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Tobacco use and occupational exposure to carcinogens, but not *N-acetyltransferase 2* genotypes are major risk factors for bladder cancer in the Japanese

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Abstract Our study investigated the risks of genotypes of *N-acetyltransferase 2* (*NAT2*), tobacco use and/or occupational exposure to carcinogens in patients with bladder cancer and in age- and sex-matched controls in Japanese. *NAT2* genotypes were categorized into two groups, homozygous mutant (slow acetylator genotype) and homozygous and heterozygous wild type (fast acetylator genotype). The percentage of *NAT2* slow acetylator types was 6.7% in the bladder cancer patients, close to the value for controls (6.1%). There was no association between *NAT2* slow acetylator genotype and the risk of bladder cancer. This association was also insignificant when subjects were restricted to those who used tobacco or those occupationally exposed to carcinogens. In contrast, tobacco use in combination with exposure to carcinogens was a significant risk factor, as based on the odds ratio and chi-square test. The combination of both factors should be an additive risk factor for bladder cancer. In this study, we demonstrated that the environmental factors of smoking habit and occupational exposure for carcinogenicity are much more important than genetic factors in bladder cancer.

Key words *N-acetyltransferase 2* · Bladder cancer · Genetic polymorphism · Japanese · Occupational exposure · Tobacco use

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Introduction

Bladder cancer is associated with occupational and environmental exposure to chemical carcinogens. The manufacture of rubber and rubber products, the manufacture of dyestuffs, gas-workers and coke ovens and laboratory work are high-risk occupations. Workers in printing, aluminum refining, drivers and transport workers, machine assemblers, hairdressers, medical and nursing professions also are at risk [5]. These occupations involve use of common chemicals, arylamines that have a carcinogenic potential. Thus, between 8% and 20% of bladder cancers are attributed to the occupational exposure [18]. Arylamines are also present in the general environment, notably from cigarette smoke [8]: smoking is an important risk factor in bladder cancer [4].

Arylamines are activated by *N*-hydroxylation in the liver via cytochrome P4501A2-catalyzed reaction [10]. *N*-hydroxyl arylamine metabolites enter blood circulation systems and react with hemoglobin, forming carcinogen-hemoglobin adducts, and may even be reabsorbed into the bladder epithelium [2]. Acetylation catalyzed by *N*-acetyltransferase (NAT) is the major route of arylamine phase II metabolism. Of the two genes (*NAT1** and *NAT2**) that encode NATs, *NAT2* exhibits polymorphism due to point mutations in the coding region, and individuals can be designated as phenotypically slow or rapid metabolizers [3, 20]. Rapid acetylators are either heterozygous or homozygous for wild-type alleles of *NAT2*. Slow acetylators that carry *NAT2* mutant alleles produce proteins that are either poorly expressed, unstable, or have partially reduced catalytic activities.

However, racial differences were seen in the distribution of *NAT2* slow acetylators: the frequency of slow acetylator phenotypes is about 10% in Japanese populations, whereas approximately 60% of Caucasians are slow acetylators [12, 14]. Therefore, data on Caucasians cannot always apply to Japanese populations. In addition, although there was no association with the *NAT2*

slow acetylator genotype and bladder cancer, there was significant relationship between the slow acetylator genotype and bladder cancer when restricting analyses to individuals exposed to potential bladder carcinogens [13]. That means that the risk of genetic factors, plus environmental factors such as smoking habit and occupational exposure, has to be investigated. From this point of view, however, there is little research regarding Japanese subjects.

We now report the relationship between *NAT2* genotypes, bladder cancer, tobacco use and occupational exposure to carcinogens in the Japanese living in Japan.

