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N-Acetyl Transferase-2 and Bladder Cancer Risk: A Meta-Analysis

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Interindividual differences in bladder cancer susceptibility may be partly mediated through polymorphic variability in the metabolism of carcinogens. N-acetyl transferase2 (NAT2) has been extensively studied as a risk factor in this context, but the results are inconsistent. In some studies the failure to demonstrate a relationship may be a consequence of a lack of statistical power. To overcome lack of power, data from 21 published case control studies were pooled in a meta-analysis using a randomeffects model. The pooled odds ratio of bladder cancer associated with slow acetylator status was 1.31 (95% CI: 1.11–1.55). The results suggest that NAT2 slow acetylator status is associated with a modest increase in risk of bladder cancer. There was, however, heterogeneity between studies. It is clear from this overview that greater attention should be paid to the design of these types of study. Environ. Mol. Mutagen. 36: 221–227, 2000. © 2000 Wiley-Liss, Inc.

Key words: NAT2; bladder cancer risk; meta-analysis

INTRODUCTION

Bladder cancer accounts for approximately 6% of all cancers, with an incidence rate of 30 per 100,000 in men and 10 per 100,000 in women, in the United Kingdom. Peak incidence of the disease is in the seventh decade [ONS, 19961. Exposure to carcinogens such as 2-naphthylamine and other amine compounds is well established as a risk factor [Vineis and Pirastu, 1997]. An increased risk is also seen in smokers, some two to six times greater than in nonsmokers [Brennan et al., 20001. Other recognized risk factors include schistosomiasis infection [Mostafa et al., 1999] and exstrophy of the bladder [Mesrobian et al., 1988].

There is a growing appreciation that the development of most cancers results from an interaction between environmental and genetic factors. Epidemiological studies have shown that relatives of bladder cancer cases are at a twofold elevated risk of developing the disease [Houlston and Peto, 1996]. It is conceivable that part of the susceptibility to bladder cancer may be determined by interindividual differences in the bioactivation of procarcinogens and detoxification of carcinogens. N-acetyltransferase-2 (NAT2) has also been of considerable interest as a bladder cancer susceptibility gene in this context, since N-acetylation is a detoxifying step in the metabolism of arylamines [Smith et al., 1995; Hivonen, 19991.

N-acetyl transferase-2, originally thought to be the only Polymorphic NAT, is responsible for the inherited interindividual variation in the ability to acetylate drugs such as isoniazid and sulfamethazine [Smith et al., 1995; Hivonen, 1999]. Individuals can readily be classified as rapid or slow acetylators, according to the activity of this enzyme, and these drugs can be used as probes to determine NAT2 acetylator status. The determination of NAT2 status using drug probes has now been largely superseded by genotyping [Hivonen, 19991.

Slow NAT2 acetylator status as a risk factor for bladder cancer was first proposed in the late 1970s and early 1980s [Lower et al., 1979; Cartwright et al., 19821. Since then a large number of studies have appeared in the literature confirming or refuting an association between NAT2 status and bladder cancer risk [Woodhouse et al., 1982; Evans et al., 1983; Miller and Cosgriff, 1983; Hanssen et al., 1985; Ladero et al., 1985; Mommsen et al., 1985; Karakaya et al., 1986; Kaisary et al., 1987; Horai et al., 1989; Hanke and Krajewska, 1990; Hayes et al., 1993; Risch et al., 1995; Brockmoller et al., 1996; Okkels et al., 1997; Schnakenberg et al., 1998; Taylor et al., 1998; Filiadis et al., 1999; Hsieh et al., 1999]. In an attempt to clarify the effect of NAT2 status on bladder cancer risk, a meta-analysis of published studies has been undertaken.

MATERIALS AND METHODS

Identification of Studies

A search of the literature was made using two electronic data-bases, MEDLINE and BIDS EMBASE, to identify articles in which NAT2 status was determined in bladder cancer patients and controls. Additional articles were ascertained through references cited in these publications.

