

# Reduced DNA Repair Capacity in Head and Neck Cancer Patients<sup>1</sup>

Lie Cheng, Susan A. Eicher, Zhaozheng Guo,  
Waun Ki Hong, Margaret R. Spitz, and Qingyi Wei<sup>2</sup>

Departments of Epidemiology [L. C., Z. G., M. R. S., Q. W.], Head and Neck Surgery [S. A. E.], and Thoracic and Head and Neck Medical Oncology [W. K. H.], The University of Texas M. D. Anderson Cancer Center, Houston, Texas 77030

## Abstract

**Head and neck cancers (HNCs) are malignancies that can be induced by tobacco use, although host-specific factors such as the DNA repair capacity (DRC) may modulate individual susceptibility to tobacco carcinogenesis. To test the hypothesis that genetically determined DRC modulates HNC susceptibility, we measured the DRC in the peripheral blood lymphocytes of 55 patients with newly diagnosed, previously untreated HNC and 61 healthy controls by the host-cell reactivation assay using a reporter gene damaged by benzo(a)pyrene diol epoxide, an ultimate tobacco-related carcinogen. The mean DRC was significantly lower in cases (8.6%) than it was in controls (12.4%;  $P < 0.001$ ). The DRC was an independent risk factor for HNC ( $P < 0.01$ ); those in the middle and lowest tertiles of DRC had increased odds ratios [2.17 (95% confidence interval, 0.74–6.39) and 4.27 (confidence interval, 1.45–12.5), respectively] for HNC. These findings suggest that individuals with reduced DRC may be at increased risk of developing HNC.**

## Introduction

HNC<sup>3</sup> includes squamous cell carcinomas of the oral cavity, pharynx, and larynx (1). In 1997, there were 41,650 new cases and 12,670 deaths from HNC disease in the United States (2). Heavy smokers have 5- to 25-fold higher cancer risks than do nonsmokers (3, 4). Alcohol consumption is also a major risk factor for HNC (5, 6).

HNC, like lung cancer, can therefore be considered a paradigm of an environmentally induced disease. However, only a fraction of exposed individuals develop these cancers (7), suggesting that there is a genetic predisposition. Susceptibility factors for HNC may include genetically determined variation in the activity of metabolic enzymes, such as cyto-

chrome P-450 (8) and DNA repair enzymes (9), that may influence the rate of removal of DNA damage (10, 11) and mutation fixation (12, 13) and cause chromosomal instability (14).

Benzo(a)pyrene, a classic DNA-damaging carcinogen in tobacco smoke and in the ambient environment, is biologically activated *in vivo* by cytochrome P-450 and peroxidases, forming highly toxic electrophilic and free-radical reactive intermediates, such as BPDE, that can irreversibly damage DNA by covalent binding or oxidation (15, 16). BPDE-induced DNA adducts are found in *p53* mutation hot spots (17) and are repaired by the nucleotide excision repair pathway (18). The premutagenic lesions induced by BPDE are repaired more efficiently in the transcribed strand than in the untranscribed strand of the hypoxanthine-guanine phosphoribosyltransferase gene, indicating that BPDE-DNA adducts may block the transcription of essential genes and cause changes in chromatin structure (19). Evidence from molecular epidemiological studies indicates that smokers often have higher polycyclic aromatic hydrocarbon-DNA adduct levels than do nonsmokers (20, 21), suggesting an association with exposure to carcinogens such as benzo(a)pyrene in tobacco smoke and the involvement of inefficient DNA repair (10, 11).

Therefore, we hypothesized that variations in DRC could modulate HNC susceptibility. To test this hypothesis, we conducted a pilot molecular epidemiological study in which we measured the DRC of BPDE-damaged plasmids harboring a reporter gene (22, 23) by the HCR assay. Cryopreserved lymphocytes were available from 55 patients with newly diagnosed, untreated HNC and 61 healthy controls and were tested for DRC. We report here an association between reduced DRC and an increased risk of HNC.

## Materials and Methods

**Study Subjects.** The 55 cases included in this study were HNC patients who were recruited from consecutively registered new patients at The University of Texas M. D. Anderson Cancer Center between 1995 and 1997 and who had not received chemotherapy or radiotherapy. The tumors that they had were histopathologically confirmed squamous cell carcinomas of the oral cavity ( $n = 17$ ), pharynx ( $n = 20$ ), or larynx ( $n = 18$ ). Patients with a prior cancer history or recurrent HNC were excluded. The 61 controls were selected from an ongoing case-control study of lung cancer in which the controls are being selected from the clinics of a large multispecialty health maintenance organization and frequency-matched to the lung cancer cases for age, sex, ethnicity, and smoking status (24). From this pool, we selected control subjects who were frequency-matched to the case for age, sex, ethnicity, and smoking status. The recruitment of subjects was approved by our institutional internal review board, and informed consent was obtained from each subject, who also completed a questionnaire that elicited information about demographic and other variables, including smoking history and alcohol use.