Materials and methods

Subjects

One-hundred and forty-nine patients (group of cancer patients, 26 women, 123 men) diagnosed as cases of bladder cancer were enrolled in this study. The median (range) of age was 68 (27–93) years for all patients, 69 (27–85) years for women, and 68 (37–93) years for men. They were either outpatients attending the Urology Department of Shinshu University Hospital or Matsumoto National Hospital, Matsumoto, Japan for follow-up cystoscopy, or were inpatients for surgical removal of a bladder tumor in the same hospitals from July 1996 to December 1997. As controls, there were 163 volunteers (19 women and 144 men) with similar generations to the cases that were outpatients and inpatients, without a diagnosis of malignancy. Patients with diagnosis of benign prostatic hyperplasia, urinary tract infection, urinary calculus or urinary incontinence in the same department of the hospital were also enrolled in this study. The median (range) of age was 71 (33–89) years for all controls, 71 (33–87) years for women, and 72 (44–89) years for men. All subjects were born and raised in Japan, of Japanese parents, and lived in Matsumoto (central area of Nagano Prefecture, Japan) and the surrounding area. Informed consent was obtained from the subjects, whose age, gender, and occupation, tobacco use (number of cigarettes per day and years of smoking), and alcohol consumption (consumption of alcohol and years of drinking) were also investigated using questionnaires. Their occupations were classified into one of three risk categories authorized by the British Association of Urology Surgeons [5]: A, high risk for developing bladder cancer; B, possible risk for developing bladder cancer; C, not a likely risk for developing bladder cancer. Patients without occupation or those whose occupation was unknown were classified into group D.

DNA preparations from blood samples and amplification of NAT alleles

One milliliter of whole blood anti-coagulated with EDTA was obtained from each bladder cancer patient, and from the controls. Genomic DNA was extracted using DNA Extractor WB Kits (Wako Pure Chemical Industries, Osaka, Japan) that contain sodium iodide as a chaotropic agent, according to the manufacturer's instructions. Amplification of genomic DNA (an aliquot containing 100 ng of DNA) was carried out by the polymerase chain reaction in a total volume of 25 μl of reaction solution containing 200 μM of each dNTPs (Idaho Technology, Idaho Falls, Idaho, USA), 1 μM each of the primers Nat-Hu 14 (5′-GAC-ATT-GAA-GCA-TAT-TTT-GAA-AG-3′) and Nat-Hu 16 (5′-GAT-GAA-AGT-ATT-TGA-TGT-TTA-GG-3′), and 1 unit of Taq DNA polymerase (Perkin Elmer, Norwalk, Conn., USA). Hickman and colleagues described these primers [7]. The Perkin Elmer 9600 DNA thermal cycler was used, under their following conditions: one cycle of denaturation at 98 °C for 1 min, followed by two cycles of denaturation at 98 °C for 30 s, annealing at 50 °C for 1 min, and extension at 72 °C for 1 min, then 28 cycles of denaturation at 94 °C for 30 s, annealing at 50 °C for 1 min, and extension at 72 °C for 1 min followed by final extension at 72 °C for 5 min.

NAT2 genotyping

Genotype for *NAT2* was determined by a PCR-restriction enzyme digest method [7, 16]. The alleles *NAT2*5A* and *NAT2*5B* were detected by digestion of the PCR products with the restriction enzyme *Kpn*I. *NAT2*5B* and *NAT2*5C* were detected by digestion with *Dde*I, *NAT2*6A* was detected with *Taq*I, and *NAT2*7B* was detected with *BamH*I. Digestion was for more than 30 min at 37 °C for *Kpn*I, *Dde*I, and *BamH*I, and at 65 °C for *Taq*I. The products of the four separate digests were run on 3% agarose gels, stained with ethidium bromide and visualized using a UV transilluminator. Thus, nine NAT alleles were detected at the *NAT2** locus in the present subjects (Table 1). *NAT2* genotypes were then categorized into two groups such as homozygous mutant (slow acetylator genotype) and homozygous and heterozygous wild type (fast acetylator genotype). The frequencies for each type were numbered. Approximately 95% of the slow acetylator alleles are identified by this method [6, 16, 17].