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TABLE I. Studies Included in a Meta-Analysis of the Relationship Between NAT2 Status and Bladder Cancer Risk

Investigator (place of study)	Analytical method[a]	Cases[b]	% Slow acetylators	Controls[b]	% Slow acetylators	Exposure
Lower et al., 1979 (Sweden, Denmark)	SMZ phenotype	71 prevalent cases from Denmark	65	74 hospital/healthy controls	51	Smoking history of cases
		115 prevalent cases from Sweden	70	118 hospital/healthy controls	67	
		Caucasian				
Cartwright et al., 1982 (UK)	DDS phenotype	111 prevalent cases (23 with occupational exposure), mean age ~70	67	95 hospital and 112 healthy controls	57	Smoking and occupational history of cases
		Caucasian				
Woodhouse et al., 1982 (UK)	INH phenotype	30 prevalent cases, 67% male, mean age 70 (57–83)	0	27 hospital controls, 48% male, mean age 77 (68–89)	≤9	
		Caucasian				
Miller and Cosgriff, 1983 (United States)	SMZ phenotype	26 prevalent cases (15 with occupational exposure)	46	26 healthy controls	69	Smoking and occupational history of cases
		Caucasian				
Evans et al., 1983 (UK)	SMZ phenotype	100 prevalent cases (19 with occupational exposure)	66	82 controls	60	Smoking and occupational history of cases
		Caucasian				
Ladero et al., 1985 (Spain)	SMZ phenotype	130 prevalent cases (55 with occupational exposure), 88% male, mean age 65.7 (8.7) 55 cases exposed	64	157 healthy controls, mean age 22.3 (3.1)	57	Smoking and occupational history of cases
		Caucasian				
Hanssen et al., 1988 (Germany)	SMZ phenotype	105 prevalent cases (27 with occupational exposure), 77% male, mean age at diagnosis 72.3 (46–93)	72	42 healthy controls	53	Smoking and occupational history of cases
		Caucasian				
Mommsen et al., 1985 (Denmark)	SMZ phenotype	228 incident cases, mean age 66.2 (29–85)	64	100 age-matched cancer free urology patients	54	
		Caucasian				
Karakaya et al., 1986 (Turkey)	SMZ phenotype	23 cases, 74% male, aged 45–70	39	109 volunteer controls, 52% male, aged 18–52	62	
		Caucasian				
Kaisary et al., 1987 (UK)	DDS phenotype	98 prevalent cases	60	110 age- and sex-matched cancer free urology patients	49	Smoking and occupational history of cases
		Caucasian				
Horai et al., 1989 (Japan)	DDS phenotype	51 prevalent cases, 80% male, mean age 68.4 (12.3)	6	202 healthy controls, 55% male, mean age 21.0 (3.4)	6	Smoking and occupational history of cases
		Asian				
Hanke and Krajewska, 1990 (Poland)	INH phenotype	67 prevalent cases (24 with occupational exposure)	70	22 healthy controls with history of exposure to benzidine	45	Occupation for cases
		Caucasian				
Hayes et al., 1993 (China)	DDS phenotype	38 prevalent cases with history of occupational exposure to benzidine	9 (phenotype)	43 age-matched controls with history of exposure to benzidine	23 (phenotype)	Smoking and occupational history of cases
	NAT2 genotype	*Asian*	13 (genotype)		23 (genotype)	