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<sup>2</sup> To whom requests for reprints should be addressed, at Department of Epidemiology, Box 189, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030. Phone: (713) 792-3020; Fax: (713) 792-0807. E-mail: qwei@request.mda.uth.tmc.edu.

<sup>3</sup> The abbreviations used are: HNC, head and neck cancer; BPDE, benzo(a)pyrene diol epoxide; DRC, DNA repair capacity; HCR, host-cell reactivation; OR, odds ratio; CI, confidence interval.

Table 1 DRC by selected factors in HNC cases and controls

Factor	Cases		Controls		<i>P</i> <sup>a</sup>	<i>P</i> <sup>b</sup>
	No.	Mean ± SD	No.	Mean ± SD		
Age (yr)						
<60	31	8.50 ± 4.3	28	13.9 ± 8.6		0.002
≥60	24	8.77 ± 4.4	33	11.9 ± 3.9	0.260	0.049
Sex						
Male	36	8.94 ± 3.9	35	14.0 ± 7.6		0.001
Female	19	8.01 ± 3.4	26	10.3 ± 4.7	0.373	0.080
Ethnicity						
Non-Hispanic white	50	8.90 ± 3.8	51	12.2 ± 6.6		0.012
Other <sup>c</sup>	5	5.80 ± 2.1	10	13.2 ± 7.8	0.242	0.063
Tobacco use						
Nonusers	11	8.83 ± 3.2	7	10.8 ± 6.5		0.391
Ever users	44	8.56 ± 3.9	54	12.6 ± 6.8	0.205	0.001
Alcohol use						
Nonusers	13	9.35 ± 3.6	14	12.0 ± 7.3		0.250
Ever users	42	8.39 ± 3.8	47	12.5 ± 6.7	0.930	0.001

<sup>a</sup> From  $\chi^2$  test for frequency distribution of cases and controls.

<sup>b</sup> From two-sided *t* test analysis of cases and controls.

<sup>c</sup> Cases include three African-Americans and two Mexican-Americans.

**The HCR Assay.** Approximately 20 ml of blood was drawn from each subject into two 10-ml heparinized Vacutainers (Becton Dickinson, Franklin Lakes, NJ). The isolated lymphocytes were frozen in a freezing medium containing 50% fetal bovine serum, 40% RPMI 1640, and 10% DMSO (Fisher Scientific Co., Pittsburgh, PA) and quickly thawed later in a thawing medium in batches for the HCR assays. The thawing medium consisted of 50% fetal bovine serum, 40% RPMI 1640, and 10% dextrose (Sigma Chemical Co.) and ensured approximately 90% viability after thawing. The plasmid (pCMV<sub>cat</sub>, a gift from Dr. Lawrence Grossman, Johns Hopkins University, Baltimore, MD) was treated as described previously (10) with 0 and 60  $\mu$ M BPDE. A dose of 60  $\mu$ M BPDE was used instead of the 75  $\mu$ M dose used in a previously published study (10) because of concerns that a fixed, high dose in the HCR assay could result in an overestimation of variation in the DRC (25). The DRC of the cells was measured by the HCR assay as described elsewhere (22).

Briefly, the HCR assay uses a nonreplicating plasmid, pCMV<sub>cat</sub>, that harbors the reporter gene chloramphenicol acetyltransferase, which is a bacterial drug resistance gene not present in mammalian cells (22). The plasmid is damaged before transfection by the DEAE-dextran method (26). Because a single, unrepaired DNA lesion such as a thymine dimer formed by UV light (27) or a bulky DNA adduct formed by BPDE (28) can effectively block reporter gene expression, the chloramphenicol acetyltransferase activity subsequently measured is the net result of repair within the host cells.

**Statistical Analysis.** DRC was first analyzed as a continuous variable. Student's *t* test was used to compare the differences between the groups. Correlation analyses were performed to compare DRC and selected host factors. For the calculation of crude ORs and CIs, the median DRC of the controls was used as the cutoff value: values greater than the median were considered high (efficient) repair; and values below the median were considered low repair. To evaluate the dose-response relationship, the subjects were categorized into tertiles of DRC according to the distribution of the controls. Ever users of tobacco or alcohol were defined as those who had smoked more than 100 cigarettes in their lifetimes or had drunk alcoholic beverages at least once a week for more than 1 year. Ethnicity

Table 2 DRC by tumor site in HNC cases and controls

	No.	Mean ± SD		<i>P</i> <sup>a</sup>
		Age (yr)	DRC (%)	
Controls	61	59.0 ± 9.4	12.4 ± 6.7	
Cases	55	56.7 ± 11.1	8.6 ± 3.8	0.001
Oral cavity	17	57.3 ± 11.7	7.9 ± 3.3	0.009
Pharynx	20	55.5 ± 11.9	9.1 ± 4.4	0.040
Larynx	18	57.4 ± 10.0	8.8 ± 3.5	0.031

<sup>a</sup> From two-sided *t* test analysis for DRC between cases and controls.

