REVIEW

Markers of DNA Repair and Susceptibility to Cancer in Humans: an Epidemiologic Review

Marianne Berwick, Paolo Vineis

DNA repair is a system of defenses designed to protect the integrity of the genome. Deficiencies in this system likely lead to the development of cancer. The epidemiology of DNA repair capacity and of its effect on cancer susceptibility in humans is, therefore, an important area of investigation. We have summarized all of the published epidemiologic studies on DNA repair in human cancer through 1998 (n = 64) that addressed the association of cancer susceptibility with a putative defect in DNA repair capacity. We have considered study design, subject characteristics, potential biases, confounding variables, and sources of technical variability. Assays of DNA repair capacity used, to date, can be broadly grouped into five categories: 1) tests based on DNA damage induced with chemicals or physical agents, such as the mutagen sensitivity assay, the G_2-radiation assay, induced micronuclei, and the Comet assay; 2) indirect tests of DNA repair, such as unscheduled DNA synthesis; 3) tests based on more direct measures of repair kinetics, such as the host cell reactivation assay; 4) measures of genetic variation associated with DNA repair; and 5) combinations of more than one category of assay. The use of such tests in human populations yielded positive and consistent associations between DNA repair capacity and cancer occurrence (with odds ratios in the range of 1.4–75.3, with the majority of values between 2 and 10). However, the studies that we have reviewed have limitations, including small sample size, "convenience" controls, the use of cells different from the target organ, and the use of mutagens that do not occur in the natural environment. The evolving ability to study polymorphisms in DNA repair genes may contribute to new understandings about the mechanisms of DNA repair and the way in which DNA repair capacity affects the development of cancer. [J Natl Cancer Inst 2000;92:874–97]

Interindividual variability in human responses to carcinogens has been described repeatedly. Much attention has been devoted to heritable polymorphisms in genes involved in carcinogen metabolism. Another potentially important source of interindividual variability in relation to the development of cancer is DNA repair capacity, including the genetic instability syndromes *(1)*. These are rare, recessive traits that include ataxia-telangiectasia (A-T), Fanconi anemia, and Bloom's syndrome (all of which are characterized by both chromosomal instability and high risk of cancer) as well as xeroderma pigmentosum (XP), a disease caused by a deficiency in nucleotide excision repair that is characterized by extreme susceptibility to ultraviolet (UV) light-associated skin cancer *(1)*. Apart from these rare syndromes, individuals differ widely in their capacity to repair DNA damage from both exogenous agents, such as tobacco smoke and sunlight exposure, and endogenous reactions, such as oxidations *(2)*. At least some of such interindividual difference is likely to have a genetic origin. A number of epidemiologic studies have been conducted to compare measures of DNA repair capacity between cancer case subjects and healthy control subjects to assess the role of repair in the development of human cancer. Such studies have used a variety of measures of DNA repair capacity. However, DNA repair capacity is extremely complex; at this time, the current assays do not measure specific aspects of repair but rather assess more global effects.

Most assays are based on an approach that compares induced DNA damage to circulating lymphocytes from subjects with cancer *with* induced DNA damage to circulating lymphocytes from subjects *without* cancer with quantitation of subsequent "repair" in both groups. Damage is usually delivered in the form of a "pulse" of carcinogen applied to cell culture (e.g., γ-rays, UV radiation, benzo[*a*]pyrene diol epoxide [BPDE], or hydrogen peroxide [H_2O_2]) or to fresh or cryopreserved lymphocytes. A period of time is allowed to elapse for repair to occur, and then damage is measured in a variety of ways (e.g., as unrepaired single- or double-strand breaks or the rate of incorporation of a radioisotope).

We have attempted a formal evaluation of the published studies of DNA repair capacity in the etiology of human cancer and have considered their design, methods, and results. In addition, we have assessed the results and the limitations of such studies. We use the term "DNA repair capacity" to describe a variety of different techniques and manifestations, not all of which are necessarily a direct expression of actual repair of DNA damage but are often a measure of unrepaired DNA damage.

METHODS

From personal archives and from a MEDLINE® search, we have identified all peer-reviewed studies published through December 1998 on DNA repair and human cancer *(3–66)* (Tables 1 and 2). The studies that we reviewed included only those published through 1998. We have tried to be widely inclusive; however, we realize that some studies may have been inadvertently left out. During 1999, there has been an explosion of new studies published in which DNA repair has been used as an end point. We are in the process of establishing a web site to track all DNA repair studies.

We have included case series in which no standard control group was used but where second primary cancers or family history of cancer were the major focus of the investigation. We excluded other studies without control groups or studies

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).

See "Notes" following "References."

Table 1. Design of studies of DNA repair and susceptibility to cancer in humans by type of assay*

Authors, y (reference No.)	Case subjects, site/No.	Control subjects, type/No.	Phenotyping technique and cells used	Sources of bias	Covariates	Comments
			1) DNA damage to cells			
Cherry and Hsu, 1983 *(3)*	25 patients with familial medullary carcinoma of the thyroid and 10 first-degree blood relatives of these patients	20 healthy control subjects	Bleomycin-induced mutagen sensitivity in lymphocytes	Potential selection bias, small sample size	None	
Hsu et al., 1985 *(6)*	75 case subjects with a variety of cancers	100 normal volunteers	Bleomycin-induced mutagen sensitivity in lymphocytes	Potential confounding by age	None	
Hsu et al., 1989 *(12)*	83 patients with colon cancer, 77 with head/neck cancer, 82 with breast cancer, and 71 with lung cancer	335 normal individuals	Bleomycin-induced mutagen sensitivity in lymphocytes	Potential selection bias	No covariates	
Rudiger et al., 1989 *(14)*	45 patients with lung cancer (24 females and 21 males; mean age, 56 y)	39 patients with cutaneous melanoma (25 females and 14 males; mean age, 35 y) and 29 healthy subjects (12 females and 17 males; mean age, 47 y) without family history of cancer	O^6MGT repair in fibroblast cultures	Potential selection bias, age difference between case subjects and control subjects	Stratification on family history of lung cancer and age	
Spitz et al., 1989 *(15)*	75 patients with squamous cell carcinoma of upper aerodigestive tract (53 males and 22 females; mean age, 57 y)	62 hospital employees and spouses of case subjects (44 males and 18 females; mean age, 46 y)	Bleomycin-induced mutagen sensitivity in lymphocytes	Control subjects only partially comparable to case subjects	Smoking status, alcohol consumption, age, sex	Case and control subjects filled out a self-administered questionnaire for risk factors. Scoring of breaks was blind as to the case–control status, based on 50 metaphases per sample. Dichotomization of breaks was based on 25th percentile.
Schantz et al., 1990 *(16)*	13 patients with multiple malignancies of the head and neck	71 patients with single primary malignancies of the head and neck	Bleomycin-induced mutagen sensitivity in lymphocytes	Short follow-up time; radiation therapy and chemotherapy in some of subjects	Sex, age, length of follow-up	Purpose of investigation was to study second malignancies in relation to mutagen sensitivity. Median follow-up was 19 mo.
Hsu et al., 1993 *(24)*	62 melanoma patients and 71 head and neck cancer patients	103 healthy individuals	4NQO-induced and bleomycin-induced mutagen sensitivity in lymphocytes	Incomplete assaying of blood samples for both mutagens	None	
Spitz et al., 1993 *(25)*	108 subjects with untreated squamous cell carcinoma of upper aerodigestive tract	108 age, sex, and ethnicity matched, without cancer history, recruited from the blood bank donors	Bleomycin-induced mutagen sensitivity in lymphocytes	Control subjects from blood bank might not be similar in SES or lifestyle habits, such as smoking and diet	Alcohol consumption, cigarette smoking, educational level	Mutagen sensitivity was calculated as >0.8 breaks per cell.
Parshad et al., 1993 *(26)*	6 family members with Li–Fraumeni syndrome (5 with diverse cancers and 1 with premalignant lesion)	2 unrelated normal control subjects and 1 spouse	G_2-phase x-irradiation (Sanford assay) in lymphocytes	Small sample size	Germline p53 mutational status	Chromatid breaks observed at G_2 phase are interpreted as unrepaired double-strand breaks.

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Table 1 (continued). Design of studies of DNA repair and susceptibility to cancer in humans by type of assay*

Authors, y (reference No.)	Case subjects, site/No.	Control subjects, type/No.	Phenotyping technique and cells used	Sources of bias	Covariates	Comments
Bondy et al., 1993 *(27)*	46 subjects with upper aerodigestive tract cancer with first-degree relatives with cancer. (These are the case subjects from Spitz et al. 1993 *above*.)	58 subjects with upper aerodigestive tract cancer with no first-degree relatives with cancer	Bleomycin-induced mutagen sensitivity in lymphocytes	Small sample size	Stratified by number of first-degree relatives with cancer	
Spitz et al., 1994 *(32)*	28 subjects who developed second primary cancers	250 subjects with first primary cancers of the upper aerodigestive tract	Bleomycin-induced mutagen sensitivity in lymphocytes		Sex, age, site, stage, smoking status	This is an extension of a previous study (Schantz et al., 1990) to investigate the association of mutagen sensitivity with second primary cancers.
Scott et al., 1994 *(33)*	50 breast cancer patients; 28 obligate A-T heterozygotes	74 healthy donors (39 males and 35 females)	G_2-phase x-irradiation (Sanford assay) in lymphocytes	Potential selection bias	Age, sex	Control group was not described. Case and control subjects have different age and sex distribution.
Cloos et al., 1994 *(34)*	52 head and neck cancer patients with single primary tumors and 20 head and neck cancer patients with multiple primary tumors	50 healthy volunteers and hospital patients without a history of cancer	Bleomycin-induced mutagen sensitivity in lymphocytes	Control subjects statistically significantly younger than case subjects; very different proportion of males to females than multiple primary tumors	Smoking, difficult to determine if other factors were used in multivariate analyses	
Strom et al., 1995 *(36)*	67 Mexican-American lung cancer case subjects (48 males and 19 females)	107 Mexican-American control subjects (68 males and 39 females)	Bleomycin-induced mutagen sensitivity in lymphocytes	Potential selection bias, data on mutagen sensitivity available for 39 case subjects and 59 control subjects with fewer females among case subjects	Age, sex, educational level, income, household size, smoking status, histologic subtype	
Spitz et al., 1995 *(38)*	90 lung cancer case subjects, all African-American (61 males and 29 females; mean age, 58 y)	119 African-American control subjects (80 males and 39 females; mean age, 58 y)	Bleomycin-induced mutagen sensitivity in lymphocytes	Comparability of case and control subjects	Age, sex, smoking status, histology	Case subjects had not been treated with chemotherapy or radiotherapy. All were African-American. Control subjects were a "convenience" sample from community centers, churches, and cancer screening programs. Mutagen sensitivity did not vary by smoking status in control subjects.
Wu et al., 1995 *(39)*	113 African-American lung cancer case subjects and 67 Mexican-American lung cancer case subjects, all previously untreated	270 control subjects (134 African-American and 136 Mexican-American) recruited from community groups	Bleomycin-induced mutagen sensitivity in lymphocytes	Potential selection bias	Age, sex, ethnicity, smoking history, histologic subtype	Mutagen sensitivity data were complete for 132 of 180 case subjects and for 240 of 270 control subjects.
Bondy et al., 1996 *(40)*	45 adult glioma case subjects	117 age-, sex-, and ethnicity-matched healthy blood donors	γ-Radiation-induced mutagen sensitivity in lymphocytes	Potential selection bias	Age, sex, ethnicity	

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Table 1 (continued). Design of studies of DNA repair and susceptibility to cancer in humans by type of assay*

