

# Acetylation Phenotype in Colorectal Carcinoma<sup>1</sup>

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## ABSTRACT

Sulfamethazine acetylation phenotype was determined in 49 patients with cancer of the colon or rectum, 41 old, and 45 young control subjects. Metabolic clearance of sulfamethazine, plasma ratio of *N*-acetylsulfamethazine:*N*-acetylsulfamethazine plus sulfamethazine and urinary ratio of *N*-acetylsulfamethazine:*N*-acetylsulfamethazine plus sulfamethazine were used to classify subjects into slow and fast acetylation phenotypes. All three measures gave similar results. The proportions of slow and fast acetylators were similar in both control groups and there were significantly more fast acetylators in the cancer group than in the control groups ( $\chi^2 = 5.0-8.5$ ;  $P < 0.05$ ). The data suggest that there may be an association between acetylation phenotype and colorectal carcinoma.

## INTRODUCTION

Acetylation is a well documented example of pharmacogenetic variability in drug metabolism (1), and polymorphism of this pathway has been recognized for almost 30 years. Acetylation rate is determined by two autosomal alleles at a single locus, and although three genotypes are possible, most commonly used phenotyping procedures can readily distinguish only fast (homozygous rapid and heterozygous intermediate) and slow (homozygous slow) phenotypes (2). Acetylation phenotype has most often been used as a predictor for toxicity (e.g., procainamide, sulfasalazine) or of dose requirement (e.g., hydralazine) (3). However, correlations between phenotype and various disease states have also been made. A number of studies suggest that both idiopathic systemic lupus erythematosus and tuberculosis are more common in slow acetylators (4, 5) while an increased proportion of fast acetylators has been found in diabetics (6-9). Several studies have described an association between slow acetylator phenotype and bladder cancer, particularly in populations with high risk due to occupational exposure to known carcinogens (10-12). Evidence has also been presented (13, 14) for a putative relationship between rapid acetylation phenotype and breast cancer. Metabolic activation of dietary or environmental carcinogens has been suggested as a mechanism for these latter observations (15). In Australia, cancer of the colon or rectum is relatively common in both males and females (13-18% of all cancers) (16), and in the present study we have sought a correlation between acetylation status and the occurrence of colorectal carcinoma.

## MATERIALS AND METHODS

### Subjects

Acetylator phenotype was determined in three groups of subjects: (a) patients who had undergone surgical resection of a primary adenocarcinoma of the colon or rectum; (b) patients or volunteer subjects who

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were of similar age, sex, and racial origin to those in (a) and who were not cancer sufferers (designated "old controls"); (c) young volunteer subjects who were matched for racial origin to those in (a) and were disease free (designated "young controls"). This latter group was either students or laboratory staff. Controls or cancer patients with diabetes or renal or hepatic dysfunction were excluded as were cancer patients with metastatic disease or who were receiving chemotherapy. (These diseases or treatments may alter the result of phenotyping with sulfamethazine.) As judged by interview, case notes review, and current medications, 39% of the cancer patients also had cardiovascular disease, 6% inflammatory joint disease, and 2% asthma. By contrast, in the old control group, 44% had cardiovascular disease, 19% inflammatory joint disease, 7% diverticulitis, and 2% asthma. The study was approved by the Human Rights Committee of the University of Western Australia and all subjects gave informed consent.

### Determination of Acetylator Phenotype

**Drug Administration and Sampling Procedure.** The method used was that of Lee and Lee (17) with minor modifications. All subjects were fasted from midnight on the day prior to study. On the study day, an aqueous solution (15 mg sulfamethazine/kg in a volume of 20 ml) of sulfamethazine sodium was administered p.o. at 7 a.m. and followed with approximately 200 ml of water. Fluids were not restricted but breakfast was delayed until 10:30 a.m. and alcohol was not permitted on the study day. Blood samples (each 5 ml) were collected by venipuncture 5, 6, 7, 8, and 9 h after dosing and placed in heparinized tubes. Two urine collections were made from 5-6 and 7-8 h, respectively, after dosage and urine volume and pH were recorded. Plasma and urine samples were stored at  $-20^{\circ}\text{C}$  until analyzed for sulfonamide content. All subjects were given a questionnaire covering their past medical history, current medications, racial origin, occupation, and smoking and drinking habits.