TABLE I. *Continued*

Investigator (place of study)	Analytical method[a]	Cases[b]	% Slow acetylators	Controls[b]	% Slow acetylators	
Risch et al., 1995 (UK)	NAT2 genotype	189 prevalent cases (62 with occupational exposure), 80% male, aged 36–89				
		Caucasian				
Brockmoller et al., 1995 (Germany)	NAT2 genotype	374 incident and prevalent cases, mean age 71.0	62	373 controls, mean age 65.8	58	Smoking and occupational history of cases and controls
		Caucasian				
Okkels et al., 1997 (Denmark)	NAT2 genotype	254 incident and prevalent cases, 52% male, mean age 69 (10)	61	242 urology patient controls, 49% male, mean age 64 (12)	56	Smoking and occupational history of cases and controls? Interaction with smoking
		Caucasian				
Taylor et al., 1998[c] (United States)	NAT2 genotype	230 prevalent cases:		203 age- and sex-matched urology patient controls		Smoking and occupational history of cases and controls
		215 *White*	58	191 *White*	54	No interaction with smoking
		15 *Black*	20	12 *Black*	42	
Schnakenberg et al., 1998 (Germany)	NAT2 genotype	60 prevalent cases, 70% male, aged 32–100	70	154 unrelated healthy controls, 57% male, aged 17–76	61	
		Caucasian				
Filiadis et al., 1999 (Greece)	NAT2 genotype	89 incident cases, 84% male, mean age 65.9 (11.9)	8	147 sex- and age-matched urology patients, 83% male, mean age 63.9 (10.9)	38	Smoking histories
		Caucasian				
Hsieh et al., 1999 (Taiwan)	NAT2 genotype	74 prevalent cases	21	184 age-matched hospital	24	Smoking data collected on

[a]Probe drug: SMZ, sulphamethazine; DDS, dapsone; INH, isoniazid.
[b]SD of ages or age range given in parentheses.
[c]Blacks and Whites considered separately.

Statistical Analysis

The odds ratio of bladder cancer associated with NAT2 slow acetylator status was estimated for each study. These odds ratios and their corresponding 95% confidence intervals were plotted against the number of participants in each of the studies to detect any obvious sample size bias. To take into account the possibility of heterogeneity between studies, a random effects model was used for the derivation of odds ratios [DerSimonian and Laird, 1986]. This model assumes that the studies in question are a random sample of a hypothetical population of studies, taking into account within- and between-study variability. Statistical manipulations were undertaken within the statistical program STATA version 6.0 (Stata Corporation, College Station, TX), using the module META [Sharpe and Sterne, 1998]. The level of risk of bladder cancer associated with slow acetylator status detectable in each study was determined for 80% power and significance of 0.05 on the basis of the method published by Fleiss et al. [1980], implemented in the statistical program POWER (Epicentre software, version 1.30; Epicentre Technologies, Madison, WI). The etiological fraction, that is. the proportion of bladder cancer that can be attributed to the NAT2, was calculated from the odds ratio (OR) under the assumption that slow acetylator status can be treated like exposure to a risk factor (Pe). The etiological fraction is then given by $\{Pe(OR - 1)/[Pe(OR - 1) + 1]\}$, under the assumption that Pe in the control group is similar to that in the target population [Schlesselman, 1982].

RESULTS

Twenty reports detailing 21 case-control studies of the relationship between NAT2 status and bladder cancer risk were identified from the literature and judged suitable for analysis (Table I). Reasons for excluding reports were that the data were available in more than one study [Wolf et al., 1980] or that NAT2 typing had been reported on only a subset of cases and controls, raising the possibility of bias [Peluso et al., 19981.

Of the reports selected for meta-analysis, 12 were assigned NAT2 status solely by phenotyping and seven by genotyping (Table I). In the study reported by Hayes et al. [1993] NAT2 status had been assigned by both phenotyping and genotyping, whereas for the purpose of this overview, only the genotyping data was used. Taylor et al. [1998] reported data on Black and White individuals separately; thus these were treated as two studies.

Healthy individuals were used as controls in some studies, but most made use of hospital patients with nonmalignant disease. Controls were age-matched to cases in a proportion of studies, but this was not universal. Smoking histories and industrial exposure to carcinogens had been ascertained from cases and controls in a number of studies (Table I). The size of studies reported varied considerably; only 18% (4/22) of studies were large enough to demonstrate a twofold increase in risk with 80% power, and 32% (7/22) were only large enough to detect a fourfold or greater risk.

