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Acetylator Polymorphism in Human Colorectal Carcinoma[1]

José M. Ladero,[2] José F. González, Julio Benítez, Emilio Vargas, María J. Fernández, Walid Baki, and Manuel Diaz-Rubio

Department of Medicine, Complutense University [J. M. L., M. J. F., M. D-R.], and Services of Digestive Diseases [J. M. L., M. D-R.], Endoscopy [J. F. G., W. B.], and Clinical Pharmacology [E. V.] of the University Hospital of San Carlos, Ciudad Universitaria, 28040 Madrid; and the Department of Pharmacology [J. B.], Facultad de Medicina, University of Extremadura, 06071 Badajoz, Spain

ABSTRACT

Acetylator phenotype has been determined using sulfamethazine in 109 patients histologically diagnosed with colorectal carcinoma (resected in 74 patients by the time of the study) and in 96 age-matched controls.

Fifty-five % of patients and 58.3% of controls were classified as slow acetylators ($\chi^2 = 0.11$, not significant). No differences were observed in the distribution of acetylator phenotype when analyzing separately male and female, surgically treated and untreated, and colonic and rectal carcinoma patients.

We conclude that acetylator polymorphism is not a genetic trait related to the risk of developing colorectal carcinoma in human beings.

INTRODUCTION

The acetylation of some homocyclic arylamines (drugs and carcinogens) is polymorphic and inherited as a mendelian genetic trait. Slow acetylators are obligate homozygotics for the recessive allele, and rapid acetylators may be homo- or heterozygotics for the dominant allele (1).

Distribution of acetylator phenotype has been studied in many diseases (2), among them the most common cancers, due to the importance of metabolic processing that many environmental carcinogens must undergo to become activated to immediate carcinogens. Results have been negative for cancers of the lung (3–6), breast (7–10), and lymphoid tissue (11), but an excess of slow acetylators has been detected among patients with gastric carcinoma (12) and the risk of bladder urothelioma of occupational origin is greater in slow than in rapid acetylators (13). Two studies on colorectal carcinoma (14, 15) have suggested an excess of rapid acetylators in patients suffering from this neoplasia.

In the present study, the aim has been to elucidate the distribution of the acetylator phenotype in a large group of patients with colorectal carcinoma, in an attempt to establish whether any relationship exists between this genetic polymorphism and the risk of developing this neoplasia.

MATERIALS AND METHODS

One hundred nine (52 male) Spanish patients histologically diagnosed of colonic (61 cases) and rectal (48 cases) carcinoma were included in the study. Mean age was 65.6 years (SD 9.7 years). Seventy-four had suffered surgical excision of the tumor by the time of their inclusion in the study. None showed clinical or ultrasonographical evidence of liver metastases, and among those in which the tumor had been resected, no signs of local recurrence were found. No patient had clinical or analytical signs of liver and kidney disease or was taking any drug known to interfere with the metabolism or the analytical determination procedure of sulfamethazine. Informed consent was obtained in every case.

The control group was composed of 96 healthy Spanish subjects (mean age, 63.4 years, SD 8.4; 42 males) not taking any drug.

Acetylator phenotype was determined using sulfamethazine (16). A blood sample was taken 6 h after an oral dose of sulfamethazine of 10 mg/kg body weight, and total and acetylated sulfamethazine in plasma were determined using a spectrophotometric method (17). The limit between slow and rapid phenotypes was established at 45% of the plasma sulfamethazine in its acetylated form (18).

The statistical analysis was made using the χ^2 test with Yates' correction for categorical variables and the Mann-Whitney U test for comparison between means. The null hypothesis was rejected when $P < 0.05$.

RESULTS

Sixty patients (55.0%) and 56 control subjects (58.3%) were classified as slow acetylators ($\chi^2 = 0.11$, not significant). The distribution of frequencies of rates of acetylation is shown in Fig. 1. Age at diagnosis did not differ between slow and rapid acetylators. No differences in the distribution of acetylation phenotype were found when comparing male with female patients, surgically treated and untreated patients, and colon cancer with rectal cancer patients.

In both cases and control groups, the distribution of the acetylator phenotype was very close to that found in a younger control group previously studied in our laboratory (19) using the same procedure, composed of 157 Spanish subjects (mean age, 22.6 years, SD 3.1, 60 of them male, 57.3% slow acetylators).

DISCUSSION

We have found no relationship between the acetylator polymorphism and the risk of suffering colorectal carcinoma. This negative result persisted when analyzing separately male and female patients, colonic and rectal tumors, and surgically treated and untreated patients.

These results do not confirm previous reports. Lang *et al.* (14) classified as rapid acetylators 46.5% of 43 patients and 26.8% of 41 controls. The proportion of slow acetylators in this control group is the highest we have found throughout the literature in any population of Caucasian origin (2, 20–22). Although the ethnic origin of this series is not cited, we assume that it is white and homogeneous, as relevant racial differences exist in the distribution of the acetylator polymorphism (22). On the other hand, the proportion of slow acetylators among patients is in the range of that found in Caucasian populations (2, 20–22).

Ilett *et al.* (15) studied 49 patients and 2 control groups, one of them in the age range of the cases and the other one being

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[2] To whom requests for reprints should be addressed, at C/Modesto Lafuente 46, 5º C, 28003 Madrid, Spain.