**Estimation of Sulfamethazine and *N*-Acetylsulfamethazine in Plasma.** HPLC<sup>4</sup> was used for these analyses. The system consisted of a Waters Associates Model 590 pump,  $\lambda_{\text{max}}$  Model 481 variable wavelength detector, Z Module with C<sub>18</sub>- $\mu$ Bondapak (8MBC1810 $\mu$ ) column, and a Hewlett-Packard Model 3380A integrating recorder. Mobile phase was pumped at a flow rate of 3.5 ml/min and eluting compounds were detected by their UV absorbance at 254 nm.

Plasma (0.1 ml) was added to polypropylene tubes containing 7.8  $\mu\text{g}$  phenazone as internal standard. Acetonitrile (1 ml) was added and the contents vortexed for 20 s. After centrifugation at  $1500 \times g$  for 5 min, 0.2 ml of the supernatant was removed to a clean tube and evaporated to dryness under N<sub>2</sub> at 50°C. The residue was redissolved in 0.1 ml of HPLC mobile phase (methanol:0.05 M phosphate buffer, pH 3.77, 29:71) and 0.02-ml aliquots were injected onto the column. Approximate retention times were 4.2 min for sulfamethazine, 6 min for *N*-acetylsulfamethazine, and 7.1 min for phenazone. A standard curve in the range of 0.005-0.1 mg sulfonamide/ml plasma was prepared as above, and unknown samples were interpolated from a plot of peak height ratio (sulfonamide:internal standard) versus sulfonamide concentration. The within-day coefficients of variation for the procedure were 2.9, 2.85, and 2.57% for sulfamethazine and 1.76, 3.65, and 2.58% for *N*-acetylsulfamethazine, respectively, at 0.01, 0.04, and 0.08 mg/ml ( $n = 5$ ).

**Estimation of Sulfamethazine in Urine.** Analyses were carried out by HPLC as above. Aliquots of the 7- to 8-h urine sample were adjusted to pH 12 with 1 M NaOH and diluted with water (approximately 1:25 for slow and 1:10 for fast acetylators). A standard curve containing 0.001-0.1 mg sulfamethazine/ml of similarly diluted blank urine was prepared for each batch of analyses. Aliquots of standards or unknown

<sup>4</sup> The abbreviation used is: HPLC, high performance liquid chromatography.

urine samples (0.02 ml) were injected directly onto the HPLC column. The mobile phase was methanol:0.05 M phosphate buffer, pH 3.77 (25:75). Approximate retention times for sulfamethazine and *N*-acetylsulfamethazine were 5.9 and 9.6 min, respectively. Unknowns were interpolated from the standard curve and corrected for dilution factor and urine volume. The within-day coefficients of variation were 3.67, 0.32, and 0.61%, respectively, at 0.01, 0.04, and 0.08 mg sulfamethazine/ml urine ( $n = 5$ ).

The Bratton-Marshall colorimetric procedure was used to measure sulfamethazine and *N*-acetylsulfamethazine concentration in the 5- to 6-h urine sample according to the method of Schroeder (18).

**Calculation of Phenotype Indices.** A one compartment open model was fitted to the plasma sulfamethazine/time data using the nonlinear least squares program NONLIN (19) and assuming a systemic availability of 1. Total body, renal, and metabolic clearances for sulfamethazine were then calculated as previously described (17). The molar ratio of *N*-acetylsulfamethazine:*N*-acetylsulfamethazine plus sulfamethazine was calculated (20) for both plasma at 6 h and the 5- to 6-h urine sample.

