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NAT2 polymorphism in Omani gastric cancer patients-risk predisposition and clinicopathological associations

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Abstract

AIM: To study whether N-acetyltransferase 2 (*NAT2*) genotypes and phenotypes are associated with increased risk factor for gastric cancer in Omani patients and to study the clinico-pathological correlations and the prognostic significance of *NAT2*.

METHODS: Genomic DNA was extracted from peripheral blood of 100 gastric cancer patients and 100 control subjects. *NAT2* genotyping was performed using DNA sequencing. The prognostic significance of *NAT2* and other clinicopathological features was assessed by univariate and multivariate analyses.

RESULTS: We observed no significant association between *NAT2* genotypes and phenotypes and gastric cancer risk. The *NAT2* phenotype polymorphisms and gastric cancer risk predisposition were not modified by concomitant *H pylori* infection and smoking. There was no significant association between *NAT2* and clinicopathological features, and *NAT2* had no independent prognostic significance.

CONCLUSION: In the current study, *NAT2* genotypes and phenotypes are not associated with gastric cancer risk predisposition. Moreover *NAT2* phenotypes had no clinicopathological associations or prognostic significance.

Key words: Gastric cancer; Polymorphism; *NAT2*; *H pylori*; Arab; Omani

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INTRODUCTION

Gastric cancer is the second most common cancer worldwide and exhibits a widely varying geographical distribution, making it a significant problem in global health[1] It is the most common cancer in the Sultanate of Oman, with an age-adjusted annual incidence in 2002 of 54/100 000 among males and 22/100 000 among females[2].

Gastric carcinogenesis is a complex process resulting from interactions between genetic and environmental factors[3]. *H pylori* infection is an established risk factor for gastric cancer, triggering chronic inflammation of the stomach leading to stepwise development of the malignancy[4,5]. Behaviors such as smoking, alcohol consumption, and low intake of fruits or vegetables have also been strongly implicated[5,6].

The genetic risk factors are less well characterized and, overall do not follow simple Mendelian inheritance patterns. Ethnic differences and familial clustering suggest a genetic susceptibility to development of gastric cancer following exposure to possible carcinogens[7]. There is increasing evidence that polymorphic genes encoding for xenobiotic-metabolizing enzymes such as *NAT2* and GST M1/T1 and for cytokines such as interleukin-1 beta and interleukin-1 receptor antagonist may play a role in determining differences in cancer susceptibility[8-10]. Therefore, they should be studied to identify links to environmental factors.

Enzymatic activation and detoxification of carcinogens is a major principle in chemical carcinogenesis. Many chemical and dietary carcinogens, such as nitrosamines and heterocyclic amines, are bioactivated and deactivated by cytochrome P-450 and N-acetyltransferase (*NAT*)

enzymes[11]. The *NAT* genotypes are polymorphic and phenotypically they are generally described as rapid and slow acetylators[9]. This genetically determined, relative *NAT* activity has been associated with several cancers[9]. It has been reported that individuals with rapid-acetylator genotypes of *NAT2* may be at increased risk of liver and colon cancer, hepatocellular carcinoma, and colorectal cancer when exposed to environmental arylamine carcinogens, due to *NAT2* rapid acetylator-mediated O-acetylation[9]. However there is scant literature on a possible association between *NAT2* polymorphism and gastric cancer. Only five previous studies have been published, with conflicting results: one of the five studies found an association[12-16].

The present study was undertaken in an Omani Arab population to examine whether *NAT2* genotypes and phenotypes are associated with increased risk of gastric cancer when compared with controls. We also investigated the association between *NAT2* polymorphisms and clinicopathological features of gastric cancer.

MATERIALS AND METHODS

Study subjects

The study population consisted of a series of consecutive unrelated gastric cancer patients diagnosed in three main hospitals in the Sultanate of Oman (Sultan Qaboos University Hospital, Royal Hospital, and Sohar Hospital). The control group was composed of apparently healthy population-based subjects of the same ethnic and geographical origin as the patients. The Medical Research and Ethics Committee of the College of Medicine of Sultan Qaboos University approved the study design. The study subjects gave informed consent prior to participation in the study.