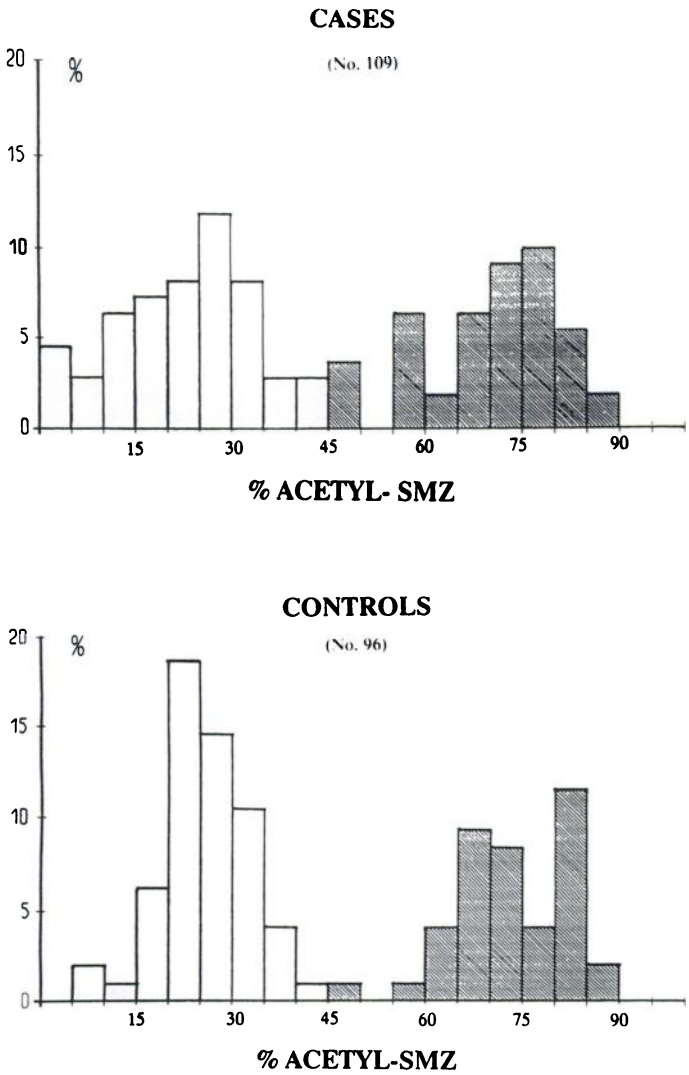

Fig. 1. Distribution of frequencies of acetylation rates of sulfamethazine (SMZ) in colorectal cancer patients (*top*) and in control subjects (*bottom*). The limit between slow (□) and rapid (▨) acetylators is fixed at 45% of the total SMZ in its acetylated form.

much younger. They found an excess of slow acetylators in old control subjects in comparison with patients and younger control subjects, interpreting this difference as suggestive of an association between the risk for developing colorectal carcinoma and the rapid acetylator phenotype.

Data on the distribution of acetylator phenotype in different age groups are not uniform. Gachalyi *et al.* (23, 24) found an excess of slow acetylators among elderly people of Hungarian origin, but Paulsen and Nilsson (25) only detected the same excess among males and suggested that drug interactions could be responsible for such a difference, and other studies (26–30) have not shown any difference in the distribution of acetylator polymorphism in relation to age. Price-Evans (2) and Weber (22) agree when considering the effect of aging on the rate of polymorphic acetylation as slight in comparison with that of hereditary origin, and not able of resulting in misclassification of the individual by acetylator phenotype. Therefore, the excess of slow acetylators reported by Ilett *et al.* (15) in their control group of advanced age could be due to the small size of their series.

Theoretically, at least 2 conditions must occur to explain any hypothetical relationship between acetylator polymorphism and the risk for developing colorectal carcinoma: procarcinogens acting as substrates for polymorphic NAT[3] must reach the large bowel, and this enzymatic activity must be present in its mucosa.

Many procarcinogens are found in stools, but NAT activities are centered on arylamine compounds, both homo- and heterocyclic. Some homocyclic arylamines are strong bladder carcinogens, and they are inactivated through polymorphic *N*-acetylation (31), a fact that may explain the higher risk for slow acetylators to develop occupational bladder carcinoma (13). Nevertheless, a role for polymorphic acetylation of homocyclic arylamines does not seem probable in colorectal cancer, because this tumor has not been recognized as an occupational disease. Probably the minute quantities of homocyclic arylamines that are ingested are absorbed in the small bowel and metabolized in the liver, and never reach the lumen of the large bowel, except if any of them were re-excreted in the bile.

Highly mutagenic heterocyclic arylamines have been identified as pyrolysis products formed during the cooking of meats and other foods (32, 33). These substances and their *n*-hydroxyarylamine metabolites seem to be acetylated primarily via the monomorphic NAT isozyme present in the colon, and they are not substrates for polymorphic NAT, at least in the hamster (34).

Human colonic mucosa is the site of both mono- (35) and polymorphic (36) NAT activities. The lack of relationship between acetylator polymorphism and the risk of colorectal cancer that we have found in this study would be due to a "lack" of adequate carcinogens in the large bowel instead of to the absence of the enzymatic machinery that converts these carcinogens into their active end-products. In this sense, if the excess of rapid acetylators among colorectal cancer patients previously reported (14, 15) were real and not due to the inadequacy of the control groups, dietary differences could explain these divergent findings. The Spanish-Mediterranean diet is rich in fiber and in monounsaturated fat (olive oil), whereas the Anglo-Saxon diet has a higher content of saturated fat and proteins of mammalian origin, from which different and more active carcinogens would be derived (37). Moreover, cooking methods, including "barbecuing," which obviously increases pyrolytic changes in food, are by far more used in the United States and in Australia than in Spain.

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[3] The abbreviation used is: NAT, *N*-acetyltransferase.

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