This meta-analysis provides an overview of 21 studies containing a total of 3462 cases and 3450 controls. Figure 1 shows a plot of odds ratios with 95% confidence limits for the risk of developing bladder cancer associated with slow acetylator status in all of the studies. The median odds ratio value was greater than unity in 16, but was statistically significant at the 0.05 level in only four.

The pooled odds ratio for bladder cancer associated with slow acetylator status in all of the studies was 1.31 (95% CI: 1.11–1.55). An impression of heterogeneity between studies was confirmed by statistical analysis ($Q = 35.6$, $df = 21$, $P = 0.024$). There was some evidence that this may be partly attributable to the differences in the method of assigning NAT2 status. Stratifying studies by methodology, the odds ratio obtained by pooling phenotyping studies was 1.34 (95% CI: 1.08–1.69; test of heterogeneity: $Q = 17.24$, $df = 12$, $P = 0.14$) and pooling genotyping studies the odds ratio was 1.27 (95% CI: 0.97–1.67; test of heterogeneity: $Q = 18.03$, $df = 8$, $P = 0.021$).

These analyses are the result of pooling data from studies based on a number of ethnic groups. The frequency of slow acetylators differs between the ethnic groups. Restricting analyses to the studies of Caucasian subjects (the major ethnic group), the odds ratio of bladder cancer associated with NAT2 status defined by phenotypes and genotypes is 1.39 (95% CI: 1.18–1.64; test for heterogeneity: $Q = 28.09$, $df = 17$, $P = 0.04$). Pooling phenotyping studies only, the odds ratio is 1.36 (95% CI: 1.08–1.70; test for heterogeneity: $Q = 16.86$, $df = 11$, $P = 0.12$) and pooling genotype studies only, the odds ratio is 1.44 (95% CI: 1.10–1.89; test for heterogeneity: $Q = 11.21$, $df = 5$, $P = 0.05$). The odds ratio derived from the three Asian studies is 0.75 (95% CI: 0.45–1.28).

Restricting the analysis to the largest studies [Cartwright et al., 1982; Evans et al., 1983; Ladero et al., 1985; Mommsen et al., 1985; Kaisary et al., 1987; Risch et al., 1995; Brockmoller et al., 1996; Okkels et al., 1997; Taylor et al., 1998; Filiadis et al., 1999; Hsieh et al., 19991, which showed no evidence of heterogeneity ($Q = 14.02$, $df = 10$, $P = 0.17$), produced an odds ratio not significantly different (OR = 1.37; 95% CI: 1.16–1.61) from the analysis of all studies. Sequential dropping of studies from the analyses (a test of sensitivity) had no effect on findings in either the analysis of all studies or only the larger studies. Therefore, although overall there is evidence of heterogeneity, studies that contributed to the heterogeneity do not significantly alter the estimate of the pooled odds ratio.

It is conceivable that slow acetylator status may be associated with a specific form of bladder cancer. In most studies, the NAT2 status of bladder cancer cases was not detailed according to histology, thereby preventing a pooled analysis to be carried out by subgroup. However, in the studies of Caucasian populations the vast majority of uroepithelial tumors presenting will be transitional cell carcinomas.

Information on smoking or occupational exposure was collected in some, but not all. studies. Table I shows the studies that examined the interaction between these risk factors on bladder cancer risk in slow acetylators. An excess of slow acetylators in bladder cancer cases who had been