Genotyping method

The methodology has been described by Tanira *et al*[17] and correlated with Restriction Fragment Length Polymorphism (RLFP). Ten ml of blood was collected in an EDTA tube and stored frozen until DNA extraction. DNA was extracted from whole blood using a commercial DNA blood kit (Puregene DNA purification kit, Gentra, USA) and stored until used for genotyping. Amplification was carried out by PCR, using 0.2 μmol/L oligonucleotide primers Nat-Hu 14 (forward primer; 5'-GAC ATT GAA GCA TAT TTT GAA AG-3') and Nat-Hu 16 (reverse primer; 5'-GAT GAA AGT ATT TGA TGT TTA GG-3') in a 100 μL mixture of 0.01 mol/L Tris buffer (pH 8.3), 2.5 mmol/L $MgCl_2$, 1.25 μmol/L each dNTP, 1.25 U Taq polymerase, and 2 μL (20 ng) genomic DNA. The reagents and mixture were kept on ice during preparation. A negative control (DNA not added) was used for quality control. Amplification conditions were as follows: 95℃ for 5 min, 35 cycles (94℃ 30 s, 56℃ 1 min, 72℃ 2 min), then 72℃ for 8 min. The PCR product was subsequently sequenced on an ABI PRISM 3100 sequencer using the BigDye Terminator v3.1 Cycle Sequencing method (Applied Biosystems) as recommended by the manufacturer. Candidate Single Nunclutide Polymprphism (SNP) regions were detected and typed with the aid of DNA Star Software. The genotype of each subject was determined as per the *NAT2* nomenclature scheme published by Hein *et al*[9] and the following website: http://www.louisville.edu/medschool/pharmacology/NAT.html.

H pylori status

H pylori status was determined using serum specimens and an enzyme-linked immunosorbent assay (ELISA) for *H pylori* IgG antibody (INOVA Diagnostics Inc., Germany). Negative status was defined as a concentration below 20 U/mL as described by the manufacturer.

Statistical analyses

The genotype distributions of different polymorphic loci in the controls were compared to those expected from Hardy-Weinberg equilibrium by χ^2 tests. The difference in frequency distributions of genotypes between the patient and the control groups was also tested by χ^2 test. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated by logistic regression analysis.

Overall survival was determined from the time of biopsy-proven diagnosis until the time of death or last known follow-up. The dates of death were obtained from medical records or by phone contact. Data of patients who died of causes other than the primary disease were censored. The Kaplan-Meier method was used to estimate overall survival time, and the statistical significance was determined by log-rank test. The Cox regression stepwise approach (proportional hazard model) was used to identify prognostic factors in multivariate analysis. The following prognostic factors were included in multivariate analysis: age, gender, tumor location, Lauren's classification, T stage, lymph node involvement, *NAT2* phenotype, and *H pylori* status. *P* values of less than 0.05 were considered statistically significant. Analysis of data was performed using SPSS 10.0 software.

RESULTS

A total of 100 gastric cancer patients and 100 unrelated controls were included. The age range for the participants included in the study was 21-82 years, where the mean and standard deviation of ages for the patients and controls were 54.6 ± 11.8 and 34.6 ± 12.7 years, respectively. The percentage of males in the patient group was 55.6% and 60% in the control group.

Gastric cancer and NAT2 polymorphism and allele

We tested SNPs in the *NAT2* gene at positions 191, 282, 341, 481, 590, 803, and 857, as shown in Table 1. In the control population, C292T was found to be the most predominant mutation whereas; the mutation G857A was the least observed. There was a strong association between *NAT2* SNP A803G and gastric cancer ($P = 0.001$), with an increase in odds ratio (OR) of 3.1 (95% CI 1.5-6.3). There was a statistical trend for SNPs T341C and C481T and gastric cancer (Table 1). No case of the mutation G191A was observed, either in cases or controls.

