Berwick and Vineis (1) recently summarized results from human studies on DNA repair and cancer susceptibility markers. They carefully discussed the aspects relating to technical validity, such as reproducibility, sample size, and selection of control subjects. However, the primary question about the biologic relevance of the assay systems used was discussed in only a few sentences. Of the 64 tabulated studies, three reported DNA polymorphisms, two reported cultured fibroblast assays, two reported kinetics from skin biopsies in situ, and the remaining 57 were different types of lymphocyte assays. The lymphocyte assays have been carried out to make inferences about DNA repair functions in other organs in situ. Circulating lymphocytes are dormant cells and any functional tests on them require extensive in vitro manipulation. The relevance of the tests remains to be established, in spite of the large number of times that they have been used. A relevant repair test measures removal of specific DNA damage in the target organ, when it has been demonstrated that DNA repair is the only means of damage removal (i.e., the adduct is chemically stable and no appreciable cell death and replication takes place). The two cited studies using kinetic tests on skin biopsies do fulfill the criterion of biologic relevance.

Recently, a repair test was developed by measuring the removal of specific UV radiation (UVR)-induced DNA damage in human skin in situ (2). The method was based on the $^{32}$P-
postlabeling technique in which two cyclobutane pyrimidine dimers, T = T and T = C, and two 6-4 photoproducts, T–T and T–C, were quantified based on external standards. Many of the findings challenge results from earlier, published in vitro assays. Repair kinetics of dimers and 6-4 photoproducts encompassed fast and slow components, probably relating to repair of transcribed and nontranscribed sequences, respectively (3).

Dimers were removed considerably more slowly than 6-4 photoproducts, with 50% removal times of approximately 15 and 5 hours, respectively; dimers at TT sites were repaired slower than those at TC sites (3). A 20-fold interindividual variation in repair rates was observed. Because we have applied this test to relatively small numbers of case subjects and matched control subjects, we need to refrain from making general conclusions. However, age does not cause a decline in repair of UVR damage in situ, in contrast to results from the host-mediated assay (4). As evidence of further contradictions, basal cell carcinoma patients have not displayed lower rates of DNA repair (5), and melanoma patients appear to repair DNA damage like healthy matched control subjects (6). The most recent development is a postlabeling assay for excised urinary photoproducts, informative of the total-body UV damage (7).

Valid DNA repair tests will also be exceedingly valuable to analyze the functional effects of DNA repair gene polymorphisms, which is currently a popular research area. Here we concur with Berwick and Vineis who state, in reference to the bewildering literature on attempts to match metabolic genotypes to risk of any cancers: “It is not clear that conducting these studies without concomitant studies of expression and/or function will be fruitful.” Conducting DNA repair tests in the relevant human organs will be fruitful and relevant.

KARI HEMMINKI
GUOGANG XU
FRANK LE CURIEUX

REFERENCES


NOTES

Affiliation of authors: Department of Biosciences at Novum, Karolinska Institute, Huddinge, Sweden.

Correspondence to: Kari Hemminki, M.D., Ph.D., Karolinska Institute, Department of Biosciences at Novum, 141 57 Huddinge, Sweden.

RESPONSE

We are pleased that Hemminki et al. have taken seriously the challenge in our recent review (1) to develop definitive molecular assays for DNA repair. Their conclusions echo ours: neither they nor we really know what the studies in lymphocytes measure. Clearly, their research publications in 1999 and 2000 will be valuable in developing the techniques for studying DNA repair.

We find it interesting that the two studies using kinetic tests on skin biopsies, which Hemminki et al. believe fulfill the criterion of biologic relevance, had positive and statistically significant results (although carried out in only a few subjects). Roth et al. (2) showed that melanoma subjects had lower DNA repair rates than control subjects (P < .001), and Alcalay et al. (3) showed that dimers in basal cell carcinoma subjects were eliminated less rapidly than in control subjects (P < .05).

The overall message that we derive from our analysis of the literature is that a considerable number of studies consistently found an association between biologic tests, whose significance is still obscure, and cancer at several sites. Looking at it this way, we agree with Hemminki and colleagues that further clarification of the biologic background is crucial. However, at this time, we think that focusing our attention on the design of the studies, reproducibility, sample size, and selection of control subjects was necessary to draw valid conclusions at the population level. The issue of biologic relevance of studies of DNA repair in lymphocytes is critical for epidemiologic studies where associations are derived from numerous subjects to define small reproducible alterations that may be important. Most of the work Hemminki et al. cite has been conducted in very small groups and has not yet been reproduced.

In sum, the issues raised by Hemminki et al. are critical for the appropriate assessment of DNA repair. We hope that other eminent scientists will join their efforts to develop appropriate assays for DNA repair.

MARIANNE BERWICK
PAOLO VINEIS

REFERENCES


(2) Roth M, Muller H, Boyle JM. Immunochemical determination of an initial step in thymine dimer excision repair in xeroderma pigmentosum variant fibroblasts and biopsy material from the normal population and patients with basal cell carcinoma and melanoma. Carcinogenesis 1987;8:1301–7.


NOTES

Affiliations of authors: M. Berwick, Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, NY; P. Vineis, Unit of Cancer Epidemiology, University of Torino, and Ospedale S. Giovanni Battista, Torino, Italy.

Correspondence to: Marianne Berwick, Ph.D., Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, 1275 York Ave., Box 588, New York, NY 10021 (e-mail: berwickm@mskcc.org).