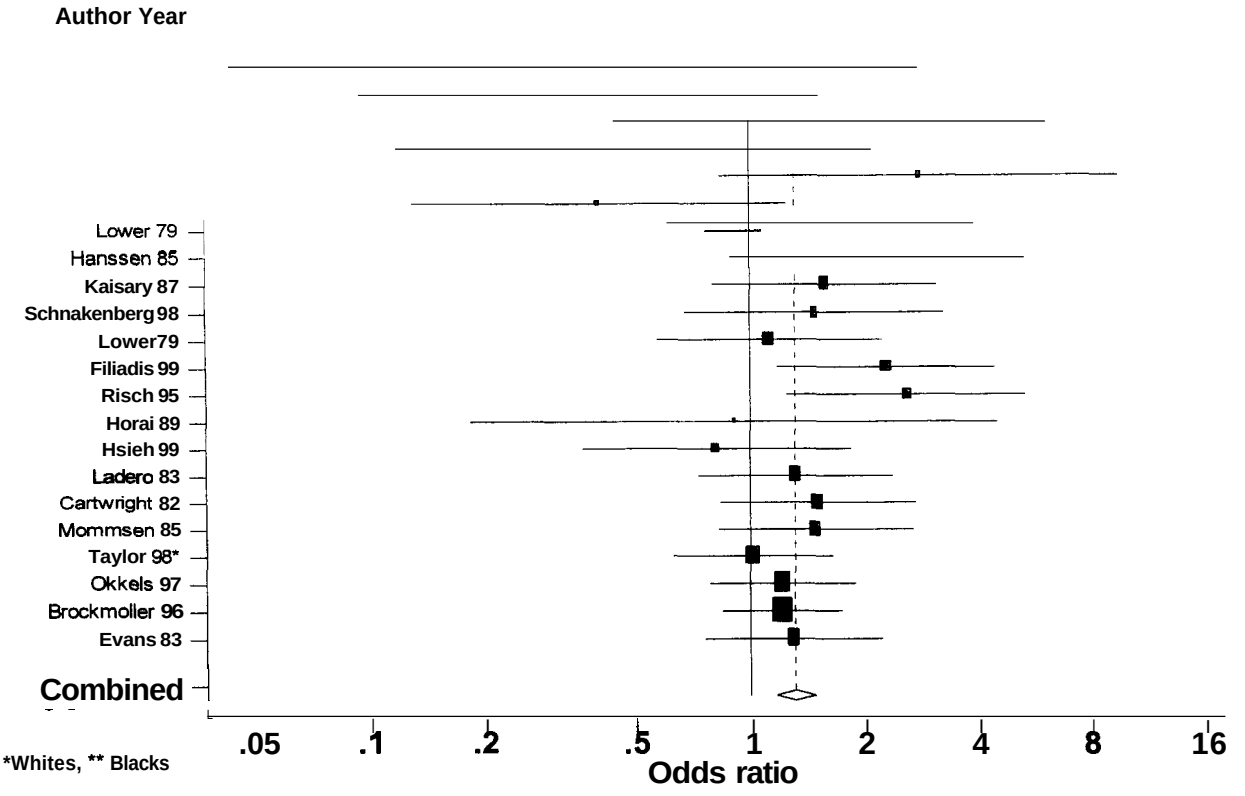

Fig. 1. Odds ratios and 95% confidence intervals for the risk of developing bladder cancer associated with NAT2 slow acetylator status in each study. Studies are stratified by increasing size. The box area is proportional to the weight of the study. The diamond (and broken line) represents the overall summary estimate, with confidence interval given by its width. The unbroken vertical line is at the null value (1).

exposed to carcinogens, or in smokers, was reported in some [Cartwright et al., 1982; Hanssen et al., 1985; Hanke and Krajewska, 1990; Risch et al., 1995; Brockmoller et al., 19961, but not all, of the studies [Miller and Cosgriff, 1983; Evans et al., 1983]. A subgroup analysis of risk of bladder cancer by exposure and acetylator status was not undertaken because the data in most studies were not in a format suitable for pooling.

DISCUSSION

Bladder cancer is one of the few cancers in which exposure to environmental carcinogens has been directly implicated [Vineis and Pirastu, 19971. These include industrial exposure to aromatic amines, principally in the rubber, dye, and printing industries, and exposure to diesel exhaust and smoking. These situations have in common a high level of exposure to aromatic amines such as naphthylamine, 4-aminobiphenyl, and benzidine, and their N-hydroxylated derivatives, all of which are known or potential NAT2 substrates. Since exposure to carcinogens is recognized to be a risk factor for bladder cancer, genetic modulation of carcinogen metabolism is a plausible mechanism for explaining interindividual susceptibility.

