Polish Journal of Occupational Medicine Vol. 1, No. 4, 1988

THE BIOCHEMICAL INDICES OF GENETIC SUSCEPTIBILITY TO CANCER. ACETYLATION PHENOTYPE AND BLADDER CANCER

JANUSZ HANKE, MD, PhD, BOŻENNA KRAJEWSKA, DSc

Department of Laboratory Diagnostics, Nofer's Institute of Occupational Medicine, Lodz, Poland

Key words: Genetic susceptibility to cancer, Ecogenetics, Acetylation phenotypes

Abstract. The human population consists of slow and fast acetylators. The hypothesis has been put forward that slow acetylators are predisposed to bladder cancer caused by exposure to aromatic amines. The present paper is devoted to the review of retrospective studies designed to prove the correctness of the hypothesis.
Prospective studies have also been undertaken aimed at eliminating some potential systematic errors. An additional report considering the results of studies will be prepared.

As regards causation, human cancer may be divided into four classes, depending on the presence or absence of detectable inheritable (H^+) or environmental (E^+) factors:

$$H^+E^+,\ H^-E^-,\ H^+E^-,\ H^-E^+$$

Some hereditary agents activate cancer to a particular susceptibility to environmental conditions. The most frequent representatives of carcinogens in the environment are procarcinogens. Many body factors contribute to the susceptibility to cancer after the influence of chemical carcinogens. In relation to procarcinogens, which may induce the carcinogenic process after metabolic activation, metabolism of these compounds is the most important marker of an individual's reaction. Particular metabolites of procarcinogens differ remarkably when analysing their reactivity towards cellular elements. On the one hand, the compounds characterized by electrophilic properties and a high affinity to nucleophilic groups are formed. On the other hand, compounds arise

Address reprint requests to Janusz Hanke, Department of Laboratory Diagnostics, Nofer's Institute of Occupational Medicine, 8 Teresy Street, P.O.Box 199, 90-950 Lodz, Poland

INSTYTUT MEDYCYNY PRACY IM. PROF. J. NOFERA

which are easily soluble in water and quickly excreted from the body and which can be designated as metabolic products. The proportion of activity of alternative metabolic pathways determines whether the dominance will be achieved by strong acting carcinogens or products quite harmless to the organism. Thus, indvidual susceptibility to the action of a particular carcinogen is regulated by the activity of determined enzymes. So, we can speak about the activation or inactivation of a carcinogen in the organism.

The first phase of metabolism of procarcinogens is generally catalysed by the multifactorial system of monooxygenases. An example of genetically determined polymorphism influencing the individual sensibility towards chemical carcinogens may be the differentation of inducibility of particular forms of aromatic hydrogen hydroxylase. Other enzymes, which play an important role in detoxification are: epoxide hydrolase and UDP-glucuronaltransferase. Glucuronaltransferase causes the synthesis of glucuronides from the phenoles formed during the metabolism of xenobiotics. The genetically determined polymorphism of this enzyme was also described. The conjunction of epoxides with glutathione also belongs to the detoxifying processes. This process is catalysed by glutathione-S epoxide transferase. This is one of the more important detoxifying reactions, and its efficiency can be regulated by the availability of reduced glutathione. Therefore, the genetically determined enzyme variants taking part in the synthesis and reduction of glutathione can also change the metabolism of carcinogenic substances.

Acetylation has been linked both to the activation of carcinogens inducing liver tumours and to carcinogenic detoxification in aromatic-amine bladder cancer. These systems have been investigated in animals. Enzymatic differences between species have been linked to different sites of malignant disease and, as a result of these studies, it has been postulated that the human liver-bound enzyme group, N-acetyltransferase, might play a significant part in the control of detoxification of carcinogenic substances metabolised from N-substituted aryl compounds. The rates of acetylation in both man and rabbit vary considerably between individuals, who may be categorised as fast and slow acetylators. Heterogeneity is controlled genetically by two autosomal alleles at a single locus, the trait for rapid acetylation being dominant and for slow acetylation recessive. An intermediate, possibly heterozygous, phenotype can be distinguished. Although not conclusively proven, the physiological determinant of acetylator status is probably the total N-acetyltransferase activity. The clinical consequences of this polymorphism are extensive, having been linked both to an increased susceptibility to adverse reactions to drug therapy and to variations in the therapeutic response.