Statistical analysis

All the subjects were divided into two groups (rapid and slow acetylators) by *NAT2* genotypes, three groups (smoker, ex-smoker and non-smoker) by smoking habits, and three groups by occupation (categories A, B, C and D). Differences in each frequency among groups were examined using chi-square test, or if the group was too small, using Fisher's exact test. Differences in each mean were examined using *t*-test after ANOVA analysis. Odds ratios and the 95% confidence interval (CI) of smoking habits and occupation to bladder cancer were also calculated as the ratio of subjects with an occupation in category C and D, but excluding smoking habits, to 1.0.

Results

NAT2 genotype frequencies

The frequencies of *NAT2* slow acetylator genotype were less than 10% in all subjects (Table 1). No significant differences were seen in the distribution of *NAT2* allele

Table 1 *NAT2* genotypes in Japanese bladder cancer patients and controls

	Bladder cancer patients *n* (%)	Control *n* (%)
Fast type		
*NAT2*4/*4*	64 (43.0)	68 (41.7)
*NAT2*4/*5A*	1 (0.7)	0 (0)
*NAT2*4/*5B*	6 (4.0)	4 (2.5)
*NAT2*4/*5C*	3 (2.0)	4 (2.5)
*NAT2*4/*6A*	42 (28.2)	47 (28.8)
*NAT2*4/*7B*	23 (15.4)	30 (18.4)
Total	139 (93.3)	153 (93.9)
Slow type		
*NAT2*5B/*5B*	1 (0.7)	0 (0)
*NAT2*6A/*6A*	4 (2.7)	7 (4.3)
*NAT2*7B/*7B*	5 (3.4)	3 (1.8)
Total	10 (6.7)	10 (6.1)

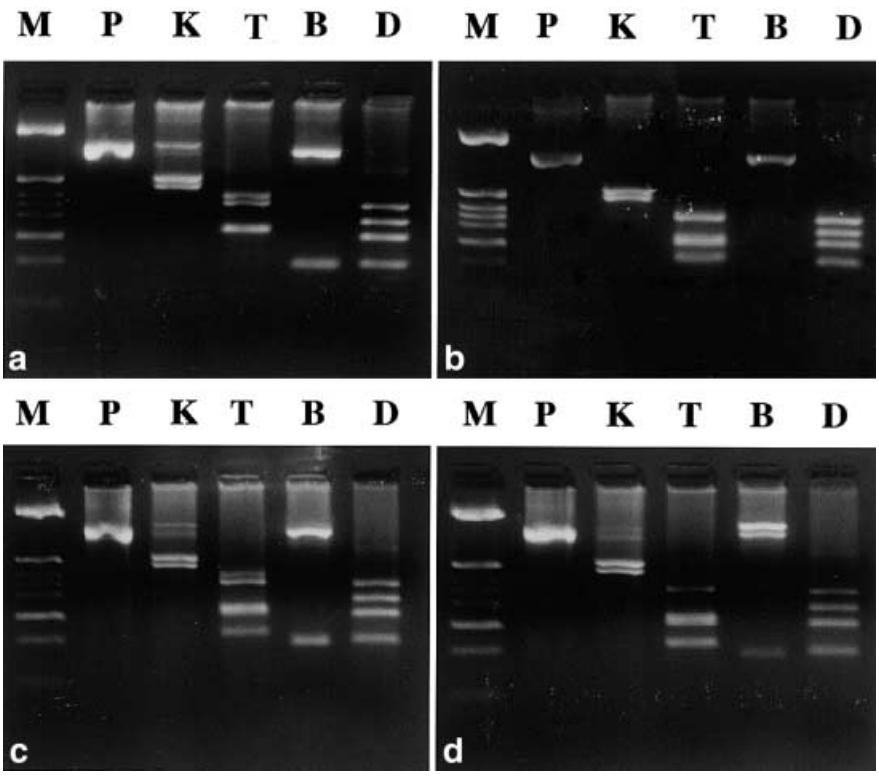

Fig. 1A–D The photos of gel image show the typical *NAT2* genotypes. **A** The genotype of *NAT2*6A/*6A* which loses *Taq*I site of nucleotide. **B** The genotype of *NAT2*7B/*7B* which is not digested by *BamH*I. **C** The genotype of *NAT2*4/*6A*. **D** The genotype of *NAT2*4/*7B*

