N*-acetylation) of aromatic amines via the polymorphic expression of *NAT2*. It has been hypothesized that the increased susceptibility to bladder cancer for slow acetylators is associated with the decreased deactivation of aromatic amines by *N*-acetylation in the liver, so that excess aromatic amines can reach the bladder epithelium.[6,11] The deactivation pathway (*N*-acetylation) may compete with the activation pathway (*N*-hydroxylation and *O*-acetylation), and both of the pathways are catalyzed by NAT and related to *NAT2* genetic variation.[1−6] Whether NAT primarily serves as an activating or a deactivating enzyme depends on the final consequence of the competition of all these pathways.

In conclusion, the present study suggests that *NAT2* slow acetylators have a higher risk of GNA than intermediate and rapid acetylators have in Taiwanese. Well-done meat consumption has a synergic interaction with slow acetylator status to the development of GNA.

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