INSTYTUT MEDYCYNY PRACY IM. PROF. J. NOFERA

Since the end of the 19th century when clinical observations of bladder cancer patients in the German dye industry gave the first evidence that occupational and environmental chemicals are responsible in many cases of disease incidence, several investigations have shown the outstanding role of arylamines and a number of related compounds in human bladder carcinogenesis. In the same way, the employees of several occupations in the chemical industry, including dye, textile, rubber, and aluminium workers as well as painters and hairdressers have been shown to be at high risk of bladder cancer. Estimations for occupational involvement in bladder cancer incidence vary from 10 to 50% depending on the local environment. Together with several cultural habits like cigarette smoking and the abuse of certain drugs and artificial sweeteners, between 50 and 60% of human bladder cancer cases can be attributed to exposure to carcinogenic chemicals. Urinary stasis or other earlier diseases of the urinary tract have been discussed as further risk factors. In the past few years, an association between bladder carcinoma formation and acetylator status has been reported by several authors considering occupational exposure, cultural habits, and stage of bladder cancer at the time of investigation (2, 6, 7, 10). The results obtained from the populations of England, the United States, Denmark and Sweden show contradictory values in some respects and display insufficient data due to the limited number of cases.

Lower et al (5) carried out an epidemiological study in Scandinavia to determine whether the difference in acetylation activity might significantly contribute to the risk of bladder cancer. Bladder cancers do not all result from occupational exposure, neither are they all caused by arylamines. Thus, any effect on N-acetyltransferase is diluted by unrelated cases. Nevertheless, the study suggested that the urban population of Denmark, presumably susceptible to occupational bladder cancer, reveals an excess of slow acetylators as compared with fast acetylators, while the rural population in Sweden suffering from bladder cancer is indistinguishable from controls. The second report was prepared by Cartwright et al (1). Among the workers employed in the Huddersfield dye-manufacturing trade who suffered from bladder cancer, only one out of twenty three dye-workers was a fast acetylator. This indicates a significant difference between the subgroup of dye-workers and the other bladder cancer patients.

The third report was prepared by Hansen et al (3). The bladder cancer group comprised 105 patients, 27 of whom stated occupational exposure to chemicals like arylamines of their derivatives which have a potential of inducing bladder cancer. A significantly higher percentage of slow phenotypes was found in this group in comparison to the control

INSTYTUT MEDYCYNY PRACY IM. PROF. J. NOFERA

group. The percentage of slow acetylators among the occupationally exposed bladder cancer patients was higher than among non-exposed patients.

In the course of these studies, a hypothesis was proposed which stated that acetylator status can be used to identify susceptible individuals in potentially hazardous occupations.

In order to verify this hypothesis, we started a retrospective study which involves the phenotyping of slow and fast acetylators among cancer patients (11). A group of bladder cancer patients was divided into two subgroups by consulting the data obtained from an interview. Patients who delivered no information concerning occupational exposure to aromatic aminocompounds were included in the first subgroup. The pheno-

TABLE 1. Percentage of Slow and Fast Acetylators Among Patients Suffering from Bladder Cancer

	Acetylation phenotype		
	Slow	Fast	Intermediate
Patients with bladder cancer not exposed to aromatic amines * n=32	17 (53.2%)	8 (25.0%)	7 (21.8%)
Patients with bladder cancer exposed to aromatic amines n=13	13 (100.0%)	—	—
Control group n=22	10 (45.4%)	3 (13.7%)	9 (40.9%)

* Examination performed in co-operation with the Department of Pharmacology of Medical Academy in Lodz.

typing of the non-exposed group revealed a normal distribution of slow and fast acetylators. The percentage of the slow acetylators' phenotype corresponded to former results with the control group (Table 1), which represents the general Polish population. Unlike the first subgroup, the second subgroup, which consisted mainly of workers who were exposed to aromatic aminocompounds eg. benzidine, exhibited only the slow acetylation phenotype. The data presented in Table 1 confirm the hypothesis that slow acetylation plays a considerable role in bladder carcinogenesis, especially in people occupationally exposed to arylamines and their derivatives. However, it must be remembered that the acetylator's phenotype, although genetically determined, can be changed during a long-

INSTYTUT MEDYCYNY PRACY IM. PROF. J. NOFERA

-term drug therapy. As a result of the study of Bulovskaya et al (12), the effect on the rate of acetylation of cancer therapy was established. It was found that in 16 of 22 patients receiving treatment for breast cancer, the level of acetylation was not changed after the treatment. In 6 patients, a change in the type of acetylation was found during repeated measurement following the treatment. In 3 cases, the "slow" type converted to the "rapid" one, while in the remaining 3 cases, the

TABLE 2. Percentage of Slow and Fast Acetylators in the Group of Healthy Persons in the Past Exposed to Aromatic Amines (Including Benzidine) and Examined During the Prospective Cohort Study

Total	Mean (years)		Acetylation phenotype		
	Age	Exposure period	Slow	Fast	Intermediate
90 (100)	47.15	21.95	60 (66.7%)	20 (22.2%)	10 (11.1%)

effect was vice versa. Changes in the phenotype of acetylating were recorded also in untreated patients with adenofibromatosis. Till now, such a phenomenon has not been discovered in healthy subjects. Repeated measurement of acetylation rates in healthy persons did not show any significant changes in the original level taken as 100%. Deviation did not exceed ±1%.