#### Drugs and Chemicals

Waters Associates HPLC grade methanol was used. Sulfadimidine sodium (British Pharmacopoeia) and phenazone (British Pharmaceutical Codex) were used while *N*-acetylsulfamethazine was synthesized by acetylation of the parent compound in acetic anhydride for 20 min at 50°C followed by recrystallization from methanol:water (mp = 255°C).

#### Data Analysis

Data are summarized as mean  $\pm$  SD or mean and range unless otherwise specified. Differences between means are assessed by Student's *t* test or the Mann-Whitney *U* test as appropriate. Acetylator phenotype categorization data for the three subject groups were compared by  $\chi^2$  analysis. Linear regression analysis was used to correlate some variables.

## RESULTS

Several of the subjects who were originally phenotyped (50 cancer patients, 46 old and 50 young controls) were later excluded from further study for various reasons. In the cancer group, one was excluded because his diagnosis was subsequently altered to polyposis, while in the old control group, four were excluded because they had coexisting ulcerative colitis, a disease having a strong association with colorectal cancer, and another because a hepatic carcinoma was subsequently diagnosed. Five young controls were excluded because it was not possible to match their racial origin (Asian) with that of subjects in the other groups (all Caucasians). Table 1 shows the characteristics of the remaining subjects.

Table 1 Demographic characteristics of the subjects

	Subject group		
	Young controls	Old controls	Cancer patients
Total no.	45	41	49
Age (yr)	21.6 $\pm$ 3.8 <sup>a</sup> (18-36) <sup>b</sup>	66.4 $\pm$ 8.7 (41-84)	64.7 $\pm$ 8.8 (41-80)
No. of males/no. of females	24/21	33/8	35/14
Body wt (kg)	68.7 $\pm$ 11.3 (47-90)	74.0 $\pm$ 12.2 (50-102)	69.4 $\pm$ 10.0 (47-95)
Smokers (% of total)	28.8	82.9	75.5
Yr smoked	5.3 $\pm$ 3.1	38 $\pm$ 16	37 $\pm$ 15
Drinkers (% of total)	77.3	76.9	76.7
Alcohol consumption (g/wk)	80 $\pm$ 16 <sup>c</sup>	160 $\pm$ 28	173 $\pm$ 20

<sup>a</sup> Mean  $\pm$  SD.

<sup>b</sup> Numbers in parentheses, range.

<sup>c</sup> Mean  $\pm$  SE.

In terms of their lifetime smoking and drinking history, the old controls were very similar to the cancer patients. At the time of survey, 30% of young control smokers, 73.5% of old control smokers, and 94.5% of cancer patient smokers had given up the habit. Mean alcohol consumption was similar in the old controls and cancer patients, but the young controls consumed significantly less alcohol than either of the other two groups (Student's *t* = 2.3 or 3.5, respectively;  $P < 0.05$ ). Only two of the older controls and six cancer patients had ceased alcohol consumption at the time of survey. The distribution of occupations was similar in the cancer patients and the old controls and no high risk occupations were identified. None of the subjects was taking medication which could interfere with the phenotyping procedure.

The phenotyping method of Lee and Lee (17) was utilized in the study since it potentially offers the ability to identify slow, fast, and intermediate phenotypes rather than just the slow and fast phenotypes as is usual with most other commonly used methods of phenotyping (18, 21, 22). However, classification by elimination rate constant, total body clearance, or metabolic clearance in most instances yielded distributions in which there was no clear delineation of the heterozygous intermediate acetylators. Only the data for metabolic clearance are shown (Fig. 1).