Authors, y (reference No.)	Case subjects, site/No.	Control subjects, type/No.	Phenotyping technique and cells used	Sources of bias	Covariates	Comments
Parshad et al., 1996 *(43)*	27 breast cancer case subjects, 8 with and 19 without a family history of breast cancer	10 normal control subjects without a family history of breast cancer and 3 normal control subjects with a family history of breast cancer	G_2-phase x-irradiation (Sanford assay) in lymphocytes	Potential selection bias	None	Cancer patients were participating in a treatment trial, and control subjects were from a convenience sample.
Cloos et al., 1996 *(44)*	19 patients with head and neck cancer who received 600 mg of NAC supplementation daily for 3–9 mo	14 patients with head and neck cancer who did not receive supplementation	Bleomycin-induced mutagen sensitivity in lymphocytes	Some patients had received chemo-therapy or radio-therapy; small sample size	None	
Cloos et al., 1996 *(45)*	18 head and neck cancer patients, untreated	19 control subjects who were healthy laboratory personnel or patients without a history of cancer	Bleomycin-induced mutagen sensitivity in lymphocytes	Patients differed by age from control subjects	None	
Cloos et al., 1996 *(46)*	313 patients with head and neck cancer in two U.S. institutions and in Europe; 108 case patients in study by Spitz et al., 1993	334 control subjects at the same institutions; 108 control subjects in study by Spitz et al., 1993	Bleomycin-induced mutagen sensitivity in lymphocytes	Control subjects more likely to have family history of cancer	Tobacco use, alcohol consumption, age	
Wei et al., 1996 *(41)*	33 lung cancer case subjects	96 healthy control subjects frequency matched on age to the case subjects (50–85 y); an additional 172 normal individuals (age range, 19–95 y), 49% non-Hispanic white, 40% Hispanic, and 11% African-American	Mutagen sensitivity assay, using BPDE	Selection of subjects, ethnic differences	Age, sex, ethnicity, smoking status, mutagen sensitivity	
Patel et al., 1997 *(47)*	14 breast cancer case subjects (mean age, 49 y) and 19 first-degree relatives (mean age, 39 y)	17 healthy blood donors (mean age, 37 y)	G_2-phase x-irradiation (Sanford assay) in lymphocytes	Comparability of case and control subjects	None	
Schantz et al., 1997 *(49)*	167 patients with upper aerodigestive tract cancer (107 males and 60 females; mean age, 61 y); 146 Caucasians	177 non-cancer subjects identified from a hospital blood bank (111 males and 66 females; mean age, 58.4 y); 157 Caucasians	Bleomycin-induced mutagen sensitivity in lymphocytes	Comparability of case and control subjects	Matched on age and sex	Very little information is given on the selection of control subjects, who are clearly more educated and have a higher income than case subjects.
Jaloszynski et al., 1997 *(50)*	28 breast cancer case subjects, before chemotherapy or radiation therapy (mean age, 56 y)	23 healthy volunteers (mean age, 36 y)	Comet assay, bleomycin assay for mutagen sensitivity in lymphocytes	Potential selection bias, large age difference between case and control subjects	Age	Case subjects were recruited prior to radiotherapy or chemotherapy. The comet assay is a single-cell gel electrophoresis of lymphocytes after mutagen-induced damage. The extent of DNA migration is considered to be an expression of DNA damage/repair. Scoring can be based on image analysis or visual inspection. Case and control subjects were not comparable for age.

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Table 1 (continued). Design of studies of DNA repair and susceptibility to cancer in humans by type of assay*

Authors, y (reference No.)	Case subjects, site/No.	Control subjects, type/No.	Phenotyping technique and cells used	Sources of bias	Covariates	Comments
Wu et al., 1998 *(56)*	67 case subjects with head and neck cancer	81 control subjects	Mutagen sensitivity using BPDE and bleomycin in lymphocytes	Potential selection bias, small sample size	Sex, age, smoking status, ethnicity	
Wu et al., 1998 *(58)*	28 patients with hepatocellular carcinoma (22 Caucasians, 3 Mexican-Americans, and 3 African-Americans)	110 healthy control subjects (88 Caucasians, 12 Mexican-Americans, and 10 African-Americans)	Mutagen sensitivity using BPDE and bleomycin in lymphocytes	Potential selection bias, small sample size	Sex, age, ethnicity	
Wu et al., 1998 *(59)*	57 lung cancer cases	82 control subjects	Mutagen sensitivity using BPDE and bleomycin in lymphocytes	Potential selection bias, BPDE quite toxic and difficult to find optimal concentration for induction and slide quality	Age, sex, smoking status	
Spitz et al., 1998 *(60)*	38 subjects with recurrences or metastases	492 subjects with upper aerodigestive tract cancers (397 males and 95 females)	Bleomycin-induced mutagen sensitivity in lymphocytes	Small sample size of subjects with recurrence	Tumor site, duration in mo to recurrence, smoking status, alcohol consumption, previous treatment, stage, age, sex	Subjects for this study of DNA repair in association with risk of recurrence were recruited at randomization for a phase III randomized trial. Median follow-up was 33.6 mo.
Sigurdson et al., 1998 *(62)*	76 patients with histologically confirmed gliomas	Survival of patients	γ-Radiation-induced mutagen sensitivity in lymphocytes	Potential selection bias, short follow-up, timing of assay in relation to diagnosis	Age, tumor histology, extent of surgical resection	Mutagen sensitivity was defined as >0.55 breaks per cell.
Wang et al., 1998 *(63)*	60 patients with squamous cell carcinoma of the head and neck	112 healthy control subjects	BPDE-induced mutagen sensitivity in lymphocytes	Potential selection bias, small sample size	Age, sex, ethnicity, smoking status, alcohol consumption	
Udumudi et al., 1998 *(64)*	77 patients with mild dysplasia (aged 17–52 y), 91 patients with severe dysplasia (aged 24–70 y), and 52 patients with cervical cancer (aged 24–85 y)	50 healthy control subjects (aged 17–70 y) with normal Pap smear	Comet assay in lymphocytes	Cross-sectional study, need for follow-up study	Age, Pap smear results	
Leprat et al., 1998 *(65)*	13 patients who developed thyroid tumors after radiotherapy	8 healthy donors and 2 case subjects with a history of neck irradiation who did not develop thyroid tumors	Comet assay in lymphocytes	Selection bias, control subjects are still quite young, small numbers	Age, sex, family history of cancer, primary disease, cumulative radiation dose to the thyroid, histology of tumor	Analysis did not actually take these variables into account.
Scott et al., 1998 *(66)*	39 breast cancer patients (mean age ± SD, 58.5 y ± 7.4)	42 healthy control subjects (mean age ± SD, 47.8 y ± 13.4)	Radiation (3.5 Gy; dose rate, 1.0 Gy/min^{-1})-induced micronucleus induction in lymphocytes	Potential selection bias, statistically significant difference between average age of case and normal subjects, but no age effect for cancer patients or normal subjects when analyzed separately	Other covariates measured were stage and grade of tumor, tamoxifen intake, menopausal status, family history of breast cancer, smoking history	
Rao et al., 1998 *(55)*	8 sporadic breast cancer patients and 6 breast cancer patients with affected first-degree relatives	26 healthy subjects with affected relatives (12 males and 14 females), 25 healthy subjects without family history of breast cancer (12 males and 13 females)	Unstimulated lymphocyte index, blast index, mitotic index in untreated and aphidicolin-treated lymphocyte cultures; chromosomal aberrations	Comparability of case and control subjects in terms of sex and exposure histories	None	Aphidicolin is an inhibitor of the DNA-repair enzyme DNA polymerase alpha. Most control subjects were laboratory personnel working with mutagens or radiation.

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Table 1 (continued). Design of studies of DNA repair and susceptibility to cancer in humans by type of assay*

Authors, y (reference No.)	Case subjects, site/No.	Control subjects, type/No.	Phenotyping technique and cells used	Sources of bias	Covariates	Comments
			2) Indirect test of DNA repair or enzyme activity			
Pero et al., 1983 *(4)*	40 male colorectal case subjects prior to chemotherapy and 28 subjects with family history of colorectal cancer (mean age, 63 y)	39 male nonsmokers undergoing preventive examinations (37 Caucasians and 2 Orientals; mean age, 46 y)	N-AcO-2-FAA-induced UDS in lymphocytes	Potential confounding by age, small sample size	Age, blood pressure, smoking habits, sex	Differential storing times of blood between case and control subjects may have biased the results. The effect of experimental HU concentration on interindividual variability has been assessed.
Pero et al., 1985 *(5)*	30 males with colorectal polyps (mean age, 57 y)	48 age-matched males undergoing preventive examinations (mean age, 55 y)	N-AcO-2-FAA-induced UDS and DNA repair proficiency index in lymphocytes	Small sample size	None	
Munch-Petersen et al., 1985 *(7)*	29 subjects with multiple nonmelanoma skin cancers (15 males and 14 females; age range, 37–80 y)	25 healthy individuals (10 males and 15 females; age range, 25–83 y)	UVC-induced UDS; cellular proliferation in lymphocytes	Small sample size	Subjects stratified as sun tolerant and sun intolerant	
Pero et al., 1986 *(8)*	13 patients with adenomatosis of colon and rectum	7 unaffected relatives and spouses of patients	N-AcO-2-FAA-induced UDS in skin fibroblast lines	Small sample size	None	
Kovacs et al., 1986 *(9)*	41 breast cancer patients (aged 33–83 y)	27 healthy women (aged 37–68 y)	UVC-induced UDS, with HU	Potential selection bias, small sample size	None	
Markowitz et al., 1988 *(11)*	22 patients with adenomatous polyps	6 patients with normal colonoscopy and 5 patients with hyperplastic polyps	ADPRT activity modulated with cumene in lymphocytes	Potential selection bias, small control group	None	
Pero et al., 1989 *(13)*	151 miscellaneous cancer case subjects (36 at MSKCC, 15 at the University of Lund, and 100 at Kriser Lung Cancer Center in New York, NY)	467 cancer-free individuals (365 at Strang Clinic in New York, NY; 97 at Kriser Lung Cancer Center; and 5 from the University of Lund Department of Neurosurgery)	H_2O_2 activation of ADPRT in lymphocytes	Potential selection bias	Age, smoking habits, sex; stage, site, and pathology considered as effect modifiers	Characteristics of control subjects were not reported. Distribution by sex was not clear. Patients had not undergone chemotherapy or radiotherapy.
Kovacs et al., 1991 *(18)*	14 case patients with advanced breast cancer (age range, 38–68 y)	92 healthy donors from Basel Blood Transfusion Service (age range, 21–68 y)	Parenteral treatment with Iscador and UV-induced UDS values in lymphocytes	Age range, different regimens for blood collection	None	
Kovacs and Langemann, 1991 *(19)*	8 cancer patients and 1 XP patient	10 age-matched patients with normal DNA repair	UDS kinetics and response to repeated UVC challenge in lymphocytes	Small sample size	None	
Kovacs et al., 1992 *(21)*	15 breast cancer patients (6 having had surgery alone and 9 having had surgery with additional chemotherapy and/or radiotherapy)	92 healthy donors from Basel Blood Transfusion Service (age range, 21–68 y)	UVC-induced UDS in lymphocytes	Different lengths of therapy and follow-up of subjects	Type of therapy	

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Table 1 (continued). Design of studies of DNA repair and susceptibility to cancer in humans by type of assay*