To exclude the possibility that the therapy of cancer can influence the acetylation phenotype, a prospective study was initiated. All workers exposed to benzidine until 1981 in a dye factory in Zgierz, and currently exposed to benzidine in a dye factory in Wola Krzysztoporska were included in the observer group. The working conditions during the preceding period have been described elsewhere (4). The percentage of "slow" and "rapid" phenotypes in the observed group is registered in Table 2.

The percentage of "slow" acetylators seems to be a little higher than among the general population of Lodz (8, 9). So far, it is difficult to draw the conclusion from the data that the long-term exposure to aromatic amines does not influence the acetylation phenotype. Our own group is too small for analysis of this kind of influence. But from the data of Cartwright et al (1), it is evident that there were statistically significant differences in the acetylation ratio when the langth of employment in the dye-manufacturing industry was taken into account between subgroups of patients and local controls.

Despite the fact that people forming our observed group are pre-

INSTYTUT MEDYCYNY PRACY IM. PROF. J. NOFERA

sently in good health, it can be expected that in the future a section of them will suffer from bladder cancer. So, it will be worth establishing the proportion of bladder cancers in the slow and fast acetylator group in order to check the hypothesis that the acetylator status has an influence on the individual's susceptibility to cancer.

ACKNOWLEDGEMENT

This work was supported by the Government Research and Development Programme: "Controlling of Neoplastic Diseases". Contract No. CPBR 11.5.108.

REFERENCES

1. Cartwright R. A., Glashan R. W. and Rogers H. J.: Role of N-Acetyltransferase phenotypes in bladder carcinogenesis: a pharmacogenetic epidemiological approach to bladder cancer. Lancet 11, 842—845, 1982. — 2. Evans D. A. P., Eze L. C. and Whibley E. J.: The association of the slow acetylator phenotype with bladder cancer. J Med Genet. 20, 330—333, 1982. — 3. Hanssen H. P., Agarwal J. P. and Goedde H. W.: Association of N-Acetyltransferase polymorphism and environmental factors with bladder carcinogenesis. Study in a North German Population. Eur Urol. 11, 263—266, 1985. — 4. Krajewska D., Adamiak-Ziemba J. and Suwalska D.: Evaluation of occupational benzidine exposure of those operating automatized benzidine production. Med Pracy 31, 5, 403—410, 1980. — 5. Lower G. H., Nilsson T. and Nelson C. E.: N-Acetyltransferase phenotype and risk in urinary bladder cancer: approaches in molecular epidemiology. Preliminary results in Sweden and Denmark. Environ Health Perspect 29, 71—79, 1979. — 6. Miller M. E. and Cosgriff J. M.: Acetylator phenotype in human bladder cancer. J Urol. 130, 65—66, 1983. — 7. Mommsen S., Sell A. and Barford N.: N-Acetyltransferase phenotypes of bladder cancer patients in a low-risk population. Lancet 11, 1228, 1982. — 8. Pawłowska J. and Rakowska Z.: Determination of the phenotype of INH inactivation in patients with pulmonary tuberculosis using an indirect method and a model of sulfamethazine. Pneum Pol. 46, 606—612, 1978. — 9. Skrętkowicz J., Mazurowa A. and Orszulak D.: Acetylation phenotype in a section of the population from the Lodz region. Pol Tyg Lek. 36, 89—91, 1981. — 10. Woodhouse K. W., Adams P. C. and Clothier A.: N-Acetylation phenotype in bladder cancer. Hum Toxicol 1, 443—445, 1982.

11. Eidus L., Varughese M. M. and Hodgkin A. H. E.: Simplification of isoniazid phenotyping procedure to promote its application in chemotherapy of tuberculosis. Bull Wld Health Org. 49, 507—515, 1973. — 12. Bulovskaya L. N., Krupkin R. G. and Bichina T. A.: Acetylator phenotype in patients' breast cancer. Oncology 35, 185—188, 1978.

Received for publication: 27.05.1988
Accepted for publication: 21.11.1988

INSTYTUT MEDYCYNY PRACY IM. PROF. J. NOFERA