types between controls and bladder cancer patients. Of the fast acetylator genotypes, *NAT2*4/*4* was the most predominant, followed by *NAT2*4/*6A* and *NAT2*4/*7B*. Frequencies of *NAT2*4/*5A*, *NAT2*4/*5B* and *NAT2*4/*5C* were rare. The percentage of *NAT2* slow acetylator types was 6.7% in the bladder cancer patients, much the same as for controls (6.1%). There was no association between *NAT2* slow acetylator genotype and bladder cancer. A photo of gel image of typical *NAT2* genotypes is shown in Fig. 1.

Risk of *NAT2* genotype, smoking, and occupation for bladder cancer

The numbers of smokers were significantly greater among bladder cancer patients (39.6%) than in controls (27.6%; Table 2). Environmental factors for the patients and controls were not discussed in connection with this result. Of interest was that ex-smokers were more numerous among controls than in bladder cancer patients. However, the percentages of smokers and ex-smokers in the patients (72.5%) did not differ from those of controls (73.6%). The frequency of *NAT2* slow acetylator among the bladder cancer patients who smoked (2.0% of cancer patients) was much the same as the frequency of *NAT2* slow acetylator among the controls who smoked (1.2% of controls). The same result was seen when distributions of each *NAT2* slow and fast acetylator genotypes were examined in the case of ex-smokers and non-smokers.

The relationship between smoking habits or occupation in bladder cancer patients and controls is shown in Table 3. Distribution of *NAT2* slow acetylator was not affected by work occupation. Eight subjects (4.9%) were engaged in occupation category A for controls, and this was not significantly different from the case in cancer patients (8.7%; $P = 0.0980$). Subjects engaged in the occupation categories A and B numbered 38 (25.5%) for cancer patients, which was somewhat larger than for controls (16.6%), but it was not statistically significant ($P = 0.0521$). In the occupation categories A and B, 22 (14.8%) subjects who smoked were cancer patients, as many as nine (5.5%) subjects who smoked were controls, and here there was significant difference ($P = 0.0064$). No differences were seen in the number of cigarettes and the duration of smoking among people engaged in occupational categories A, B, C and D in the cancer patients. The smoking habits and alcohol consumption did not influence the risk for bladder cancer (data not shown). Working history was also investigated: the duration of cancer patients engaged in the occupation category A was significantly longer than that of control patients engaged in the same category, and also that of cancer patients in occupation category B ($P < 0.05$).

When odds of occupations C and D in non-smokers for bladder cancer was 1.0, odds ratios of each occupational category and/or smoking habit were calculated, as shown in Table 4. A significant association was seen between tobacco use combined with occupational category B (2.98) or B and A (3.40) for bladder cancer, although smoking or an occupation itself was a weak risk for bladder cancer (1.43 for smoking or 1.16 for occupation B, and 1.39 for occupation A). The

Table 2 *NAT2* genotypes and smoking in bladder cancer patients and controls (control-smoker: 17.0 ± 9.7 cigarettes for 43.2 ± 13.4 years; cancer-smoker: 18.2 ± 9.3 cigarettes for 40.3 ± 12.7 years; control-ex-smoker: 20.6 ± 11.6 cigarettes for 27.6 ± 12.7 years but stopped 18.3 ± 13.0 years ago; cancer-ex-smoker: 21.8 ± 16.7 cigarettes for 31.6 ± 15.1 years but stopped 13.6 ± 9.6 years ago)