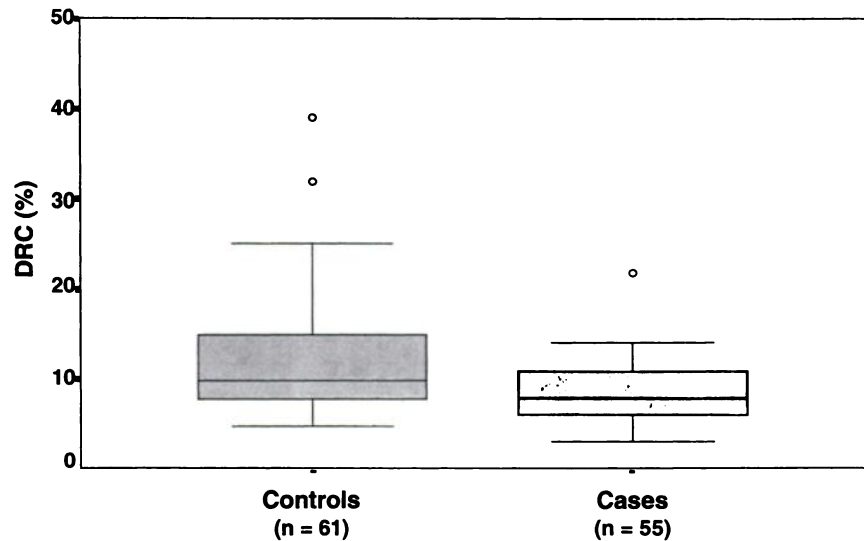
was recoded as non-Hispanic white or others. For logistic regression analysis, the tertile of DRC was recoded as a dummy variable [0,0 = < 8.0% (lowest tertile); 0,1 = 8.0–13.2% (middle tertile); and 1,0 = > 13.2% (highest tertile)]. To assess a trend, the tertile variables were recoded as a continuous variable and fit into the logistical regression model. All of the statistical analyses were performed with Statistical Analysis System software (Version 6; SAS Institute Inc., Cary, NC).

## Results

The mean age was 56.7 years for the cases and 59.0 years for the controls. Sixty-five percent of the cases and 57% of the controls were men. Most of the cases (91%) and the controls (84%) were non-Hispanic whites. Eighty percent of the cases and 88% of the controls were ever smokers, and 76% of the cases and 77% of the controls were alcohol users. None of these differences in frequency distributions was statistically significant (*P* > 0.05), indicating that the frequency matching was adequate (Table 1).

As shown in Table 2, the controls had significantly higher DRC (12.4% for the residual repair of plasmid damaged by 60  $\mu$ M BPDE compared with 100% for undamaged plasmid) than the cases (8.6%) did (*P* < 0.01); there was an overall 31% reduction of DRC in the cases. Stratified analysis by tumor sites was performed to compare the differences in the mean DRC for each tumor site and the controls. The 55 cases had squamous cell carcinomas of the oral cavity (*n* = 17; 30%), pharynx (*n* =

Fig. 1. Distribution of DRC in cases and controls. Horizontal lines through each box, medians; upper and lower limits of each box and vertical lines above and below each box, cutoff points for percentiles, respectively; ○, outlier. The cases' DRCs were skewed to lower values than the controls' values were, indicating that the cases tended to have lower DRCs than the controls ( $P < 0.01$ ).



20; 36%), and larynx ( $n = 14$ ; 34%). There were no significant differences in DRC by tumor site. Further analysis of stages I–IV did not show any significant differences or trends in DRC (data not shown).

The variation of DRC in the controls was as high as 5-fold (approximately 5–25%, except for two high outliers), but the distribution of DRC was skewed to lower values in the cases than it was in the controls (Fig. 1), suggesting that the cases tended to have a lower DRC. The younger cases (age  $< 60$  years) also had a significantly lower mean DRC (8.5%) than did controls of the same ages (13.9%;  $P < 0.01$ ). Younger cases tended to have lower a DRC than older cases, whereas younger controls tended to have a higher DRC than older controls, but these differences were not statistically significant (Table 1). The crude OR for the risk of HNC associated with reduced DRC was 2.2 (95% CI, 1.0–4.77) when the median of the controls' DRCs was used as the cutoff value and was essentially unchanged after adjustment for age, sex, ethnicity, and use of tobacco and alcohol. In addition, the differences in DRC between cases and controls were greater in smokers and alcohol users (Table 1), suggesting that reduced DRC may be the underlying biological mechanism for the increased smoking- and alcohol-related risk for HNC.