Table 1 Distribution of seven polymorphisms in the *NAT2* gene among 100 gastric cancer patients and 100 controls, and cancer risk predisposition

	G191A		C282T		T341C		C481T		G590A		A803G		G857A	
	Con	C	Con	C	Con	C	Co	C	Co	C	Co	C	Co	C
Frequency	0.0	0.0	0.39	0.35	0.36	0.44	0.31	0.41	0.35	0.29	0.39	0.52	0.09	0.05
W/W	100	76	46	43	42	29	49	35	42	49	39	17	83	87
W/M	0	0	30	44	44	53	39	47	46	44	44	60	17	10
MM	0	0	24	13	14	18	12	18	12	7	17	22	0	1
P	NS		0.8		0.08		0.06		0.4		0.001		0.6	
OR	-		1.1		1.3		1.8		0.7		3.1		0.7	
(95% CI)			(0.6-2.1)		(0.9-1.7)		(0.9-3.3)		(0.4-1.4)		(1.5-6.3)		(0.3-1.7)	
M carrier														

Table 2 *NAT2* genotype frequencies among 100 gastric cancer patients and 100 controls, and gastric cancer risk

Genotype	Patients	Controls	OR	95% CI
Rapid				
#4#4	1	4	0.3	0.01-2.4
#12B#12B		1		
#12#12		1		
Intermediate				
#4#5B	14	10	1.4	0.6-3.6
#4#6A	6	4	1.5	0.4-6.6
#4#6B		3		
#5B#13	1	1		
#6A#12C	2			
#6B#13	2			
#12#6B	1			
#12#7B	1			
#12C#6A		2		
#12C#6B		1		
Slow				
#5A#6A	2	1		
#5B#5B	18	13	1.4	0.6-3.2
#5B#5C	2	2		
#5B#6A	19	13	1.5	0.6-3.3
#5B#6B	2	4	1	
#5B#7A	1	1		
#5B#7B	4	1	1	
#5C#5A	2			
#5C#5C	2	1		
#5C#6A	4	4		
#5C#7B	1			
#6A#6A	4	11	0.4	0.1-1.3
#6A#7B	1	4		
#6C#6C	5	4		
#7A#7A	1	2		
#7A#11A	1	2		
#6A#6C	5	4		
#7B#7B	1	1		
#5D#5D, #5D#7A, #5D#7B, #6#7B, #7B#5A, #7B#6B, #5C#6B		7[1]		

[1]Each of these genotypes had an incidence of one per genotype.

Table 3 Frequency of *NAT2* phenotypes, *H pylori* status in gastric cancer cases and controls, and gastric cancer risk predisposition

Characteristics	Cases (*n* = 100)	Controls (*n* = 100)	Odd ratio (95% CI)	*P*
Nat-2 phenotype				
Slow	72	73	1	
Rapid + intermediate	28	27	1.1 (0.5 – 2.1)	0.90
H pylori+				
Negative	28	43	1	
Positive	57	41	2.1 (1.1 – 3.9)	0.02

+*H pylori* serology was determined in 85 patients and 84 control subjects.

Table 4 Relationship between NAT-2 and gastric cancer after adjusting the effect of *H pylori*

H pylori+ serology	NAT-2 phenotype	Cases (*n* = 85)	Controls (*n* = 84)	Total	Odd ratio (95% CI)	*P*
Positive	Slow	42	29	71	1	
	Rapid	16	12	28	0.92 (0.35, 2.45)	0.85
Negative	Slow	17	33	50	1	
	Rapid	10	10	20	1.94 (0.60, 6.35)	0.21

+*H pylori* serology was available for 85 patients and 84 control subjects.

We did not observe any significant association between any *NAT2* genotype and gastric cancer (Table 2).

Gastric cancer and NAT2 phenotype

The predominant phenotype in control and gastric cancer patients was the slow phenotype (Table 3). Both homo- and heterozygotes for the rapid acetylation allele behave phenotypically as rapid acetylators. Therefore, calculation of OR based on two categories, slow versus rapid and intermediate, revealed no significant increase in gastric cancer risk, with OR 1.1 (95% CI 0.5-2.1). However, the presence of *H pylori* shows an important role in the causation of the disease (OR = 2.1, $P = 0.02$).