Authors, y (reference No.)	Case subjects, site/No.	Control subjects, type/No.	Phenotyping technique and cells used	Sources of bias	Covariates	Comments
Pero et al., 1992 *(22)*	82 patients who had surgery for removal of breast cancer who were randomly assigned into one of two groups: no drug treatment (n = 40) and 20 mg of tamoxifen/day for 2 y (n = 42); median age, 62 y	Randomized trial of those receiving no drug and those receiving 20 mg of tamoxifen/day for 2 y	H_2O_2 activation of ADPRT in lymphocytes		Age, smoking habits, estrogen use, tamoxifen treatment	
Pero et al., 1992 *(23)*	32 of 50 patients with malignant glioma receiving corticosteroids (age range, 15–81 y)	18 of the 50 patients untreated with corticosteroids	H_2O_2 activation of ADPRT in lymphocytes	Conducted postoperatively; no comparison group	Age, sex, smoking habits, alcohol consumption, use of antiepileptic medications, corticosteroid use, tumor grade	
Ranjit et al., 1995 *(37)*	81 oncology clinic patients with a variety of cancers	66 healthy blood donors	Two-color flow cytometry analysis of PADPRP in lymphocytes	Sample selection, cell replication status, heterogeneity of cellular components	Sex, type of cancer (breast cancer, esophageal cancer, lymphatic and other malignancies)	
			3) Direct measure of repair kinetics			
Roth et al., 1987 *(10)*	16 patients with basal cell carcinoma and 10 with melanoma	30 normal subjects without cancer	RIA measuring loss of antigenicity of thymine dimers and UDS (assumption: loss of antigenicity = repair) in fibroblasts and biopsy specimens	Small sample size	None	
Alcalay et al., 1990 *(17)*	22 patients with basal cell carcinoma (14 females and 8 males; age range, 31–84 y)	19 healthy volunteers (15 females and 4 males; age range, 25–61 y)	Rate of removal of pyrimidine dimers induced by one minimal erythemal dose in skin biopsy specimens	Selection bias, control subjects younger than case subjects	Age, sex, skin type	
Athas et al., 1991 *(20)*	38 subjects with basal cell carcinoma (24 females and 14 males; age range, 28–55 y)	27 patients with benign skin disease (13 females and 14 males) included subjects with solar keratoses (age range, 28–55 y)	Host cell reactivation assay in lymphocytes	Potential selection bias	Sunlight exposure, skin type, hair and eye color, sex, ethnicity, smoking status	A damaged recombinant plasmid DNA-harboring CAT reporter gene was introduced into lymphocytes, and repair activity was measured as a function of the reactivated CAT enzyme. The validity of the method was tested in XP cell lines.
Wei et al., 1993 *(28)*	88 subjects with basal cell carcinoma (55% males; mean age, 49 y), extension of study by Athas et al., 1991	135 cancer-free control subjects with mild skin diseases (50% males; mean age, 46 y)	Host cell reactivation assay in lymphocytes	Multiple comparisons, potential selection bias	Age, sex, smoking status, use of medicines	Assay was based on pilot study by Athas et al., 1991. Results are independent of immunologic function as tested by CD4/CD8 counts.
Wei et al., 1994 *(29)*	88 subjects with basal cell carcinoma (age range, 20–60 y), same subjects as Wei et al., 1993	135 cancer-free control subjects (age range, 20–60 y)	Host cell reactivation assay in lymphocytes	Multiple comparisons, potential selection bias	Age	Although multiple papers have been published from this study, these findings may be useful to focus future studies of DNA repair capacity and cancer.

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Table 1 (continued). Design of studies of DNA repair and susceptibility to cancer in humans by type of assay*

Authors, y (reference No.)	Case subjects, site/No.	Control subjects, type/No.	Phenotyping technique and cells used	Sources of bias	Covariates	Comments
Wei et al., 1994 *(30)*	88 subjects with basal cell carcinoma (age range, 20–60 y), same subjects as Wei et al., 1993	135 cancer-free control subjects (age range, 20–60 y)	Host cell reactivation assay in lymphocytes	Multiple comparisons, potential selection bias	Stratified data by DNA repair level, adjusted for age and family history of skin cancer, to investigate risk factors: skin type, number of severe sunburns, and actinic elastosis	
Hall et al., 1994 *(31)*	86 subjects with nonmelanoma skin cancer from Australia	87 control subjects without nonmelanoma skin cancer from Australia	Host cell reactivation assay in lymphocytes	Transportation of samples, no data on age at first occurrence of skin cancer	Date assay performed, nonmelanoma skin cancer status of subjects, age, sex, viability of lymphocytes, blastogenic rate of lymphocytes, scientist performing assay	This is a formal population-based case–control study. Case subjects were identified through a skin cancer-screening clinic in Geraldton, Australia. Control subjects were a random sample of subjects without a history of cancer. None of the covariates measured (date assay performed, scientist who performed assay, age, or lymphocyte viability) were associated with DNA repair capacity.
Wei et al., 1995 *(35)*	88 patients with basal cell carcinoma (age range, 20–60 y), same subjects as Wei et al., 1993	135 healthy control subjects (age range, 20–60 y)	Host cell reactivation assay in lymphocytes	Multiple comparisons, potential selection bias	Age and sex matched; no additional adjustments	
Wei et al., 1996 *(42)*	51 incident lung cancer case subjects in African-Americans (n = 17), Mexican-Americans (n = 20), and Caucasians (n = 14) (32 males and 19 females)	56 control subjects, convenience sample (*see* Spitz et al., 1995) (38 males and 18 females)	Host cell reactivation assay using BPDE in lymphocytes	Scarcity of available cells, no test of transfection efficiency; selections of subjects	Age, sex, ethnicity, smoking status	Case subjects had not been treated with chemotherapy or radiotherapy.
Cheng et al., 1998 *(53)*	55 newly diagnosed previously untreated head and neck cancer patients (mean age, 57 y), 65% male and 91% Caucasian	61 healthy control subjects (mean age, 59 y), 57% male and 84% Caucasian	Host cell reactivation assay using BPDE in lymphocytes	Potential selection bias	Age, sex, ethnicity, smoking status, alcohol consumption	
			4) Genetic variation in DNA repair genes			
Price et al., 1997 *(51)*	19 cancer patients (8 clinically radiosensitive)	34 non-tumor-bearing volunteers of unknown radiosensitivity	Microsatellite polymorphisms in DNA repair genes (XRCC1, XRCC3, and XRCC5)	Potential selection bias, small sample size	None	Rare polymorphisms were found only among the cancer patients.
Wei et al., 1998 *(52)*	78 patients with newly diagnosed head and neck cancer (mean age, 60 y; 91% Caucasian, 45 males and 33 females)	86 healthy control subjects (mean age, 58 y; 88% Caucasian; 36 males and 50 females)	Multiplex RT–PCR	Potential selection bias, sex differences	Age, sex, ethnicity, smoking status, alcohol consumption	

(Table continues)

Table 1 (continued). Design of studies of DNA repair and susceptibility to cancer in humans by type of assay*

Authors, y (reference No.)	Case subjects, site/No.	Control subjects, type/No.	Phenotyping technique and cells used	Sources of bias	Covariates	Comments
			5) Multiple measures			
Hu et al., 1997 *(48)*	70 breast cancer cases (incident and prevalent)	128 benign breast disease patients plus 111 other women recruited at the same hospital	RFLP analysis for genetic polymorphism for PARP; PARP enzyme measures in a small subset in lymphocytes	Benign breast disease may not be a suitable control group	Age, parity, family history of breast cancer, age at menarche and first birth	Case subjects with a history of chemotherapy, radiation therapy, or hormonal therapy were excluded; 80% of the case subjects had invasive, lymph node-negative breast cancer. RFLP analysis of chromosome 13 (digestion with *Hin*dIII) was conducted for the PARP pseudogene polymorphism.
Moller et al., 1998 *(54)*	20 nonmelanoma skin cancers (15 females and 5 males) + 20 cancers and psoriasis (15 females and 5 males); mean age, 47 y	20 healthy volunteers (15 females and 5 males; mean age, 46 y) and 20 psoriasis patients (15 females and 5 males; mean age, 47 y)	Comet assay and UV-induced UDS in lymphocytes	Comparability of case and control subjects	Matched on age and sex, ambient solar radiation	Only persons who had not undergone genotoxic and psoriasis treatment in the 3 mo preceding recruitment were included. Data on solar radiation were obtained from the Danish Meteorological Institute.
Wu et al., 1998 *(57)*	121 lung cancer case subjects (80 African-Americans and 41 Mexican-Americans)	171 matched control subjects	PARP genotype, mutagen sensitivity with bleomycin in lymphocytes	Selection bias, sex difference	Sex, age, mutagen sensitivity, smoking status	
Miller et al., 1998 *(61)*	18 subjects with ⩾3 primary cancers	18 age- and sex-matched control subjects	Bleomycin- and 4NQO-induced mutagen sensitivity; host cell reactivation assay in lymphocytes	Potential selection bias, small sample size	Age, sex	

***Abbreviations used:** ADPRT = adenosine diphosphate ribosyl transferase; A-T = ataxia-telangiectasia; BPDE = benzo[*a*]pyrene diol epoxide; CAT = chloramphenicol acetyltransferase; Gy = gray (radiation unit equal to 100 rads); H_2O_2 = hydrogen peroxide; HU = hydroxyurea; mitotic index = number of mitoses per square millimeter near the tumor; MSKCC = Memorial Sloan-Kettering Cancer Center; NAC = *N*-acetylcysteine; N-AcO-2-FAA = *N*-acetoxy-*N*-2-fluorenylacetamide; 4NQO = 4-nitroquinoline-1-oxide; O^6MGT = *O*-6-methylguanine transferase; PADPRP = poly(adenosine diphosphoribose)polymerase; PARP = poly(ADP-ribose)polymerase; RFLP = restriction fragment length polymorphism; RIA = radioimmunoassay; RT–PCR = reverse transcription–polymerase chain reaction; SD = standard deviation; SES = socioeconomic status; UDS = unscheduled DNA synthesis; UV = ultraviolet radiation; UVC = ultraviolet C radiation, 254 nm; XP = xeoroderma pigmentosum; XRCC1, 3, and 5 = x-ray-sensitive DNA repair genes.

that examined only healthy subjects, except, in the text, to illustrate a principle (such as confounding). We have considered the design, the characteristics of the patients and control subjects, potential biases, confounding variables, and sources of technical variability. Covariates have been noted when they were considered in the design. The coefficient of variation (CV) has been computed as the ratio between the standard deviation (SD) and the mean in control subjects (whenever possible); when the SD was not available, it was computed from the standard error (SE). When possible (i.e., when DNA repair was categorized), we have reported the odds ratios (ORs) with their associated 95% confidence intervals (CIs) as a measure of association and sometimes calculated the ORs from the data presented. All *P* values that we calculated were two-sided.

Characteristics of Tests

In most assays currently used, it is not possible to make a distinction between DNA damage and repair. The test developed by Athas and collaborators *(20,28)* has the advantage of relying on a plasmid that is damaged and then transfected into the host cell rather than on direct damage to the host cell. This technique minimizes the cytotoxic effects of damaging agents that might indirectly compromise the repair mechanisms of the cell. However, an important limitation of this assay is the fact that repair of DNA damage (e.g., adducts) in a plasmid transfected into cells has been shown to differ substantially from the process of repair of genomic damage [e.g., *(67)*]. There is greater overlap between damage and repair in the other assays. For example, one of the commonly reported tests, the mutagen sensitivity assay developed by Hsu et al. *(6)*, is based on the induction of chromosome damage in lymphocytes by bleomycin. This is a relatively simple test in which a higher number of bleomycin-induced chromatid breaks is assumed to express higher "mutagen sensitivity" and lower DNA repair (an assumption that has not been tested directly). Wei et al. *(68)* compared the mutagen sensitivity assay with the host cell reactivation assay and found a correlation of $r = -.70$ ($P<.01$) with 4-nitroquinoline-1-oxide (4NQO)-induced mutagen sensitivity, although the authors suggested that each assay is actually measuring a different function. On the other hand, although Miller et al. *(61)* found no clear association between mutagen sensitivity and the host cell reactivation assay within case or control subjects, we calculated among all subjects a smaller but statistically significant correlation between the host cell reactivation assay and 4NQO-induced mutagen sensitivity ($r = -.43$; $P = .01$) but not bleomycin-induced mutagen sensitivity ($r = -.12$; $P = .48$).

Wu et al. have shown that BPDE-induced *(69)* and bleomycin-induced *(70)* chromatid breaks in the lymphocytes of lung cancer patients have nonrandom distributions and occur more frequently in chromosomes 2, 3p21, 4, and 5, with a statistically significant gradient of increasing risk with increasing number of aberrations. What this means for the interpretation of DNA repair capacity measurements is unclear. It does suggest that mutagen sensitivity may be more prevalent in chromosomes previously identified as critical in the pathway of development of specific cancers.

