DNA repair capacity is a system of defenses designed to protect the integrity of the genome. The difficulty in studying DNA repair capacity in relationship to cancer etiology stems from the costs inherent in conducting whole cell assays, which represent an integrated response to DNA damage, and from the lack of specificity of the current genetic assays, which generally focus on the role of single nucleotide polymorphisms. Studies of DNA repair capacity and cancer etiology require careful consideration of design, potential bias and confounding, and, importantly, assessment of assay variability, both intra-individual and inter-individual, as well as biologic plausibility (1).

Design issues center on the difficulty of selecting appropriate subjects for study. A major problem with almost all studies of DNA repair capacity and its role in cancer etiology is that susceptible individuals should be identified before the development of cancer, rather than after cancer has been diagnosed and treated. This is because the cancer itself and likely its treatment may result in observations slanted toward lower DNA repair capacity among case patients who may have been treated with radiation or chemicals. Therapies may modify DNA repair capacity, and, in fact, are designed to knock out the DNA repair capacity of the tumor.

Potential biases and confounding in studies of DNA repair capacity can result from several factors: an inability to identify all relevant exposures; the inducibility of some DNA repair genes (1), which can occur as a result of exposure to many different agents; and those that represent biologic cross reactivity, age, dietary habits, and exposure to pro-oxidants (2).

Measurement of assay variability is critical for assessing the true, underlying risk estimates. Because DNA repair capacity may be modified by environmental exposures—which could be useful as we consider the potential of DNA repair capacity to be a target for intervention (3)—and a potential therapeutic target (4)—it is critical to understand the inter- and intra-individual variability in any particular set of assays.

In this issue of the Journal, Kennedy et al. (5) report on the assay they developed for DNA repair capacity that takes advantage of the adducts induced by the carcinogenic metabolite of benzo[a]pyrene, benzo[a]pyrene diol epoxide (BPDE). BPDE adducts are repaired by the nucleotide excision repair pathway, which has been implicated along with the homologous recombination and the non-homologous end joining repair pathways in BRCA1/2 associated breast cancer. Kennedy et al. found that this measure of DNA repair capacity was lower in breast cancer case patients than control subjects. This study overcomes some previous limitations of case–control studies of breast cancer by using a robust study design, using a functional and specific characterization of nucleotide excision repair, BPDE, and controlling for daily assay variation using cell lines. Although some limitations are present, the findings should lead to renewed interest in DNA repair capacity as a risk factor for cancer and suggest new avenues for investigation.

A major strength of the study is the family-based design using sisters from the same families that are discordant for breast cancer. The authors report that not only do younger breast cancer patients have statistically significantly lower DNA repair capacity than their sisters without breast cancer, but that also in multivariable models, breast cancer patients have a dose response increase in the odds of breast cancer with decreasing DNA repair capacity, ranging from odds of 1.23 (95% CI = 0.57 to 2.65) to 2.38 (95% CI = 1.17 to 4.86) to 2.99 (95% CI = 1.45 to 6.17) ($P_{\text{trend}} = .002$). The potential confounder body mass index (BMI) was statistically significantly different in simple comparisons between case patients and control subjects. At a BMI equal to or greater than 25, indicative of overweight and obesity, case patients were statistically significantly more likely to have lower DNA repair capacity than control subjects. To our knowledge, this is the first evidence that overweight/obesity may affect DNA repair capacity.

The critical issue of whether breast cancer patients have experienced therapy—either radiation or chemotherapy—has, unfortunately, not been mentioned or controlled for in this study. Radiation therapy, and possibly chemotherapy, appears to lead to decreased DNA repair capacity (6–8). Kennedy et al. (5) measured the daily variation in two cell lines, one DNA repair deficient and one DNA repair proficient. We would also be interested in the repeatability and variation of these assays on the individual lymphoblastoid cell lines over time. There is also the

**Affiliations of authors:** Division of Epidemiology, University of New Mexico, Albuquerque, NM (MB); University of Torino, Imperial College, London, UK (PV).

**Correspondence to:** Marianne Berwick, PhD, MPH, Division of Epidemiology, Epidemiology and Cancer Prevention, MSC 08 4630, CRF 103A, University of New Mexico, Albuquerque, NM 87131–0001 (e-mail: mberwick@salud.unm.edu).

DOI: 10.1093/jnci/dji038

*Journal of the National Cancer Institute*, Vol. 97, No. 2, © Oxford University Press 2005, all rights reserved.
The possibility of technician variability in performing the assays, and this deserves mention.

The data generated by the Kennedy et al. (5) study may add to our ability to develop new hypotheses regarding the etiology of breast cancer. Progress in understanding the role of DNA repair capacity in the etiology of breast cancer has, unfortunately, been slow for a variety of reasons (9). Investigators should be cautious, however, in assigning breast cancer causation to DNA damage from environmental agents such as BPDE, because the potential for confounding by unknown or unmeasured exposures remains high. Nucleotide excision repair is the “generalist” of the DNA repair family and as such performs multiple functions, particularly when other repair pathways exhibit reduced function.

The utility of assays such as that developed by Kennedy et al. (5) should be emphasized. Critical needs for progress in understanding the potentially important role of DNA repair capacity in the development of cancer and thus the ability to mount effective interventions at both the preventive and therapeutic level lies in the development of new functional assays such as this developed in the Santella laboratory. However, high throughput functional assays [e.g., (10)] must be developed to make prospective studies of the role of DNA repair capacity feasible. When DNA repair capacity can be measured easily and quickly, the scientific community will be able to clearly understand the role of DNA repair capacity in the development of cancer and possibly to develop interventions to reduce cancer incidence and mortality.

REFERENCES