It was therefore decided to analyze the data in two classifications only: slow acetylators (homozygotes) and fast acetylators (heterozygotes plus homozygotes). Data assessed in this way were the urinary ratio in the 5- to 6-h sample, the plasma

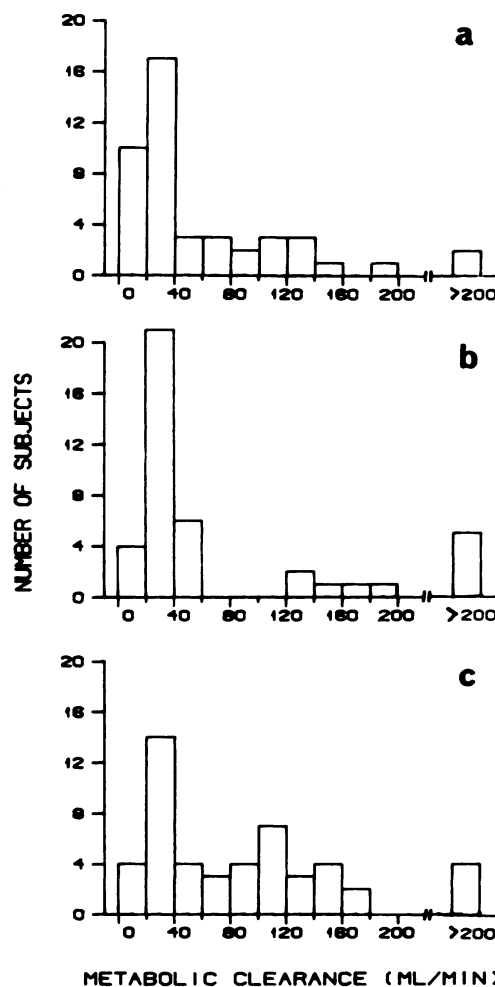


Fig. 1. Frequency histograms for metabolic clearance of sulfamethazine in (a) young control subjects, (b) old control subjects, and (c) cancer patients.

ratio at 6 h, and the metabolic clearance of sulfamethazine. Probit plots of cumulative number of subjects *versus* three different phenotyping indices (log scale) are shown in Figs. 2, 3, and 4. In the case of plasma ratio (Fig. 2), there was a clear separation of slow and fast phenotypes for all subject groups ( $>0.6 = \text{fast}$ ;  $<0.6 = \text{slow}$ ). For urinary ratio (Fig. 3), while there was no doubt that two populations were identifiable, the cutoff point was distinct only in the young control group. In considering this data, a cutoff point of 0.7 has been applied on the basis of our own findings and because of its use in previous studies (18, 20). For metabolic clearance (Fig. 4), it was also possible to distinguish two distinct populations, but a clear separation was seen only in the old control group. In the other two groups of subjects, there was a continuity of observations joining the data at the two extremes of the population. In the data analysis, a cutoff of 55 ml/min was chosen on the basis of frequency histogram plots of the data which indicated that the slow acetylator mode for all three groups was in the range 20–40 ml/min (see Fig. 1) and is consistent with previously published data.

The distribution of subjects into slow and fast acetylator

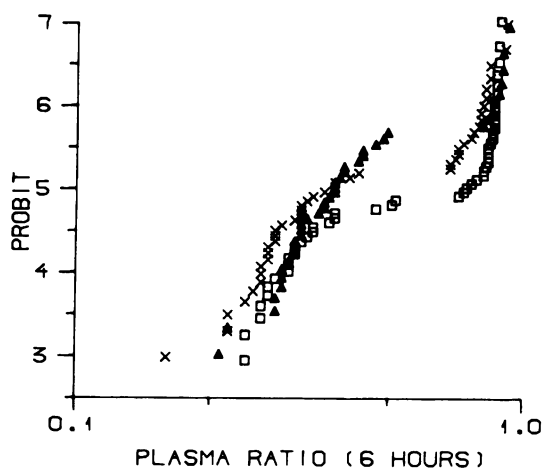


Fig. 2. Probit plot of cumulative number of subjects *versus* plasma ratio (*N*-acetylsulfamethazine:*N*-acetylsulfamethazine plus sulfamethazine at 6 h; log scale) for cancer patients (□), old control subjects (▲), and young control subjects (×).