Hall et al. *(31)* analyzed in detail the sources of variation for the test based on the host cell reactivation assay, and Scott et al. *(71)* discussed sources of variation for the G_2-phase X-ray-induced chromosome damage. We have assembled

Table 2. Results of studies on DNA repair and cancer in humans by type of assay*

Authors, y (reference No.)	Variability measures	Repair in case subjects (±SE)	Repair in control subjects (±SE)	OR (95% CI)	*P*	Comments
			1) DNA damage to cells			
Cherry and Hsu, 1983 *(3)*	Cannot calculate CV	Case subjects, 1.24 (±0.49)	Control subjects, 0.89 (±0.54)	Not able to calculate	$P = .03$	
Hsu et al., 1985 *(6)*		60.1% of cases are "mutagen sensitive," i.e., breaks per cell >1.00	12% of control subjects are "mutagen sensitive," i.e., breaks per cell >1.00	Calculated OR = 11.6	Not given	
Hsu et al., 1989 *(12)*	CV in control subjects, 58%	Breast cancer = 0.64 breaks per cell; colon cancer = 1.00 break per cell; head/neck cancer = 1.03 breaks per cell; lung cancer = 0.98 breaks per cell	Control subjects = 0.60 breaks per cell	Calculated OR for breaks per cell >1.0: breast cancer = 1.4; colon cancer = 6.4; head/neck cancer = 7.0; lung cancer = 6.9	Not given	
Rudiger et al., 1989 *(14)*	CV in control subjects, 52.4%	Lung cancer case subjects: 6.64 (±4.32) pmol O^6MGT repaired/8 million cells	Healthy control subjects: 10.35 (±5.42) pmol O^6MGT repaired/8 million cells	Calculated OR for breaks per cell >1.0 = 4.4	$P<.01$	
Spitz et al., 1989 *(15)*	Cannot calculate CV	65.2% subjects with >0.8 breaks per cell	23.6% subjects with >0.8 breaks per cell	ORs (95% CI): pharynx cancer = 10.3 (3.2–33.7); larynx cancer = 8.0 (3.6–25.0); oral cavity cancer = 3.8 (1.4–10.2)		ORs are based on dichotomizing chromosome breaks at 0.80 breaks per cell. The joint effect of mutagen sensitivity and smoking or alcohol consumption was compatible with a multiplicative model. Mutagen sensitivity was an independent risk factor in multivariate analyses.
Schantz et al., 1990 *(16)*	Cannot calculate CV	Second primary cancers; 4 of 51 patients <1.0 breaks per cell; 9 of 33 patients >1 break per cell		OR = 4.4 (95% CI = 1.2–15.8)	$P<.05$	No statistically significant differences were noted between the two groups, stratified by the number of breaks per cell according to sex, age, length of follow-up, tobacco or alcohol use, and primary cancer treatment.
Hsu et al., 1993 *(24)*	CV in control subjects, 64%	Melanoma patients, mean breaks per cell = 0.80 (±0.43); head neck cancer patients, mean breaks per cell = 0.58 (±0.51)	Control mean breaks per cell, 0.47 (±0.30)	Calculated ORs, 4NQO: melanoma = 4.7 (95% CI = 1.2–20.4); head and neck cancer = 2.0 (95% CI = 0.05–8.49). OR (bleomycin): melanoma = 2.2 (95% CI = 0.59–8.21); head and neck cancer = 8.5 (95% CI = 2.75–27.72)	$P = .01$ $P = .18$ $P<.001$	
Spitz et al., 1993 *(25)*	Cannot calculate CV	Case subjects (n = 108): overall 69% mutagen sensitive (>0.8 breaks per cell)	Control subjects (n = 108): overall 44% mutagen sensitive	OR = 2.9 (95% CI = 1.5–5.4); smokers: OR = 23.0 (95% CI = 5–106); alcohol users: OR = 5.8 (95% CI = 2.3–14.2)		Mutagen sensitivity was expressed as ⩾0.8 breaks per cell. OR was adjusted for smoking. No difference was observed by social class. Combined effect of smoking and mutagen sensitivity was compatible with a multiplicative effect.

(Table continues)

Table 2 (continued). Results of studies on DNA repair and cancer in humans by type of assay*

Authors, y (reference No.)	Variability measures	Repair in case subjects (±SE)	Repair in control subjects (±SE)	OR (95% CI)	*P*	Comments
Parshad et al., 1993 *(26)*	Cannot calculate CV	Family members: 0.94–1.19 breaks per cell	Control subjects: 0.21 breaks per cell			The higher frequency of breaks in the family members occurs only at G_2 phase. Immediately after irradiation, there were no differences between the 2 groups; i.e., there was equivalent chromosome damage. This kinetics is interpreted as representing DNA repair deficiency.
Bondy et al., 1993 *(27)*	Cannot calculate CV	58.2% of those who were mutagen sensitive had a first-degree relative with cancer	28.6% of those who were *not* mutagen sensitive had a first-degree relative with cancer	OR for 1 first-degree relative = 2.6 (95% CI = 1.0–6.5); OR for ⩾2 first-degree relatives = 6.6 (95% CI = 1.7–25.7)		
Spitz et al., 1994 *(32)*	CV, 45%	Case subjects (n = 28): mean breaks per cell = 1.17 (±0.54)	Control subjects (n = 250): mean breaks per cell = 0.98 (±0.44)	Adjusted OR = 2.7 (95% CI = 1.2–5.8) for mutagen hypersensitive	Univariate $P = .04$	The multivariate model includes age, sex, smoking status, and chemotherapy or radiotherapy. The OR is based on mutagen sensitivity as a continuous variable (Cox model).
Scott et al., 1994 *(33)*	CV, 14%	A-T: mean breaks per cell, 1.45 (±0.40); breast cancer: mean breaks per cell, 1.09 (±26.8)	Healthy control subjects: mean breaks per cell, 0.94 (±13.6)	Calculated OR = 6.9	$P<.001$	Radiosensitivity was defined on the basis of overlapping with A-T heterozygote range.
Cloos et al., 1994 *(34)*	CV, 25%	SPT, 0.96 breaks per cell (±0.31): MPT, 1.20 breaks per cell (±0.47)	Control subjects: 0.77 breaks per cell (±0.19)		SPT, $P<.001$ (compare with control subjects); MPT, $P<.025$ (compare with SPT HNSCC)	
Strom et al., 1995 *(36)*	CV in male control subjects, 43.6%; CV in female control subjects, 52.2%	Mean breaks per cell for males, 1.25 (±0.55); mean breaks per cell for females, 0.93 (±0.30)	Mean breaks per cell for male control subjects, 0.78 (±0.34); mean breaks per cell for female control subjects, 0.90 (±0.47)	OR for former smokers who were mutagen sensitive, 4.5 (95% CI = 0.9–21.9); OR for subjects <55 y old who were mutagen sensitive, 15.0 (95% CI = 1.0–228.9)		
Spitz et al., 1995 *(38)*	CV in males, 45.9%; CV in females, 71.4%	Case subjects, mean breaks per cell (±SD): males, 1.24 (±0.66); females, 1.00 (±0.39)	Control subjects: mean breaks per cell (±SD): males, 0.74 (±0.34); females, 0.98 (±0.70)	OR (95% CI) for smoking status: never = 2.2 (0.4–13.3); former = 5.4 (1.8–16.2); current = 3.1 (1.1–8.6)		ORs are based on dichotomized values of breaks per cell (<1 vs. ⩾1). ORs were higher for squamous cell carcinoma (8.5) and adenocarcinoma (4.8). Effect modification was exerted by age at diagnosis and smoking characteristics. (ORs are higher for heavy smokers.)
Wu et al., 1995 *(39)*	Cannot calculate CV	Mean breaks per cell for case subjects, 1.11	Mean breaks per cell for control subjects, 0.78	OR (95% CI): bleomycin mutagen sensitivity, 3.8 (2.3–6.3); wood dust exposure, 1.9 (0.8–4.3); wood dust and mutagen sensitivity, 19.7 (4.0–96.8); combination of smoking and wood dust, 43.9 (9.5–203.2)	Trend test $P<.0001$	

(Table continues)

Table 2 (continued). Results of studies on DNA repair and cancer in humans by type of assay*

Authors, y (reference No.)	Variability measures	Repair in case subjects (±SE)	Repair in control subjects (±SE)	OR (95% CI)	*P*	Comments
Bondy et al., 1996 *(40)*	CV in control subjects, 78%	0.72 breaks per cell (±0.45)	0.45 breaks per cell (±0.35)	Crude OR = 5.4 (95% CI = 2.1–13.7); adjusted OR = 5.8 (95% CI = 2.3–14.8)	Statistically significant difference in means, *P*<.0001	
Parshad et al., 1996 *(43)*	Cannot calculate CV	1.46 breaks per cell in 7 patients with preinvasive lesions; 1.46 breaks per cell in 6 of 12 cancer patients without an FH of breast cancer; <0.60 breaks per cell for other 6 patients; in 7 patients with an FH of breast cancer, 1.48 breaks per cell	Control subjects: no FH of breast cancer (n = 10); 9 patients ≤6.0 breaks per cell; 1 patient >6.0 breaks per cell		Not given	The way the results are reported does not allow one to obtain average estimates of DNA repair. In addition to the 10 control subjects mentioned in the "Results" section, the authors state that, in 133 of 136 control subjects previously studied (ages 1–96 y), the frequency of breaks was <0.6 breaks per cell.
Cloos et al., 1996 *(44)*	CV of variation in control measures, 14%	Mean difference between treatments, 0.004 breaks per cell (±0.31)	Mean difference between treatments, 0.06 breaks per cell (±0.34)		Not statistically significant	
Cloos et al., 1996 *(45)*	CV, 34%	HNSCC patients: mean breaks per cell, 0.85 (±0.27); oral cavity cancer patients: 0.82 (±0.24); larynx cancer patients: 0.88 (±0.31)	Control subjects: 0.68 breaks per cell (±0.23)	Laryngeal cancer: OR = 4.25; oral cancer OR vs. control subjects = 1.06	*P* = .04 for laryngeal cancer; no significant difference for oral cancer	
Cloos et al., 1996 *(46)*	CV, 45%	Case subjects: mean breaks per cell, 1.01 (±0.4)	Control subjects: mean breaks per cell, 0.82 (±0.37)	OR = 11.5 for nonsensitive heavy smokers (95% CI = 5.0–26.6); OR = 44.6 for sensitive heavy smokers (95% CI = 17.4–114.0); OR = 57.5 for alcohol consumption + smoking (95% CI = 17.5–188.0)	Case subjects consistently higher than control subjects, *P*<.0001	
Wei et al., 1996 *(41)*	Spontaneous breakage CV, 89%; induced breakage CV, 58.5%	Mean breaks per cell, 0.67 (±0.39)	Mean breaks per cell, 0.41 (±0.24)	OR = 2.26 comparing baseline <0.26 breaks per cell with 0.26–0.45 breaks per cell (95% CI = 0.5–9.7); OR = 8.4 comparing >0.45 breaks per cell with baseline (95% CI = 2.1–33.9)		
Patel et al., 1997 *(47)*	CV, 26.4%	Breast cancer case subjects: mean = 1.59 gaps and breaks per cell (±0.14); relatives: 1.36 gaps and breaks per cell (±0.09)	Control subjects: 0.92 mean gaps and breaks per cell (±0.06)	Case subjects: OR = 23.8 (95% CI = 2.1–622.1); first-degree relatives: OR = 6.9 (95% CI = 1.3–41.3)	*P*<.0001 for both groups	Optimal DNA repair is defined as <95 gaps and breaks per 100 cells. An interaction between snuff use and DNA repair is suggested.
Schantz et al., 1997 *(49)*	Cannot calculate CV	61% case subjects >1 break per cell	23% control subjects >1 break per cell	OR = 4.95 (95% CI = 2.7–9.2)	*P* for trend = .0001	ORs derived from logistic regression analysis including age, sex, race, and educational level. Mutagen sensitivity was not affected by tobacco smoking, alcohol drinking, or vitamin intake in control subjects.