	Cancer patients (n = 149)			Control (n = 163)		
	Smoker n (%)	Ex-smoker n (%)	Non-smoker n (%)	Smoker n (%)	Ex-smoker n (%)	Non-smoker n (%)
Fast	56 (37.6)	47 (31.5)	36 (24.2)	43 (26.4)	69 (42.3)	41 (25.1)
Slow	3 (2.0)	2 (1.3)	5 (3.4)	2 (1.2)	6 (3.7)	2 (1.2)
Total	59 (39.6)*	49 (32.9)	41 (27.5)	45 (27.6)	75 (46.0)**	43 (26.4)

* Significant difference in current smoking habit between controls and bladder cancer patients (P = 0.0058)
** Significant difference in smokers and ex-smokers between controls and bladder cancer patients (P = 0.0096)

Table 3 Relationship among occupation, smoking habits and bladder cancer (figures *in parentheses* represent number)

Occupation	Cancer patients (smoker) (n = 149)	Control (smoker) (n = 163)
A		
Sex	M12, F1	M7, F1
Age (means ± SD)	67.5 ± 13.8	61.7 ± 7.5
Working history (years, means ± SD)	36.4 ± 7.4*	24.7 ± 7.7
Slow acetylators	2 (2)	0 (0)
Manufacture of dyestuffs	5 (1)	4 (1)
Manufacture of rubber, rubber products	2 (1)	2 (0)
Gas workers and coke ovens	3 (2)	2 (1)
Laboratory work	3 (3)	0 (0)
Total	13 (7)	8 (2)[a]
B		
Sex	M24, F1	M18, F1
Age (means ± SD)	64.3 ± 10.0	68.0 ± 11.0
Working history (years, means ± SD)	23.6 ± 14.1	23.9 ± 12.8
Slow acetylators	1 (0)	3 (1)
Printing	0 (0)	0 (0)
Aluminum refining	8 (4)	5 (3)
Drivers and transport workers	12 (8)	8 (2)
Machine assembler	3 (1)	1 (0)
Hairdresser	1 (1)	2 (1)
Medical and nursing	1 (1)	3 (1)
Total	25 (15)	19 (7)[b]
C		
Sex	M82, F14	M119, F11
Age (means ± SD)	68.4 ± 1.2	70.9 ± 1.1
Working history (years, means ± SD)	32.5 ± 14.6	36.2 ± 13.2
Slow acetylators	5 (0)	7 (1)
Agriculture and forestry	20 (6)	33 (11)
Building industry	18 (9)	15 (7)
Manufacturing industry	2 (1)	11 (2)
Service industry	13 (1)	15 (4)
Self-employed	17 (8)	10 (2)
Office clerks	26 (10)	46 (10)
Total	96 (35)	130 (36)[c]
D		
Sex	M5, F10	M0, F6
Age (means ± SD)	68.5 ± 3.9	70.3 ± 17.9
Slow acetylators	2 (0)	0 (0)
Without occupations	13 (2)	6 (0)
Unknown	2 (1)	0 (0)
Total	15 (3)[c]	6 (0)

[a] Smokers of A: 24.0 ± 8.9 cigarettes for 36.0 ± 11.4 years (40.0 ± 7.9 pack years) in cancer case; 20 and 30 cigarettes for 30 years, respectively (30 and 60 pack years, respectively), in control
[b] Smokers of B: 20.2 ± 10.8 cigarettes for 40.0 ± 9.3 years (40.2 ± 23.0 pack years) in cancer case; 18.6 ± 14.4 cigarettes for 42.4 ± 17.8 years (37.2 ± 23.2 pack years) in control
[c] Smokers of C and D: 16.8 ± 8.4 cigarettes for 41.0 ± 14.3 years (34.0 ± 20.6 pack years) in cancer case; 15.9 ± 8.1 cigarettes for 44.1 ± 12.6 years (36.8 ± 19.7 pack years) in control
* Significantly different from control patients with occupation category A or cancer patients with occupation category B (P < 0.05)