In order to investigate whether H pylori modifies the risk behavior of *NAT2* phenotypes in the development of gastric cancer, we estimated the pooled odds ratio for *NAT2* phenotype and gastric cancer status after adjusting the effect of *H Pylori* as shown in Table 4. Test for homogeneity of odds ratios shows $\chi^2 = 1.134$, df = 1, $P = 0.28$. Therefore, no significant difference exists between the two odds ratios ($P > 0.050$). From the 2 X 2 X 2 data layout in Table 4 the Woolf-Haldane estimator of the common odds ratio is obtained as OR = 1.25 (95% CI 0.60-2.64)[18,19]. The significance of the estimated common OR was tested using Mantel Haenszel Chi-square statistic which gave a p value of 0.06[20]. Therefore, it may be concluded that in the presence of *H pylori* the risk behavior of *NAT2* increases to some extent, however, not statistically significant ($P > 0.05$).

Table 5 Association between *NAT2* phenotype and clinicopathological characteristics in 100 gastric cancer patients

Characteristics	Slow	Intermediate and rapid	*P*
Age			
Less than 40 yr	8	64	0.1
More than 41 yr	0	28	
Sex			0.7
Male	39	17	
Female	33	11	
Location			0.8
Distal	41	17	
Non-distal	31	11	
Histologic type			0.7
Intestinal	37	16	
Non-intestinal	35	12	
T stage+			0.1
T1 + T2	11	7	
T3 + T4	47	13	
N stage+			0.7
Negative	52	7	
Positive	16	3	
Overall stage[1]			0.6
Ⅰ + Ⅱ	12	6	
Ⅲ + Ⅳ	60	22	

+T and N staging was available in 78 patients were surgical resection was done. [1]Stage Ⅳ diagnosis was based on clinical staging in presence of metastatic disease.

Table 6 Independent prognostic factors for survival identified by multivariate analysis in 78 gastric cancer patients who underwent surgical resection

Characteristics	Risk Ratio	95% CI of risk ratio	*P*
Age			0.30
Less than 40 yr	1		
More than 41 yr	2.1	0.4-9.6	
Sex			0.70
Male	1		
Female	0.7	0.3-1.7	
Location			0.02
Distal	1		
Non-distal	3.2	1.3-7.8	
Histologic type			0.70
Intestinal	1		
Non-intestinal	0.5	0.3-1.7	
T stage			0.02
T1 + T2	1		
T3 + T4	4.1	1.2-13.6	
N stage			0.05
Negative	1		
Positive	7.7	1-61.5	
NAT2			0.18
Slow	1		
Rapid	1.9	0.7-5.0	
H pylori Status			0.90
Negative	1		
Positive	1.1	0.4-3.0	

The numbers of smokers in the gastric cancer group and among the control subjects were 12 and 9, respectively. There was no significant interaction between smoking and any *NAT2* phenotype and gastric cancer risk, most likely due to the small number of subjects who smoked (data not shown).

NAT2 phenotype and clinicopathological features

We examined the relationship between *NAT2* phenotype and cancer prognostic factors, such as staging, differentiation, and histologic type (intestinal *vs*. diffuse) (Table 5). We found no significant association between any of the clinicopathological features and *NAT2* phenotype. There was a statistical trend for more advanced T stage with the slow phenotype ($P = 0.1$).

Survival analysis

By the time of analysis in February 2007, the median survival rates for rapid and slow acetylators were 10.0 mo (95% CI 7.7-12.3) and 15 mo (95% CI 8.4-21.6), respectively. The 5-year survival rates were 10% and 34%, respectively ($P = 0.5$). In the non-metastatic group, the median survival for rapid acetylators was not reached, and for slow acetylators was 36 mo (95% CI 15.4-56.6), with 5-year survival rates of 50.4% and 43%, respectively ($P = 0.8$).

The multivariate analysis carried out for 78 patients who underwent surgical resection (non-metastatic and locally advanced) is presented in Table 6. There was an increased risk associated with the rapid *NAT2* phenotype (OR 1.9), but it did not reach statistical significance. Advanced stage, non-distal location, and lymph node involvement were independent negative prognostic factors.