(Table continues)

Table 2 (continued). Results of studies on DNA repair and cancer in humans by type of assay*

Authors, y (reference No.)	Variability measures	Repair in case subjects (±SE)	Repair in control subjects (±SE)	OR (95% CI)	*P*	Comments
Jaloszynski et al., 1997 *(50)*	At 10 μg/mL bleomycin after 1 h, CV = 90.5%; at 20 μg/mL bleomycin after 1 h, CV = 64.3%	After 1 h, 10 μg/mL bleomycin: 116% repair of damage; at 20 μg/mL bleomycin, 101% repair of damage	After 1 h, 10 μg/mL bleomycin: 211% repair of damage; at 20 μg/mL bleomycin, 176% repair of damage	Calculated OR: 20 μg/mL bleomycin, 6.55 (95% CI = 1.82–23.58)	Difference between bleomycin-induced and noninduced in control subjects, $P = .026$; difference in cancer subjects, $P = .00002$; no significant difference in untreated repair values between groups, $P = .13$	Dose–response relationship is found between exposure to bleomycin and the extent of DNA damage. A weak association is suggested between age and DNA damage. Most information is descriptive or graphically presented.
Wu et al., 1998 *(56)*	CV for BPDE in control subjects, 51%	BPDE sensitivity: mean breaks per cell, 0.77 (±0.38)	BPDE sensitivity: mean breaks per cell, 0.49 (±0.25)	OR (95% CI)—BPDE sensitive among those not bleomycin sensitive: 4.9 (1.6–14.8); BPDE sensitive among those bleomycin sensitive: 19.2 (6.4–57.5)	$P<.001$	
Wu et al., 1998 *(58)*	Cannot calculate, CV	Mean bleomycin-induced breaks per cell, 0.92; mean BPDE-induced breaks per cell, 0.90	Mean bleomycin-induced breaks per cell, 0.55; mean BPDE-induced breaks per cell, 0.46	OR (95% CI)—bleomycin sensitive: 5.6 (2.3–13.8); BPDE sensitive: 14.1 (3.5–56.7); bleomycin and BPDE sensitive: 35.9 (5.5–234.4)		
Wu et al., 1998 *(59)*	CV for BPDE sensitivity, 45%	BPDE sensitivity: mean breaks per cell for males = 0.83 (±0.35); for females = 0.73 (±0.35)	BPDE sensitivity: mean breaks per cell for males = 0.46 (±0.20); for females = 0.46 (±0.21)	OR (95% CI)—bleomycin sensitive, BPDE nonsensitive: 4.2 (1.3–13.6); BPDE sensitive, bleomycin nonsensitive: 7.6 (2.2–25.6); both bleomycin and BPDE sensitive: 38.4 (9.8–149.7)		Mutagen sensitivity was defined as >0.58 breaks per cell for BPDE-induced and >0.68 breaks per cell for bleomycin-induced mutagen sensitivity
Spitz et al., 1998 *(60)*	CV, 45%	Mean breaks per cell: 1.06 (±0.41); recurrence rate: 11.5% in mutagen-sensitive patients; 5.3% in nonsensitive patients	Mean breaks per cell, 0.89 (±0.40)	OR = 2.56 (95% CI = 1.34–4.91)	At 3 y, recurrence rate for mutagen sensitivity, $P = .02$	Mutagen sensitivity was defined as ⩾1 break per cell. OR was based on Cox proportional hazards model. None of the covariates exerted an appreciable confounding effect.
Sigurdson et al., 1998 *(62)*	CV cannot be calculated	Mean survival for γ-ray mutagen-sensitive patients = 12 mo	Mean survival for nonsensitive patients = 16 mo	Hazard rate ratio = 2.4 (95% CI = 1.3–4.6)	$P = .0081$	Patients included 16 patients who had radiotherapy or chemotherapy prior to phlebotomy.
Wang et al., 1998 *(63)*	CV, 40%	Mean breaks per cell, 0.65 (±0.23)	Mean breaks per cell, 0.53 (±0.21)	OR (dichotomized) = 2.4 (95% CI = 1.2–4.8); OR (tertiled) = 4.1 (95% CI = 1.7–10.0)	$P = .02$ $P = .0009$	
Udumudi et al., 1998 *(64)*	CV, 73%	Mean tail length of comet for mild dysplasia = 2.51 (±0.15); severe dysplasia = 3.14 (±0.11); cancer case subjects = 7.03 (±0.08)	Mean tail length of comet in control subjects, 1.04 (±0.11)	Not able to calculate	Difference between normal control subjects and all 3 dysplasia/cancer case subjects, $P<.001$	Interindividual and intraindividual variabilities were maximal in the cancer group.
Leprat et al., 1998 *(65)*	Cannot calculate CV	Residual DNA damage after 60 min in 5 of 13 patients	Residual damage after 60 min in 1 of 8 control subjects	Not able to calculate	$P<.01$	Interindividual response is more variable among cancer case subjects than among control subjects.

(Table continues)

Table 2 (continued). Results of studies on DNA repair and cancer in humans by type of assay*

Authors, y (reference No.)	Variability measures	Repair in case subjects (±SE)	Repair in control subjects (±SE)	OR (95% CI)	*P*	Comments
Scott et al., 1998 *(66)*	CV, 19%	Radiation-induced micronucleus yields in breast cancer case subjects, 60.7 (±9.6)	Radiation-induced micronucleus yields in control subjects: males, 44.6 (±7.0); females, 46.4 (±9.8)		*P*<.001	Authors suggest that discrimination between normal subjects and A-T heterozygotes is possible. The proportion of radiation-sensitive cases is highly dependent on the cutoff used.
Rao et al., 1998 *(55)*	Cannot calculate CV	Mitotic index for both unaffected family members and breast cancer patients = 0.4	Mitotic index for control subjects = 1.4	Difference in APC-stimulated cultures only	Depression of unstimulated lymphocytes, mitotic index, and blast index in case subjects compared with control subjects (*P*<.05 for all three)	A reduction in mitotic index after inhibition with APC was considered an expression of a DNA repair defect.
			2) Indirect test of DNA repair or enzyme activity			
Pero et al., 1983 *(4)*	CV, 26.6%	UDS: case subjects, 380 cpm (±23); subjects with predisposition, 338 cpm (±18)	UDS: 516 cpm (±22); above age 50 y: 566 cpm (±46)	Calculated, dividing control subjects at median; OR = 2.9 (95% CI = 1.1–7.3)	*P*<.001 for comparison of means; 0.03 for OR calculation	Potential confounding by age (mean = 34 in control subjects and 63 in case subjects) was only partially controlled for. The mean time from surgery for colorectal cancer in case subjects was 39 mo.
Pero et al., 1985 *(5)*	CV, 37.7%	UDS: 351 cpm (±18)	UDS: 441 cpm (±24)	Cannot calculate	*P*<.01	
Munch-Petersen et al., 1985 *(7)*	CV for UV-induced UDS, 20%	UDS: case subjects, 5293 cpm (±1755); multiple skin cancers, 6479 cpm (±1701)	UDS: control subjects, 4721 cpm (±949)	Mean values did not differ between groups; control subjects were more UV tolerant than case subjects	No statistically significant difference between case and control subjects for mean UVC-induced UDS. Subjects with multiple BCCs had significantly higher values.	
Pero et al., 1986 *(8)*	CV for UDS in control subjects, 25% at 24 h and 17.5% at 34 h; CV for chromosome aberrations, 50.1%	Mean UDS after 34 h: 29.5 cpm (±1.8)	Mean UDS after 34 h: 31.8 cpm (±2.1)	Difference in mean UDS after 34 h was not statistically significant, but difference in increase in UDS between 24 and 34 h was. Calculated OR = 7.7	Mean UDS not significant; percent increase, *P*<.001	
Kovacs et al., 1986 *(9)*	CV in UVC-induced UDS at 8 J/m^2, 58%	Decreased DNA repair synthesis in 20 of 41 case subjects	Decreased DNA repair synthesis in 3 of 27 control subjects		*P* = .003	In case subjects, the spontaneous DNA synthesis and HmdU-inhibited synthesis were higher than in control subjects (*P*<.05) because of 4 females, before irradiation, but not after 9 mo or more from surgical treatment or after chemotherapy or radiotherapy.

(Table continues)

Table 2 (continued). Results of studies on DNA repair and cancer in humans by type of assay*

Authors, y (reference No.)	Variability measures	Repair in case subjects (±SE)	Repair in control subjects (±SE)	OR (95% CI)	*P*	Comments
Markowitz et al., 1988 *(11)*	CV overall, 22.6%	Mean activated ADPRT values for case subjects: 1399 cpm (±67)	Control subjects: 1876 cpm (±128)	Calculated OR (activated) = 5.3 (95% CI = 1.0–27.4)	OR *P* value = <.05; *t* test = <.001	Values shown are those after activation with cumene. No data on ADPRT activation by plasma or vitamin E are shown for the whole group.
Pero et al., 1989 *(13)*	CV: 54.5% for all noncancers, 47.2% for smokers, and 55.7% for nonsmokers	Mean activated ADPRT values for case subjects—all cancers: 1263 cpm; lung cancers: 1224 cpm	Control subjects—all: 2946 cpm; smokers: 3628 cpm; nonsmokers: 2723 cpm	OR (noncancer vs. cancer) = 13.8; OR (smoking, noncancers vs. lung cancers) = 73.5	All noncancers vs. all cancers: *P*<.01; smoking, noncancers vs. lung cancers: *P*<.01	Values shown are those after activation with H_2O_2; dichotomized ADPRT values are shown for ORs. Stage, site, or pathology did not act as confounders or effect modifiers.
Kovacs et al., 1991 *(18)*	CV pre-Iscador treatment among control subjects, 109%	Mean UDS—pretreatment, 237.7 cpm; post-treatment, 851.1 cpm	Mean UDS—pretreatment, 480 cpm; post-treatment, 872 cpm	After 7–9 days of treatment, UDS increased an average of 2.7 times	*P*<.05	Data on control subjects are not shown.
Kovacs and Langemann, 1991 *(19)*	CV at 2× exposure, 35%; CV at 3× exposure, 11%	Case subjects, 1.9 RU (±0.2)	Control subjects, 2.4 RU (±0.1)		*P*<.05	Values shown are the relative uptake of [^{3}H]thymidine into lymphocytes after exposure to 8 J/m^2 UVC light. The thymidine incorporation curves for patients were shifted compared with those for control subjects
Kovacs et al., 1992 *(21)*		2 of 6 without chemotherapy or radiotherapy had reduced repair 3–5 y after diagnosis; 9 of 9 with chemotherapy or radiotherapy had reduced repair 3–5 y after diagnosis	No data given	Reduced repair defined as being outside the 99% confidence range	Not reported	
Pero et al., 1992 *(22)*	CV in control subjects, 10.7% (Ln ADPRT)	1–368 days of tamoxifen treatment (n = 42): mean Ln H_2O_2-activated ADPRT, 6.92 (±0.65)	No tamoxifen treatment (n = 40): mean Ln H_2O_2-activated ADPRT, 6.71 (0.72, SD)	Tamoxifen treatment significantly improved ADPRT (*P*<.02); linear increase with time (*P*<.009)	*P*<.02 (adjusted)	
Pero et al., 1992 *(23)*	Control subjects, 7.3% CV (Ln ADPRT)	Treated with betamethasone: Ln H_2O_2-activated ADPRT, cpm = 6.77 (±0.62)	Untreated: Ln H_2O_2-activated ADPRT, cpm = 7.63	Betamethasone treatment associated with a decrease in ADPRT (*P*<.001)	Linear decrease over time (*P*<.03)	
Ranjit et al., 1995 *(37)*	CV in normal donor T cells, 23.8% MFI	All case subjects, 4.3 (±1.2) MFI	Control subjects, 4.2 (±1.0) MFI	—	Not reported	
			3) Direct Measure of repair kinetics			
Roth et al., 1987 *(10)*	CV in control subjects at 10-min repair is 8%; at 30 min, it is 14%; and at 60 min, it is 19%	Mean % loss of antigenicity after 60 min: melanoma = 50.5 (±18.2); BCC = 35.4 (±9.0)	Mean % loss of antigenicity after 60 min: control subjects, 29.8 (±5.7)		Analysis of variance: melanoma vs. healthy (*P*<.001); BCC vs. healthy (*P* = .02)	Values are percentage of bound antibody; loss of antigenicity increases with time.