Table 4 Odds ratio (95% CI) of occupation and smoking habits

Occupation category	A		B		C and D[a]	
Smoking habit[b]	+	–	+	–	+	–
Cancer patients (*n*)	7*	6	15*	10	37	72
Control (*n*)	2	6	7	12	36	100
Odds ratio	4.86	1.39	2.98	1.16	1.43	1.00
(95% CI)	(0.98–24.09)	(0.43–4.48)	(1.16–7.67)	(0.47–2.83)	(0.82–2.47)	
Odds ratio[c]	2.03		1.64		1.0	
(95% CI)	(0.81–5.07)		(0.86–3.14)			

[a] Excluding individuals whose occupations were unknown
[b] + Current smokers, – non-smokers plus ex-smokers
[c] Odds ratio of occupational category A or B to occupational category C and D; odds ratio (95% CI) of occupation A and B, and smoking habit was 3.40 (1.48–7.81); that of occupation A and B, but not smoking habit was 1.23 (0.59–2.58)
*Significantly different from groups C and D but not having smoking habit ($P < 0.05$), odds ratio of occupation A was 2.78 (1.00–7.76)

combination of occupation category A and smoking habit was not significantly different from having occupation C or D and no smoking in judging from the 95% CI; even the odds of the former ratio were very high compared to those of the latter.

Discussion

Our study demonstrated the relationship between bladder cancer, *NAT2* acetylator genotype, smoking and occupational exposure to carcinogens in Japanese. We demonstrated that there was a lack of interaction between *NAT2* acetylator genotype and bladder cancer. It is suggested that there might be some differences concerning the relationship between *NAT2* acetylator genotype and bladder cancer among the different races because most of the reports studied in Caucasian subjects demonstrated that *NAT2* acetylator genotype is one of the most important risk factors for bladder cancer [1, 12, 14–16, 19]. The frequency of *NAT2* slow acetylator genotypes is about 60% in Caucasian subjects, and as few as 6.7% of Japanese have *NAT2* slow acetylator genotypes in our study. However, Blum et al. reported the same results as ours in Caucasians [3]. In the Japanese population, Katoh et al. reported that the slow acetylation genotype of *NAT2* was a significant risk factor to urological cancer (bladder, renal pelvis and ureter) [9, 11]. We would be able to explain that the reasons for this discrepancy between our results and theirs come from the setting of control group. We selected the controls from the patients without a diagnosis of malignancy in the same department of our hospital, while Katoh et al. used subjects who had visited different facilities unlike the cases for regular medical health check-ups. The other major reason is that they include the patients of renal pelvic cancer and ureteral cancer in their study. However, there is some possibility that the relatively small size in this case might mask the true influence of *NAT2* genotypes on the results although we carefully selected the subjects.

In this study, *NAT2* slow acetylator genotypes were not associated with the risk for smoking- and occupation-related bladder cancer. However, a significant association was reported in Caucasian subjects when restricting analysis to those exposed to potential carcinogens (i.e., smokers and high-risk occupation for bladder cancer) among cases and controls [13].

In contrast, we demonstrated that the combination with smoking and occupations dealing with arylamines (occupation categories A and B) contributed to the risk for bladder cancer, though smoking and occupation category did not contribute by themselves judging from the 95% CI. One reason why the occupation category did not contribute to the bladder cancer by itself as in the past study in the UK [18] would be because of the prohibition of manufacturing of the chemical with carcinogenicity included in occupation category A in 1972 in Japan. Meanwhile only focusing on the duration time of occupation, we can suggest that the individuals who have longer duration time of occupational category A have a significant risk for bladder cancer (Table 3). We suggest that the participation of occupation category or smoking in bladder cancer may be masked by the small number of these subjects. Ex-smoking was not a risk factor for bladder cancer because the percentages of ex-smokers in controls were greater than those percentages in cancer patients. It would be suggested that an early time abstinence from this habit-forming is important to prevent bladder cancer (Table 2).

In conclusion, we found a lack of interaction between *NAT2* slow acetylator genotype and bladder cancer in Japanese. In contrast, the environmental factors of smoking habit and occupational exposure to carcinogenicity are much more important than genetic factors in bladder cancer.

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