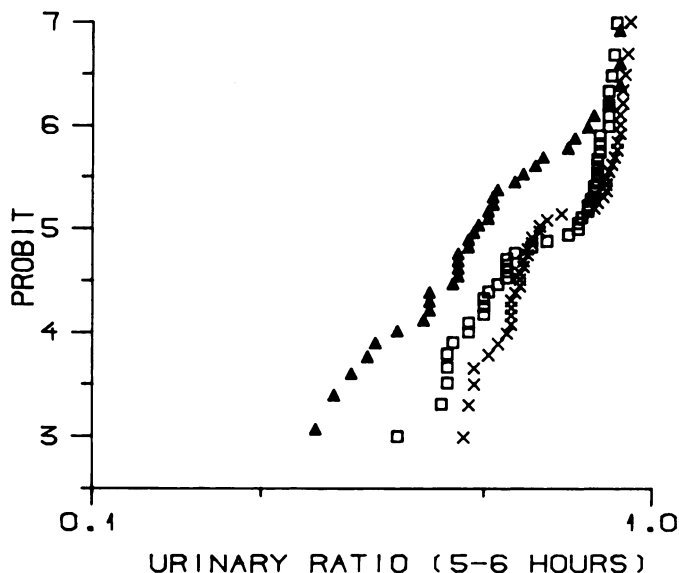


Fig. 3. Probit plot of cumulative number of subjects *versus* urinary ratio (*N*-acetylsulfamethazine:*N*-acetylsulfamethazine plus sulfamethazine; log scale) for cancer patients (□), old control subjects (▲), and young control subjects (×).

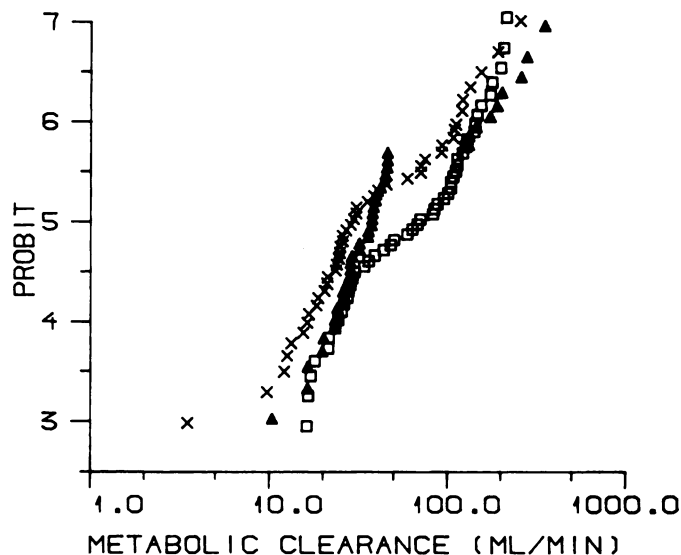


Fig. 4. Probit plot of cumulative number of subjects *versus* metabolic clearance of sulfamethazine (log scale) for cancer patients (□), old control subjects (▲), and young control subjects (×).

Table 2. Distribution of acetylator phenotypes in control and cancer groups

Acetylation index	Number of slow/fast acetylators for		
	Young controls	Old controls	Cancer patients
Plasma ratio (6 h)	26/19	31/10 ( $\chi^2 = 7.5$ ; $P = 0.006$ ) <sup>a</sup>	22/27 ( $\chi^2 = 5.03$ ; $P = 0.023$ ) <sup>b</sup>
Urinary ratio (5–6 h)	25/20	28/9 ( $\chi^2 = 6.4$ ; $P = 0.01$ ) <sup>a</sup>	20/24 ( $\chi^2 = 3.57$ ; $P = 0.055$ ) <sup>b</sup>
Metabolic clearance	29/16	31/10 ( $\chi^2 = 8.5$ ; $P = 0.003$ ) <sup>a</sup>	21/28 ( $\chi^2 = 8.3$ ; $P = 0.004$ ) <sup>b</sup>

<sup>a</sup> Pearson's  $\chi^2$  with Yates' correction for comparison of old controls with cancer patients.