NAT2 status has been evaluated as a risk factor for bladder cancer in a number of reports. In some studies the failure to demonstrate a relationship may partly be a consequence of lack of statistical power. It is unlikely that any predisposition allele will confer more than a twofold difference in risk of bladder cancer. Only a small number of the studies had 80% or greater power to demonstrate a twofold difference in risk at the 5% significance level. To overcome lack of power, a meta-analysis was undertaken, pooling data from published studies. The underlying basis of meta-analysis is, not to directly combine results from studies, but to obtain a relative measure of the observed effect, supporting or rejecting a specific hypothesis. An advantage of this statistical procedure is the amalgamation of data collected and analyzed by different methods. There are, however, certain caveats. In any systematic review, publication bias is clearly of great concern. The most common scenario is that negative findings may go unreported and we cannot entirely exclude this possibility in this analysis. It has been proposed that quality scoring of studies should be employed to determine which studies to include in any meta-analyses [Sacks et al., 1987]. This was not carried out in the current analysis because existing scales have not been validated [Dickersin and Berlin, 19921 and it is also unclear how they could

easily be applied to these types of published case-control studies. Furthermore, the validity of this strategy has been questioned on the basis that this practice may merely subjectively merge objective information [Greenland, 19941. It is assumed that each polymorphism is functional with respect to risk in each study population. If the polymorphism is a neutral marker for another variant, this assertion may well not apply, since linkage disequilibrium is often population dependent.

Association studies are capricious and it is clear from this overview that some of the studies are far from perfect in design. The issue of false positive findings in association studies is a great concern. Any stratification within a population sample can lead to spurious evidence for an association between the marker and disease. Avoidance of this problem requires the identification of subpopulations defined in terms of factors that can influence disease and marker allele frequencies. These include ethnicity and geographical origin. In a number of the studies it is likely that the ethnicity of cases and controls were mixed. The frequency of NAT2 slow acetylators varies between ethnic groups; therefore, a failure to match cases and controls represents a source of bias. Furthermore, as stated earlier, given that any polymorphism in carcinogen-metabolizing enzymes is unlikely to increase the risk of bladder cancer by more than twofold, and will more realistically be associated with a risk of 1.5-fold or less, most published studies of NAT2 status are underpowered. A number of the published reports were based on a comparison of cases and noncancer disease controls. It is clearly desirable to base any comparison on healthy population controls, since it is conceivable that slow NAT2 acetylator status may confer susceptibility to noncancer disease.

Substantial research has been carried out evaluating the possible association of NAT2 status on the risk of bladder cancer. Has this been worthwhile? Accepting the caveats of meta-analyses, despite some evidence of heterogeneity, this review (and a review by Marcus et al., 2000) suggests that a small increase in risk of bladder cancer is associated with slow acetylator status. Although this risk may be modest, the high frequency of this trait in the population implies that NAT2 status may well have considerable impact on bladder cancer incidence. For example, in Caucasians a 1.3-fold increase in risk corresponds to a population attributable fraction of ~16%.

Although **NAT2** is present in bladder epithelium [Windmill et al.. 20001, its expression is not high [Stanley et al., 1996}, and hence rapid acetylator status may well afford protection from bladder cancer through systemic detoxification of foreign compounds in the liver or other tissues.

If genetic susceptibility to bladder cancer is mediated in part by polymorphic variation. it is probable that the risk associated with any one locus will be small. However, combinations of certain genotypes may be more discriminating as risk factors than a single locus genotype; for example, NAT2 slow acetylator status in combination with ***GSTMI*** deficiency. The studies that have examined such possibilities (e.g., Brockmoller et al., 1996) are inconclusive to date, but are all underpowered. In any future analyses of sub-group-specific relationships it is appropriate to impose relatively strict significance levels to account for multiple testing. A clearer picture of the interaction between different polymorphisms and environmental factors on bladder cancer risk will be adequately addressed only by studies of sufficient size, commensurate with the detection of small effects.

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