(Table continues)

Table 2 (continued). Results of studies on DNA repair and cancer in humans by type of assay*

Authors, y (reference No.)	Variability measures	Repair in case subjects (±SE)	Repair in control subjects (±SE)	OR (95% CI)	*P*	Comments
Alcalay et al., 1990 *(17)*	CV repair in control subjects, 52.8%	BCC: ESS/kb = 0.039 (±0.0026); excision repair: 22 (±4%); repair of at least 30% of BCC by 23% of subjects	Control subjects: ESS/kb = 0.037 (±0.003); excision repair: 33 (±4%); repair of at least 30% of dimers by 53% of subjects	—	ESS/kb: $P > .05$; excision repair: $P = .06$; repair of BCC/dimers: $P < .05$	ESS/kb = endonuclease-sensitive sites per kb DNA; excision repair: (ESS/kb at time 0 − ESS/kb at 6 h)/(ESS/kb at time 0) × 100.
Athas et al., 1991 *(20)*	CV in case subjects, 15%	Male case subjects: % CAT = 10.1; female case subjects: % CAT = 7.2	Male control subjects: mean % CAT = 9.6; female control subjects: mean % CAT = 9.1	—	$P < .05$	Lower repair in case subjects was apparent only in women.
Wei et al., 1993 *(28)*	CV: control subjects without an FH of BCC or actinic keratosis = 27.5%; control subjects with FH or actinic keratosis = 30.2%	DRC: BCC patients (n = 88) = 7.35 (±2.0)	Control subjects without an FH of BCC or actinic keratosis (n = 106) = mean % CAT = 8.00 (±2.2); control subjects with an FH of BCC or actinic keratosis (n = 29) = 7.28 (±2.2)	OR (high repair capacity) = 1.9; 6+ sunburns (low repair capacity) = 5.3	Not significant $P < .01$	DRC was strongly related to age, with a 0.61% decline per year among control subjects. BCC case–control differences are more evident at younger ages. Interaction between sunburns and DNA repair is more evident in females.
Wei et al., 1994 *(29)*	CV, 28% for CAT activity at 700 J/m^2	DRC: BCC patients = increasing trend with number of BCCs and for those with an FH of skin cancer	% CAT activity: control subjects: 7.84 (±2.2)	OR using cutoff value maximizing risk related to DNA repair levels = 2.3 (95% CI = 1.2–4.5)		DRC decreased with increasing numbers of BCCs. *P* for trend = .02.
Wei et al., 1994 (30)	CV, 28% for CAT activity at 700 J/m^2	DRC: BCC patients = 7.35% (±2.0)	Mean % CAT activity: control subjects = 7.84 (±2.2)	OR (95% CI) among low DNA repair subjects: light skin type = 3.2 (1.5–7.3), 6+ sunburns = 4.2 (1.6–10.7), and actinic elastosis = 4.4 (1.5–12.8)		
Hall et al., 1994 *(31)*	CV, 47% for CAT activity at 700 J/m^2	Mean % CAT activity (700 J/m^2): BCC case subjects = 13.0% (±6.2); SCC case subjects = 12.2% (±7.1)	Mean % CAT activity (700 J/m^2): BCC control subjects = 12.0% (±5.6); SCC control subjects = 11.3% (±5.0)	BCC case subjects at 350 J/m^2 had DRC 1.07 times that of control subjects; SCC case subjects had DRC 1.04 times that of control subjects	BCC: $P = .30$; SCC: $P = .71$	The effect is measured in terms of mean % CAT activity of case subjects compared with that of control subjects for each 350-J/m^2 increment of radiation dose level. Regression analysis used CAT activity as a continuous variable.
Wei et al., 1995 *(35)*	CV, 28% for CAT activity at 700 J/m^2	Mean % CAT activity: BCC patients (n = 88) = 7.35% (±2.0)	Mean % CAT activity: control subjects = 7.84% (±2.2)	—	Tendency to sunburn, $P = .05$; frequent sunbathing, $P = .03$; poor tanning ability, $P = .05$; 6+ severe sunburns, $P = .04$; telangiectasia, $P = .04$; occupational chemical exposures, $P = .04$; multiple medical radiation exposure, $P = .02$	
Wei et al., 1996 *(42)*	CV, 58.5%	Mean DRC: 3.30% (±2.6)	Mean DRC: 5.10% (±3.6)	OR = 5.47 (95% CI = 1.56–19.2) comparing with baseline <3.0%	*P* for trend <.006	ORs are based on logistic regression, including age, sex, ethnicity, and smoking status.

(Table continues)

Table 2 (continued). Results of studies on DNA repair and cancer in humans by type of assay*

Authors, y (reference No.)	Variability measures	Repair in case subjects (±SE)	Repair in control subjects (±SE)	OR (95% CI)	*P*	Comments
Cheng et al., 1998 *(53)*	CV, 54%	Mean DRC: 8.6%	Mean DRC: 12.4%	4.3 (95% CI = 1.5–12.5)	*P*<.008	
			4) Genetic variation in DNA repair genes			
Price et al., 1997 *(51)*	Not applicable	Microsatellite repeats of variable length in cancer patients: $[AC]_{12,20}$ repeats in XRCC1 and $[AC]_{20}$ repeats in XRCC3	No "rare" (e.g., $[AC]_{12,20}$) microsatellite polymorphisms present in "normal" volunteers	Cannot calculate OR	Cancer status: XRCC1, *P* = .005; XRCC3, *P* = .004; XRCC5, *P* = .59	
Wei et al., 1998 *(52)*	CV ranges from 26% for hPMS2 to 51% for hMSH2	Case subjects range from 29.1% relative expression for hMLH1 to 56.0% relative expression for hPMS2	Control subjects ranged from 35.1% relative expression for hMLH1 to 59.5% relative expression for hPMS2	OR comparing low expression of hMLH1 with high = 4.4 (95% CI = 2.1–9.1)		Densitometric analysis was used to calculate gene expression in the multiplex RT–PCR.
			5) Multiple measures			
Hu et al., 1997 *(48)*	CV: H_2O_2 induced = 52.0%; oligonucleotide induced = 38.6%	Frequency of PARP B allele in breast cancer patients = 0.13; mean H_2O_2-induced PARP enzyme activity (±SD) = 36 839 (±14 916); oligonucleotide-induced enzyme activity = 44 652 (±17 739)	Frequency of PARP B allele: study control subjects = 0.14; reference control subjects = 0.15; H_2O_2-induced PARP enzyme activity = 41 786 (±21 712); oligonucleotide-induced enzyme activity = 58 566 (±22 624)	H_2O_2-induced ADPRT: OR = 1.21 (95% CI = 0.3–5.5); oligonucleotide-induced ADPRT: OR = 3.40 (95% CI = 0.70–19.54)	*P* = .81 *P* = .53 *P* = .08	OR is age adjusted and based on values dichotomized at the median oligonucleotide-induced PARP activity. The study shows genotype–phenotype association: The mean H_2O_2-induced PARP activity was significantly higher in women with the B allele (*P* = .02) and of borderline significance for oligonucleotide-induced activity (*P* = .08).
Moller et al., 1998 *(54)*	UV-induced UDS CV, 58%	UV-induced UDS in cancer and psoriasis patients = 95 cpm (±92); UV-induced UDS in cancer patients = 114 cpm (±81)	UV-induced UDS in psoriasis patients = 150 cpm (±118); UV-induced UDS in control subjects = 124 cpm (±72)		UV-induced UDS: cancer + psoriasis patients compared with control subjects, *P* = .08; cancer patients compared with noncancer patients, *P* = .07; interaction between skin cancer and psoriasis, *P* = .02, and for psoriasis vs. no psoriasis, *P*<.05; no significance test given for comparison of cancer to noncancer	The mean daily flux of solar radiation correlated with DNA damage (*r* = .65; *P*<.001). The tail moment in the comet assay and UV-induced UDS depended on the period of sampling (*P*<.001). UDS and the comet assay did not differ by smoking status.
Wu et al., 1998 *(57)*	Cannot calculate CV	PARP susceptibility genotype: African-Americans, 82.5%; Mexican-Americans, 53.7%; B-allele frequency: AA = 0.594 and MA = 0.317	PARP susceptibility genotype: African-Americans, 79.4%; Mexican-Americans, 32.4%; B-allele frequency: AA = 0.598 and MA = 0.196	PARP susceptibility genotype: African-Americans, 2.3 (95% CI = 0.7–8.0); Mexican-Americans, 3.2 (95% CI = 1.0–10.3); interaction effects in Mexican-Americans were 17.1 (95% CI = 3.2–112.0); mutagen sensitivity was significantly associated with increased ORs above 2 for all ethnic groups	Genotype, *P* = .60 in African-Americans and .026 in Mexican-Americans; interaction *P* value for genotype and mutagen sensitivity was <.001	

(Table continues)

Table 2 (continued). Results of studies on DNA repair and cancer in humans by type of assay*

Authors, y (reference No.)	Variability measures	Repair in case subjects (±SE)	Repair in control subjects (±SE)	OR (95% CI)	*P*	Comments
Miller et al., 1998 *(61)*	Host cell reactivation assay, 7%; 4NQO, 54%; bleomycin, 41%	Mean DRC = 64.4% (±10.6); mean mutagen sensitivity (bleomycin) = 0.99 breaks per cell (±0.46); mean mutagen sensitivity (4NQO) = 0.67 breaks per cell (±0.38)	Mean DRC = 85.04% (±6.45); mean mutagen sensitivity (bleomycin) = 0.88 breaks per cell (±0.36); mean mutagen sensitivity (4NQO) = 0.44 breaks per cell (±0.24)	OR DRC = 14.0 (95% CI = 2.13–591.3); OR mutagen sensitivity (bleomycin) = 5.00 (95% CI = 0.56–236.51); OR mutagen sensitivity (4NQO) = 4.00 (95% CI = 0.80–38.62)	Mean difference between case subjects and control subjects: DRC, *P*<.0001; mutagen sensitivity (bleomycin), *P* = .44; mutagen sensitivity (4NQO), mean difference *P* = .11	

***Abbreviations used:** AA = African-American; $[AC]_{12}$ and $[AC]_{20}$ = microsatellite repeat sequence; ADPRT = adenosine diphosphate polyribosyl transferase; APC = aphidicolin; A-T = ataxia-telangiectasia; BCC = basal cell carcinoma; BPDE = benzo[*a*]pyrene diol epoxide; CAT = chloramphenicol acetyltransferase; CI = confidence interval; cpm = counts per minutes; CV = coefficient of variation (variability of the measure); DRC = DNA repair capacity; ESS = endonuclease-sensitive sites; FH = family history; hMSH2 = a mismatch repair gene; H_2O_2 = hydrogen peroxide; hPMS2 = a mismatch repair gene; HMdU = 5-hydroxymethyl-2′-deoxyuridine; HNSCC = head and neck squamous cell carcinoma; kb = kilobase; Ln = log-transformed value; MA = Mexican-American; MFI = mean fluorescence intensity; mitotic index = number of mitoses per square millimeter near the tumor; MPT = multiple primary tumor; 4NQO = 4-nitroquinoline-1-oxide; O^6MGT = *O*-6-methylguanine transferase; OR = odds ratio; PARP = polyp(ADP-ribose)polymerase; RT–PCR = reverse transcription–polymerase chain reaction; RU = relative uptake of tritiated thymidine after repeated exposure in comparison to uptake after a single exposure; SCC = squamous cell carcinoma; SD = standard deviation; SE = standard error; SPT = single primary tumor; UDS = unscheduled DNA synthesis; UV = ultraviolet radiation; UVC = ultraviolet C radiation, 254 nm; XRCC1 = x-ray-sensitive gene 1; XRCC3 = x-ray-sensitive gene 3.

the papers that described any of the variation in DNA repair capacity among these studies (Table 3).

Sources of Potential Confounding or Bias

Inducibility. Some DNA repair genes seem to be inducible (e.g., the nucleotide excision repair genes by UV radiation) *(1)*. In fact, there is wide overlap among mammalian genes induced by UV radiation and those induced by phorbol ester promoters or by growth factors [p. 601 in *(1)*]. Such inducibility can occur as a result of exposure to many different agents, indicating a biologic cross-reactivity. This leads to the potential for epidemiologic confounding when assessing causal pathways; induction by one agent can be wrongly attributed to another agent. However, investigators may not measure that agent; therefore,

Table 3. Measures of variability in studies of DNA repair capacity*

Authors, y (reference No.)	Measure of technical variability	Measure of observer variability	Measure of intraindividual variability	Measure of interindividual variability
Hsu et al., 1985 *(6)*	Comparison of 2 sets of metaphases, *r* = .61	*r* = .69; *P*<.01	*r* = .74	Not given
Markowitz et al., 1988 *(11)*	Not given	*r* = .87; *P* = .002	Calculated CV, 10.7% and 14.7%	CV, 22.6%
Hsu et al., 1989 *(12)*	ND	ND	4 repeats, 15 individuals; mean CV, 36.3% (range, 2.2%–50.2%)	15 individuals; mean CV, 37.6%
Pero et al., 1989 *(13)*	ND	Between two technicians: 0.77, 11 samples; *P*<.005	23% and 26%, 1 male + 1 female, 9 times, once a wk	CV, 54%
Athas et al., 1991 *(20)*	ND	ND	3 repeats, 8 individuals, 15% error rate	Error rate; variation ranges from 7.8% to 24.0%
Kovacs et al., 1992 *(21)*	Technical variability 13%–15%; daily variability <30%	ND	ND	ND
Wei et al., 1993 *(28)*	No CV data; rank order of replicates maintained	ND	Calculated CV on 7 individuals = 12%	CV in control subjects without a family history of basal cell carcinoma or actinic keratoses, 27.5%
Hall et al., 1994 *(31)*	Day of assay, 43% of total variance of 0.183; replicates, 15% of variance	Technician 0.5% of variance in 29 subjects	ND	42% of variance
Cloos et al., 1996 *(44)*	14% technical variability			
Scott et al., 1998 *(66)*	ND	ND	CV within individuals, 9%	Significant interindividual difference (*P* = .006)
Leprat et al., 1998 *(65)*	ND	ND	6 patients' intraindividual variability ranged from 3% (in a control) to 43% (in a patient)	ND

***Abbreviations used:** CV = coefficient of variation; ND = no data.

variation in repair activity due to the measured exposure may be confounded or spurious.