<sup>b</sup> Pearson's  $\chi^2$  with Yates' correction for comparison of combined control groups with cancer patients.

classifications is summarized in Table 2. The index used did not appear to have much influence on the overall results. There were no significant differences in phenotype distribution between the young controls and either the old controls or the cancer patients, but the cancer patients had a consistently and significantly greater proportion of fast acetylators than did the old control group. Both plasma ratio and metabolic clearance were also significantly different between the cancer patients and the combined control groups.

Renal clearance of sulfamethazine was significantly lower ( $z = 2.82$ ;  $P < 0.05$ ) in the young controls ( $3.66 \pm 0.44$  ml/min) than in the cancer patients ( $6.21 \pm 0.96$  ml/min), who were similar to the old controls ( $5.6 \pm 0.82$  ml/min). When the subjects were classified according to plasma index, renal clearance of sulfamethazine was found to be 1.5- to 2-fold greater in fast acetylators than in slow acetylators in all three groups of subjects.

In the cancer group, the time between resection of the tumor and the phenotyping study varied between 0.01 and 15 years. Linear regression analysis showed that there was no significant correlation between either total body ( $r = 0.03$ ;  $P = 0.86$ ) or metabolic clearance ( $r = 0.03$ ;  $P = 0.86$ ) and the time between resection and phenotyping.

## DISCUSSION

The influence of age on sulfamethazine phenotype is controversial, with one large study (22) showing an increased propor-

tion of slow acetylators in the elderly and several other small studies showing that age had no significant influence (10, 23, 24). Because of this we included a young control group and an older control group in our study design. In the final analysis, although there was a trend towards more slow acetylators in the older group, the difference was not statistically significant.

Values for renal clearance of sulfamethazine in the cancer patients and older controls were similar to previously reported values (17, 21). The slightly but significantly lower renal clearance in young controls is most likely a reflection of a more efficient renal reabsorption mechanism in these subjects.

Classification of our subjects into slow and fast phenotypes indicated that there were significantly more fast acetylators in the cancer group than in the older controls (Table 2). The difference was apparent, irrespective of which index of acetylation status was used. While this finding is similar to the situation for patients with breast carcinoma (13, 14), it is opposite to that pertaining for bladder carcinoma (10–12). This raises the question of whether the disease is a result of the phenotype or the phenotype a result of the disease. Bulovskaya *et al.* (13) presented some evidence suggesting that acetylator phenotype changed as a result of tumor resection and associated chemotherapy. However, their results were complex since four patients changed from slow to rapid status while another three changed in the opposite direction. Moreover, this phenomenon was difficult to interpret because of concurrent therapy with various anticancer drugs. In the present study, no patients received chemotherapy and we reasoned that if the disease itself had an influence on the phenotype, then such influence would be expected to decrease with time after resection of the tumor. In this regard we found no correlation between phenotype and time after tumor resection, and hence we consider that the observed distribution suggests that phenotype is a factor associated with the occurrence of colorectal carcinoma.

In the general sense, the mechanism whereby acetylation might be linked to the carcinoma is unknown since both phenotypes have been implicated in cancers occurring in different tissues (10–14). Differences in metabolic activation pathways of xenobiotics in different tissues or differences between substrates in their pathways of metabolism could explain these findings. In relation to colorectal carcinoma, our findings confirm that further research should be directed to the identification of xenobiotics which are subject to metabolic activation by acetylation and which may thereby become contributory factors in the pathogenesis of this disease. Human feces have been shown to contain mutagens (25), and these were more frequently identified in populations with high risk of colorectal carcinoma (19%) than in low risk populations (0–2%) (26). Recent studies with dinitropyrenes from diesel exhaust (27) have shown that binding of these known mutagenic and carcinogenic compounds to DNA is mediated by sequential nitroreduction and acetylation steps. Similarly, using cultured rabbit hepatocytes, genotoxicity of benzidine (28) and 2-aminofluorene (29) was shown to be greater in fast than in slow acetylator rabbits. Acetylation may well be an important step in the metabolism of carcinogens which affect the colon or rectum and further studies of this pathway of metabolism may assist in their eventual identification.

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