DISCUSSION

We have assessed the association between *NAT2* gene polymorphisms and the risk of developing gastric cancer by correlation with clinicopathological features and survival in an Omani Arab population. In keeping with four of the five previously published studies, we found no difference between the rapid and slow *NAT2* phenotypes and gastric cancer risk predisposition[12-16]. Also, there was no association with any of the *NAT2* genotypes and gastric cancer. The solitary study showing a positive association between the rapid *NAT2* acetylator phenotype and gastric cancer risk by Ladero *et al*[14] has been criticized because of its small number of subjects and the inclusion of incident and prevalent cases. Of note is the great variation in the frequency of the slow acetylator phenotype in the control subjects of the different ethnic groups in these studies. The frequency of the slow acetylator phenotype was around 54% in Caucasian studies and around 6% in East Asian studies[12-16]. The frequency of slow acetylators in our control subjects was 72%, which is higher than in the Caucasian population, although consistent with previously published data from Arabs[17,21]. Given the ethnic variation in frequency it is unlikely that *NAT2* genotype and phenotype studied in isolation will impart a conclusive finding applicable to different ethnic groups. Therefore, it is important to study *NAT2* polymorphism in relation to other environmental risk factors, in particular *H pylori* infection and smoking.

We have demonstrated that positive *H pylori* serology is associated with increased gastric cancer risk in the current case-control study. Therefore, we have examined the interaction between *NAT2* phenotype and *H pylori*

infection and predisposition to gastric cancer as none of the previous studies have done so. This interaction is intriguing because several theoretical reasons. First, evidence suggests that *H pylori* infection byproducts such as ammonia (NH3) interact with several carcinogens that may be activated or deactivated by *NAT2* enzymes[22]. NH3 increases the incidence and size of gastric adenocarcinomas in rats pretreated with N-methyl-N' -nitro-N-nitrosoguanidine[23,24]. Moreover, *H pylori* infection plays a role in the pathogenesis of active chronic gastritis by generating toxic monochloramine (NH_2Cl) from an oxidant (HOCl) that is a product of activated neutrophils and NH3[25]. Second, *NAT2* enzymes may be altered by concomitant *H pylori* infection. No studies have examined this issue, but other xenobiotic-metabolizing enzyme activity is known to be altered by concomitant *H pylori* infection. Kim *et al*[26] demonstrated that diminished GST enzyme activity and increased cytochrome P-450 activity in adjacent normal and gastric cancer tissues is due to the direct effect of the *H pylori* infection. Third, it has also been suggested that *H pylori* has a *NAT* activity and that its bio-activation of food-borne heterocyclic aromatic amines into genotoxic and carcinogenic products in the stomach is a possible promoter of gastric cancer[27]. However, we found no significant modulation of gastric cancer risk by between *NAT2* phenotype and *H pylori* infection, although, estimator of the common odds ratio was OR = 1.25 with 95% CI (0.60, 2.64) with statistical trend with $P = 0.06$. This observation should be further tested in a larger scale study to examine this interaction.

To better understand the role of *NAT2* in gastric cancer, the predictive and prognostic values of *NAT2* phenotypes were evaluated. Particular attention was paid to tumor prognostic criteria, such as stage and histological type (Table 5). We found no specific prognostic significance for slow or rapid phenotypes. Similarly, univariate analysis showed no survival benefit for any of the phenotypes. In our multivariate analysis of prognostic factors in operable cancer ($n = 78$), *NAT2* was not a significant independent prognostic factor, unlike T and N stage (Table 6). These results may be interpreted as involvement of *NAT2* in the early, initiating carcinogenic steps rather than in subsequent molecular events that determine the aggressiveness of biological behavior, such as p53 or Her-2/neu mutation.

Overall, the lack of independent and consistent association between *NAT2* and gastric cancer suggests that their role may be dependent on other variables, such *H pylori* infection, smoking, or other detoxifiers of xenobiotics, such GST.

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