The repair of some types of lesions is inducible, e.g., cyclobutane pyrimidine dimers produced by UV radiation. Repair of other lesions, such as 6-4 pyrimidine dimers repaired by XPA-G (i.e., complementation groups of XP), is not inducible. Preferential repair (repair that occurs more quickly than overall genome repair and on the transcribing strand of DNA) is not inducible *(1).* Induction of DNA repair by different exposures may be an important source of unmeasured confounding for studies of DNA repair and cancer.

Other potential confounders. Age, smoking habits, sex, dietary habits, sunlight exposure, and exposure to pro-oxidants appear to influence some assays. These, too, should be regarded as potential confounders.

With regard to age, Wei et al. *(28)* have shown that the repair capacity of a UV-damaged plasmid cat (i.e., chloramphenicol acetyltransferase) gene inserted into human lymphocytes declined with increasing age at a rate of about 0.61% per year, as did Moriwaki et al. *(72),* among others. Stierum et al. *(73)* observed a decrease in BPDE-induced unscheduled DNA synthesis with increasing age, and Barnett and King *(74)* found a higher level of single-strand breaks in older individuals, aged 65–69 years, than in younger individuals, aged 35–39 years.

In *in vitro* experiments with cultured lymphocytes, antioxidants such as α-tocopherol, *N*-acetyl-L-cysteine, and ascorbic acid inhibited bleomycin-induced chromosome damage in a dose-dependent manner *(75,76).* In a study of 25 healthy individuals, Kucuk et al. *(77)* found strong inverse correlations between plasma nutrients and the mutagen sensitivity assay based on bleomycin-induced chromatid breaks. Correlations were as follows: $r = -.76$ ($P \leq .01$) with β-carotene and $r = -.72$ ($P < .05$) with total carotenoids (monthly mean levels). In contrast, a positive correlation was found with triglyceride levels ($r = .60$; $P < .01$).

In contrast, Cloos et al. *(44)* found that *N*-acetylcysteine supplementation did not modify DNA repair capacity, as measured by bleomycin-induced mutagen sensitivity. King et al. *(78)* found no association between supplemental ascorbic acid and mutagen sensitivity. In a crossover design, Goodman et al. *(79)* were unable to find an effect of either α-tocopherol or β-carotene on mutagen sensitivity values. One problem with the mutagen sensitivity assay, pointed out by the authors, is that the 3-day culture of cells required is likely to dilute the circulating antioxidants in the plasma and, thus, diminish the antioxidant's ability to inhibit damage. However, the ability of humans to modify DNA damage/repair by short-term ingestion of supplements is cast into further doubt by the data of Hu et al. *(80).* In a randomized, double-blind trial of α-tocopherol, Hu et al. did not find any association between supplementation and DNA repair activity when they used two different measures of DNA repair capacity, adenosine diphosphate polyribosyl transferase (ADPRT) and unscheduled DNA synthesis.

There is fairly good evidence that caffeine inhibits DNA repair. p53 null cells (i.e., those in which both p53 alleles were disrupted) were more sensitive to UV light only in the presence of caffeine *(81),* and a comet assay study indicated that a caffeine-mediated increase in radiation risk of embryos is due to inhibition of DNA repair *(82).* Caffeine inhibited gene-specific repair of UV-induced damage in hamster cells and in human XP cells *(83).* The relevance of these observations to human cancer is still unclear.

Sunlight exposure can actually induce DNA repair, as measured by unscheduled DNA synthesis. In one study *(54),* DNA damage and repair were statistically significantly affected by the season of testing, with unscheduled DNA synthesis tending to be higher in the summer than in the winter.

Pero et al. *(84)* studied 40 healthy volunteers for ADPRT- and *N*-acetoxy-2-acetylaminofluorene (NA-AAF)-induced unscheduled DNA synthesis after exposure of mononuclear lymphocytes to pro-oxidants. They found that repair of DNA lesions induced by NA-AAF was inhibited in a dose-dependent manner by exposure to H_2O_2 and other pro-oxidants. In another study, ethanol at high doses (in cultured lymphocytes) interfered with the repair of bleomycin-induced chromosome breaks (mutagen sensitivity assay), and the researchers *(85)* suggested that it might inactivate enzymes involved in DNA repair.

Population Stratification

DNA repair defects are presumed to have a genetic origin and to be associated with polymorphic alleles in subgroups of the population. Extreme examples are represented by conditions like XP or A-T; genetic polymorphisms in DNA repair genes have been proposed to be responsible for other, less dramatic, DNA repair deficiencies *(86).* Altschuler et al. *(87)* have raised some concerns about potential confounding related to population admixture that has the potential to cause an artificial association if a study includes genetically distinct subpopulations, one of which coincidentally displays a higher frequency of disease and allelic variants. As Mark *(88)* has shown, population admixture can give rise to spurious associations and can mask a true association. If two genotypes have a beneficial joint effect but neither is effective alone, measuring only one of them in two populations with different allele frequencies can result in completely different results (including a beneficial effect in one population and not in the other).

Alternative Explanations

Effects of therapeutic agents. Most studies have compared patients diagnosed with cancer with subjects without a cancer diagnosis. This method is quite appropriate for early transitional studies. The use of cancer patients, however, may introduce a bias due to treatment. Patients undergoing chemotherapy or radiation therapy may have reduced DNA repair in lymphocytes (although the tumor itself may have increased repair). A study of 41 cancer patients *(9)* indicated that the [^{3}H]thymidine incorporation into UV-damaged DNA was affected by chemotherapy or radiotherapy. There is a substantial body of literature [e.g., *(89)*] indicating that drug-resistant tumors have enhanced DNA repair capacity. This potential source of confounding has not been well studied.

In addition, immunologic status may be relevant. Interferon may stimulate repair processes and may reduce chromosome aberrations. In a study of 14 breast cancer patients treated with Iscador, an extract of *Viscum album* (mistletoe) that is a known immunomodulator, DNA repair increased 2.7 times over baseline *(18).*

Tamoxifen has been suggested to enhance immune cell responsiveness by increasing the activity of ADPRT, an enzyme involved in DNA repair, in lymphocytes *(22).* Therefore, comparisons of subjects who have received treatment with healthy control subjects can yield biased comparisons and may misrepresent the constitutive or unstimulated repair capacity of the individual.

Effect of cancer itself. Tumor burden is a potentially important confounding factor in the measurement of DNA repair capacity. Its role in terms of repair in lymphocytes (thought to express germline genetic tendencies) versus repair in the tumor itself is unclear at present. On the one hand, the tumor itself may have a substantially enhanced DNA repair capacity, which is sometimes a cause of drug resistance and therapeutic failure. On the other hand, however, tumor burden might suppress or decrease DNA repair activity through high metabolic rate and excessive endogenously generated oxidative stress, which might affect lymphocytes and their repair values *(13).* In the light of such uncertainties, it would be preferable to have measures of DNA repair capacity that are unaffected by cancer status. Germline genetic measures are one approach that would avoid this problem because they are static. However, to our knowledge, definitive studies relating genetic polymorphisms with functional measures of repair have not yet been published. To date, the data on polymorphisms in repair genes and their functions are extremely scant. The specific DNA repair genes and the polymorphisms in alleles of these genes are still very poorly understood. An important alternative, that of a cohort study that measures repair prior to the development of cancer, has not yet been published.

RESULTS

The analytic design of the studies is shown in Table 1, while the results are given in Table 2. Table 2 also gives the CV of the repair assays among control subjects from individual studies, and Table 3 reports data on the published variability and reproducibility of the tests. The results can be broadly grouped into five categories, depending on the tests used.

Category 1 includes tests based on DNA damage to cells (usually chromatid breaks in lymphocytes) induced with a chemical (e.g., bleomycin or BPDE) or with physical agents (e.g., ionizing radiation): the mutagen sensitivity assay, the G_2-radiation assay, the micronucleus assay, and the comet assay (also known as the single-cell gel electrophoresis assay). The mutagen sensitivity assay is generally thought to measure strand breaks, although its specificity is as yet undetermined. As currently performed, it could simply be indirectly measuring the scavenging of free radicals generated by ionizing radiation or bleomycin, resulting in altered levels of DNA damage. Both the micronucleus assay and the comet assay have been used most

often in studies as markers of DNA damage. However, recent investigations have assessed these end points as repair, either after a single time period has elapsed for repair or at multiple end points to estimate the rate and extent of repair.

Category 2 includes indirect tests of DNA repair, such as unscheduled DNA synthesis, and activity of the repair enzyme ADPRT. These assays are usually conducted on isolated lymphocytes that have been damaged by UV radiation or by a chemical. The level of enzyme activity or of DNA synthesis is measured in radiolabeled cells, usually by scintillation counting but also by radiography.

Category 3 encompasses tests based on more direct measures of repair kinetics, such as the plasmid host cell reactivation assay. In the host cell reactivation assay, separate sets of fresh or cryopreserved lymphocytes are transfected with both a damaged plasmid and an undamaged plasmid. Repair is then measured as a "rate," i.e., the amount of radiation or fluorescence at specific points in time. Usually, the chloramphenicol acetyltransferase gene, or cat, has been incorporated into the plasmid. (More recently, the Luciferase gene has been used because it gives better precision and does not require radioactivity.)

Category 4 includes measurement of genetic variation, usually as polymorphisms in the genes associated with DNA repair. In addition to the four broad categories used in epidemiology studies, a number of methods have been used in one or two studies only. Category 5 includes studies that examined more than one category of DNA repair.

In category 1, DNA repair capacity is inferred from unrepaired damage: the number of chromatid breaks, the numbers of micronucleated cells, or the length of the "tail" of a comet, after treatment for a standard period of time; there is not an actual measure of DNA repair capacity. Category 2 includes tests in which the cellular incorporation of activity is measured by scintillation counting or visualization. In category 3, the kinetics of repair are measured, i.e., the rate at which lymphocytes from a cancer patient or from a healthy control repair a damaged plasmid. In category 4, polymorphisms in repair genes are assessed to estimate the distribution of polymorphic alleles, and differences between case and control subjects are measured through tests of association. And, finally, in category 5, it is sometimes possible to examine the correlation between assays conducted on the same individuals.

With the use of these five categories, as indicated in Table 2, 31 of the 38 studies based on tests belonging to category 1 (i.e., tests based on induced DNA damage) showed statistically significant results. (*Note* that, in each category, there are one to three studies that appear in category 5 [multiple tests] and overlap categories. Thus, the number of studies within each category will actually include more studies than are counted under each category.) Two studies did not report statistically significant findings: One was a randomized intervention with antioxidants *(44)*, and the other belonged to category 5. That study *(61)* investigated both the mutagen sensitivity assay (with the use of both bleomycin and 4NQO) and the host cell reactivation assay. The mutagen sensitivity assays showed increased ORs that were not statistically significant, whereas the host cell reactivation assay did have statistically significant results (OR = 14.0; 95% CI = 2.1–591.3). As noted previously, we conducted a correlation analysis on the data given and found that there was an inverse correlation between the host cell reactivation assay and the mutagen sensitivity assay using 4NQO ($r = -0.43$; $P = .01$) but not the mutagen sensitivity assay using bleomycin ($r = -.12$; $P = .48$). Another five studies *(6,12,26,43,54)* did not report significance levels for the relationship between cancer case and control subjects, or they could not be calculated from the data given. When ORs were available or could be calculated, they ranged between 1.4 *(12)* and 38.4 *(59)*.