Because the cases and controls were frequency matched for age, sex, ethnicity, and smoking status, these variables were further adjusted for any residual effect of the matching variables by logistic regression analysis. In a logistic regression model that included age, sex, ethnicity, smoking status, alcohol use, and DRC (Table 3), DRC remained an independent risk factor. There was also evidence of a dose-response relationship (trend test,  $P < 0.01$ ); those in the middle (8–13.2%) and lowest ( $< 8.0\%$ ) tertiles of the DRC in the controls had increased ORs for HNC [2.17 (95% CI, 0.74–6.39) and 4.27 (95% CI, 1.45–12.5), respectively]. The interactions between smoking status and DRC could not be evaluated because of the relatively small number of subjects in each group.

## Discussion

In this report, we demonstrated that the reduced repair of BPDE-induced DNA damage was associated, in a dose-dependent manner, with an increased risk of developing HNC. The

Table 3 Logistic regression analysis of adjusted ORs and CIs in HNC cases and controls

DRC, %	No.		Crude OR (CI)	Adjusted OR (CI) <sup>a</sup>
	Cases	Controls		
>13.2	8	20	1.00	1.00
8–13.2	19	22	2.16 (0.77–6.01)	2.17 (0.74–6.39)
<8.0	28	19	3.68 (1.34–10.7)	4.27 (1.45–12.5)
Trend test			$P < 0.011$	$P < 0.008$

<sup>a</sup>ORs were adjusted in a logistical regression model including age, sex, ethnicity, smoking status, alcohol use, and DRC.

lower DRC in cases than in controls among smokers and alcohol users suggests that reduced DRC may play a role in the etiology of smoking- and alcohol-related HNC. Because the DRC was measured in untreated peripheral blood lymphocytes, the data presented here provide evidence that individuals with genetically determined low DRC may have a predisposition to HNC.

The findings are consistent with several lines of evidence that the risk of HNC is genetically determined. In two published case-control studies (14, 29) of patients with previously untreated upper aerodigestive tract cancers (one with 75 cases and 62 controls and the other with 108 cases and 108 controls), bleomycin-induced chromatid breaks were counted as an indirect measure of DRC (30). Mutagen sensitivity [defined as an increased frequency of chromatid breaks ( $> 0.8$  breaks/cell)] was a significant risk factor (OR, 4.3 and 2.5, respectively) for these cancers after adjustment for the effect of smoking and alcohol use (14, 29). The relationship between the family history of cancer and the frequency of chromatid breaks in 669 first-degree relatives of the 108 patients was also examined. There was an increased risk of familial aggregation of cancer in mutagen-sensitive patients with one (OR, 2.6; 95% CI, 1.1–6.5) or two or more first-degree relatives with cancer (OR, 6.6; 95% CI, 1.7–25.7) (31). In a longitudinal study of mutagen sensitivity in patients with HNC, mutagen sensitivity was a significant predictor of the risk of secondary primary tumors after adjustment for the effect of tobacco use (32).

In a case-control study of DRC and the risk of lung cancer, another tobacco-related cancer, reduced DRC was a significant risk factor for lung cancer in 51 patients with newly diagnosed lung cancer and 56 healthy controls (10). Further analysis of *in vitro* BPDE-induced DNA adducts in peripheral lymphocytes revealed that lung cancer patients have significantly higher levels of BPDE-DNA adducts than controls do (11). Moreover, the host cells' repair capacity for BPDE-induced DNA damage is inversely correlated with the level of *in vitro* induced BPDE-DNA adducts (33). In addition, the frequency of BPDE-induced chromatid breaks is also higher in lung cancer patients than it is in healthy controls (34). It has been shown that a single unrepaired DNA lesion can efficiently block gene transcription (27, 28). Therefore, unrepaired DNA damage such as BPDE-adducts in *p53* hot spots (17) will cause mutation fixation that leads to carcinogenesis. Taken together, these studies support the hypothesis that the reduced repair of tobacco carcinogen-induced DNA damage may be the underlying mechanism for smoking-related cancer.

Identifying individuals at high risk of developing tobacco-related cancer by using biomarkers such as DRC should enhance other preventive measures such as smoking cessation. Because of the relatively small number of subjects in this study and the use of a non-population-based control group, the results may be biased by unmeasured factors. Therefore, our findings should be verified in a larger, well-designed case-control study in which the interactions among smoking exposure, DNA repair, and other factors that may influence DNA repair, such as family history of cancer, diet, and occupational exposure, are comprehensively evaluated.

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