With regard to category 2, indirect tests of DNA synthesis, 11 of the 15 studies showed statistically significant results. Two *(7,48)* of the 15 studies did not attain statistical significance, and two *(21,37)* did not report significance levels. The ORs available ranged from 1.2 *(48)* to 73.5 *(13)*.

In category 3, tests based on repair kinetics, 10 of 11 studies were statistically significant; one *(31)* of 11 investigations did not find a statistically significant association between the results of the host cell reactivation assay and cancer—in this instance, basal cell carcinoma. The ORs in these 10 investigations with positive results ranged from 1.9 *(28)* to 14.0 *(61)*. Finally, of the four studies based on genotyping, one study *(48)* did not find a statistically significant association with breast cancer occurrence, although the phenotypic expression, i.e., oligonucleotide-induced poly(ADP-ribose)polymerase (PARP) activity, showed a statistically nonsignificant OR of 3.4 (95% CI = 0.7–19.5). A second study *(57)* found a statistically significant association between the PARP genotype and lung cancer among Mexican-Americans (OR = 3.2; 95% CI = 1.0–10.3) but not among African-Americans (OR = 2.3; 95% CI = 0.7–8.0). A third study *(51)* found statistically significant associations between polymorphisms in two DNA repair genes and both cancer status and clinical radiosensitivity. The fourth study *(52)*, examining mismatch repair gene expression, found varied levels of reduced expression among case subjects with head and neck cancer compared with control subjects, with low expression of hMLH1 (a human mismatch repair gene) 4.4 times more likely (95% CI = 2.1–9.1) among case subjects than among control subjects.

In category 5, multiple measures, positive correlations between two or more assays were evident in two *(54,61)* of the four studies, but in the other two studies *(48,57)* insufficient data were presented for conclusions to be drawn.

DISCUSSION

Design

All of the studies that we have examined were case–control studies, except for four prospective investigations designed to study second primary cancers, recurrence, or survival *(16,32* [an extension of *(16)*]*,60,62)*. In most of the studies, it was difficult or impossible to judge whether cases were newly diagnosed (incident) or prevalent. The exact source of control subjects was not always clear, although most were based on "convenience" samples.

Selection Bias

Selection bias might be a problem in many of the studies, although seldom is sufficient detail presented to judge the comparability of case and control subjects. Control subjects were typically blood donors, hospital personnel, and other types of convenience samples. The extent of their comparability to case subjects is difficult to evaluate, even though they were often frequency matched on sex, age, and ethnicity.

Only one study *(31)* had a population-based design; ironically, this was the only clearly negative study. However, reasons

for this negative result have been listed below, and these are separate considerations from selection bias. It is hard to imagine that selection bias has affected all of the positive studies (which are the vast majority), since they were based on different series of subjects and sampled from different populations. It is unlikely that the same type of bias in sampling has occurred in all of these studies. In addition, to explain ORs with a magnitude of 4 or higher, the bias would have to be quite strong.

Confounding

Confounding describes the possibility that some exposure or characteristic of the patients is associated with both DNA repair capacity and risk of cancer, creating a spurious relationship between DNA repair capacity and the disease. Repair enzymes can be induced in several ways by stresses that damage DNA, e.g., oxidative stress. According to recent investigations based on microchip technology *(90)*, in yeast treated with an alkylating agent, the expression of more than 300 gene transcripts was increased, while that of approximately 75 gene transcripts was decreased. However, no information is available on the persistence of gene induction.

In human studies, several assays for DNA repair were affected by characteristics, such as age, sunlight exposure, dietary habits (with an inverse relationship between carotenoids and mutagen sensitivity), exposure to pro-oxidants, and cancer therapies. While age and therapies were usually controlled for, dietary habits might have acted as confounders, since both the intake and the plasma levels of carotenoids and other antioxidants have been shown to be lowered in cancer patients compared with those in healthy control subjects [e.g., *(91)*]. The extent of such potential confounding is hard to estimate because it is not clear that this is a confounding effect, since DNA repair might be one of the mechanisms by which antioxidants and other constituents of fruits and vegetables affect the risk of cancer. In this case, controlling for such constituents in the analysis might lead to inaccurate conclusions because DNA repair would be an intermediate step between exposure and cancer risk. In one study *(49)*, dietary habits were not associated with mutagen sensitivity in control subjects; rather, vitamins seem to act as effect modifiers, not as confounders.

How persistent the effect of potential confounders could be is unknown. In fact, we know little about the duration of DNA damage induced by different agents. It has been suggested *(92)* that DNA damage induced by coal tar treatment of psoriasis could persist for more than 3 months.

Strength of Association, Internal-Coherence, Dose–Response Relationship

The reported ORs of DNA repair measures and cancer range from 1.4 to 75.3, with the majority of point estimates ranging between 2 and 10. When stratified by exposure groups, the ORs are often quite high, over 30 in several instances. Few studies were able to examine dose–response relationships, although Bondy et al. *(27)* found increased ORs with an increased number of family members with cancer.

Consistency of Results

The one study by Hall et al. *(31)* that did not find an association between DNA repair capacity and the occurrence of basal cell carcinoma used a test based on a damaged plasmid transfected into the subject's lymphocytes and not on direct damage to the host cell. This technique minimizes cytotoxic effects from damaging agents that might indirectly compromise the repair mechanisms of the cell. The authors attribute the negative finding to a number of factors, including delayed transportation of samples, with a resultant impaired viability of lymphocytes, and variability between the two technicians conducting the assay. Finally, of course, there may not be an association between DNA repair and the occurrence of basal cell carcinoma in this population. All of the other studies were positive, although with the differences in the strength of association discussed above.

Test Reliability

Few authors (11 of 64) included measures of variability or reliability of assays (Table 3). Several studies *(6,21,28,31,44)* reported on technical variability, i.e., the same sample measured more than once. Four studies *(6,11,13,31)* measured variability due to different observers. Intraindividual variation was also rarely reported and was relatively high when assessed, ranging from 3% to 43% (*see* Table 3). Several authors [e.g., *(28)*] did comment on measures that might affect the reliability of their results, using characteristics such as rank order, range of bias, and variance of the outcome measure. In no study was the intraclass correlation coefficient reported.

Publication Bias

We plotted the log of the OR by the inverse of the SE for the studies for which this information was available or could be calculated (Fig. 1). This plot represents the precision in estimating the underlying true associations (i.e., between DNA repair deficiency and the development of cancer) in relationship to the size of the sample. We also calculated the Begg–Mazumdar test for publication bias *(93)*, which was not significant ($P = .93$), indicating no observable publication bias. On the basis of this plot and the statistical test, we found no evidence of publication bias in this selection of studies.

Time Sequence and Biologic Plausibility

Most studies had a case–control design; i.e., DNA repair was evaluated in a cross-sectional fashion among case subjects with cancer and control subjects. In addition, with few exceptions *(48,51,52,57)*, the studies were based on phenotypic expression

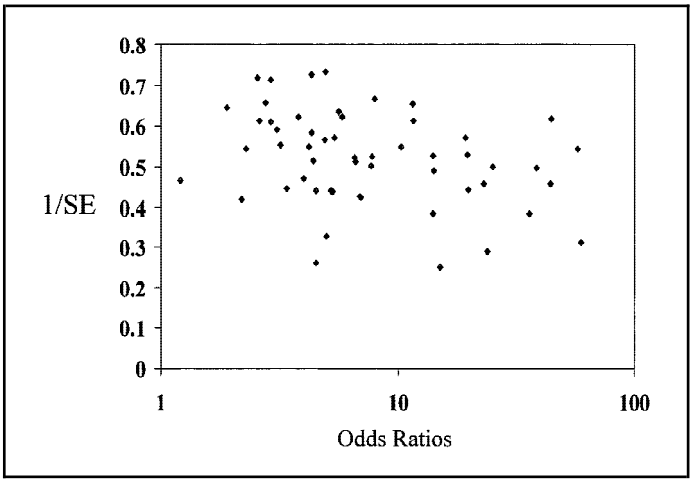

Fig. 1. Funnel plot showing the inverse of the standard error (SE) (of the odds ratio) plotted by the odds ratios. This funnel plot has no particular pattern and shows no evidence of publication bias.

of repair that the cancer process itself or the use of cellular damaging agents might impair. Only one study *(60)* was prospective, where mutagen sensitivity was measured at the time of patient recruitment and recurrence rate was determined. This study, however, was aimed at evaluating the ability of the mutagen sensitivity results to predict clinical outcome, not its relationship to disease risk.

With regard to biologic plausibility, a major limitation of many tests (particularly those belonging to category 1 discussed above) is that DNA repair capacity is only indirectly inferred from cellular DNA damage remaining after exposure to mutagens for a specific time period. In many of these studies, the mutagen used to induce damage is not known to initiate tumors and, methodologically, it would be extremely useful to extend this assay to carcinogens specific to tumor types, such as *N*-ethylnitrosourea.

We have learned from Table 2, in fact, that most of the studies based on tests belonging to category 1 showed statistically significant results. Those belonging to category 2, indirect tests of DNA repair, were often not statistically significant. This result could be due to a high background level when using scintillation counting that is not amenable to chemical damping by such agents as hydroxyurea.

The results of studies based on category 3, assessing the kinetics of repair, were mixed. Studies in category 4, those based on genotyping, were limited in number and were, unfortunately, small with limited power, similar to many studies of metabolic polymorphisms. It is not clear that conducting these studies without concomitant studies of expression and/or function will be fruitful.

To draw firm conclusions about a cause–effect relationship, therefore, we need more evidence about the biologic meaning of the current tests. In particular, evidence has not been provided that tests belonging to category 1 really express DNA repair. They do appear to express unrepaired DNA. One possible interpretation is that category 1 tests refer to a general and nonspecific impairment of the DNA repair machinery, while tests belonging to categories 2 and 3 explore more specific aspects of DNA repair capacity. This working hypothesis, however, requires further evidence.

Conclusion

We have summarized what we believe to be all of the relevant human epidemiologic studies that have addressed the role of a defect in DNA repair capacity in the development of cancer. That is, many of the assays are measuring a response of phytohemagglutinin-stimulated lymphocytes to a mutagenic agent and, as stated in the "Discussion" section under the subheading entitled "Confounding," we do not know the extent to which the results may depend on responses to unmeasured endogenous sensitizing or protective agents rather than on intrinsic DNA repair capacity. However, it must be stressed that the results shown in the tables represent the state of the art for measurements of DNA repair (through 1998) in human epidemiology studies. While associations with cancer risk have been observed in the assays described, the specificity of these assays as measures of DNA repair and, more importantly, as repair of carcinogenic or even mutagenic lesions in DNA is as yet undetermined.

We hope that a presentation of these studies will stimulate the field to develop definitive molecular assays that may define not only the potential genetic defects themselves but also the repair pathways that might be affected by such defects. Although a firm conclusion cannot be drawn, there are a few aspects that are worth noting: *(a)* The vast majority of studies show a difference between cancer case subjects and control subjects; *(b)* although this observation is compatible with a chromosomal instability due to cancer itself (with an inversion of the cause–effect relationship), it is notable that impaired mutagen sensitivity was also observed in healthy relatives of cancer case subjects; *(c)* there are a variety of functional tests that only indirectly address DNA repair and that show high variability in their expression; and *(d)* the issue of confounding is almost totally unexplored, although many of the observed associations are too strong to be attributable to confounders.

As new functional assays are developed and the current assays are made more precise, the role of DNA repair capacity will be clarified, particularly as more relevant mutagens specific to particular cancers are employed. All such studies should evaluate and report the variability of the assay used and the intraindividual and interindividual variabilities. Prospective studies will be critical and should eliminate concern over the role of cancer itself leading to associations. New studies are appearing on the DNA repair genotypes. Those that compare genetic polymorphisms with functional assays will likely be valuable. It is likely that the study of interindividual variability in DNA repair will greatly contribute to our knowledge of human carcinogenesis.

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NOTES

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