[CANCER RESEARCH 58, 1605–1608, April 15, 1998]

Advances in Brief

Benzo[*a*]pyrene Diol Epoxide-induced 3p21.3 Aberrations and Genetic Predisposition to Lung Cancer[1]

Xifeng Wu,[2] Ying Zhao, Susan E. Honn, Gail E. Tomlinson, John D. Minna, Waun Ki Hong, and Margaret R. Spitz

Departments of Epidemiology [X. W., Y. Z., S. E. H., M. R. S.] and Thoracic and Head and Neck Medical Oncology [W. K. H.], The University of Texas M. D. Anderson Cancer Center, Houston, Texas 77030; School of Public Health [X. W., Y. Z.], The University of Texas Health Science Center at Houston, Houston, Texas 77030; and Department of Pediatrics and Hannon Center for Therapeutic Oncology [G. E. T., J. D. M.], The University of Texas Southwestern Medical Center, Dallas, Texas 75235

Abstract

3p deletion, a common chromosome defect in lung cancer, occurs more frequently in the lung tumor tissues of smoking patients than it does in those of nonsmoking patients. This pilot study evaluated whether 3p aberrations induced by benzo[*a*]pyrene diol epoxide (BPDE), the metabolic product of benzo[*a*]pyrene, a constituent of tobacco smoke, were more common in the peripheral blood lymphocytes of 40 lung cancer patients than they were in those of 54 matched controls. Our hypothesis was that 3p sensitivity to BPDE reflects the susceptibility of a specific locus to damage from carcinogens in tobacco smoke. BPDE-induced chromosome 3p21.3 aberrations were significantly more frequent in cases (34.1 per 1000) than they were in controls (22.1 per 1000; $P < 0.0001$). However, no such difference was observed for 6q27, a control locus. Using the median value in the controls (20 per 1000) as a cutoff point to classify BPDE-induced sensitivity at 3p21.3 and after adjustment by age, sex, ethnicity, and smoking status, 3p BPDE sensitivity was associated with an elevated risk of 14.1 (95% confidence interval: 3.5, 56.2) for lung cancer. There was also a dose-response relationship between the degree of BPDE sensitivity at 3p21.3 and increased risk for lung cancer. Therefore, 3p may be a molecular target for BPDE damage in lung cancer cases.

Introduction

Most lung cancers (85%) develop in heavy cigarette smokers (1). However, only a fraction of smokers develop neoplastic lesions, suggesting that there is interindividual variation in susceptibility to tobacco carcinogenesis (1, 2). BPDE[3] is the metabolic product of benzo[*a*]pyrene, a major constituent of tobacco smoke (3). Our data have suggested that chromosomal sensitivity to *in vitro* BPDE exposure is a constitutional phenomenon and a risk predictor for lung cancer (4). We have also shown that mutagen-induced chromosome aberrations are not random but may reflect the inherited genetic susceptibility of specific loci to damage by carcinogens (5). The short arm of chromosome 3 may be a hot spot for such damage. 3p deletion is a common finding in lung cancer (6–9) and occurs more frequently in the lung tumor tissues of patients who smoke than it does in those of nonsmoking patients (10). The specific aim of this pilot study was to determine whether BPDE-induced chromosome aberrations on 3p in cultured peripheral blood lymphocytes were more common in 40 lung cancer patients than they were in 54 controls matched to the cases on sex, age (±5 years), ethnicity, and smoking status. Our working hypotheses were that 3p BPDE sensitivity reflects the inherited genetic susceptibility of a specific locus to carcinogens in tobacco smoking, that chromosome 3p is the molecular target of carcinogen damage in tobacco smoke, and that individuals with such aberrations are at increased risk for lung cancer.

Subjects and Methods

Study Subjects. Cases and controls were identified from two ongoing molecular epidemiological studies of lung cancer that have been described previously (11). The cases were patients with newly diagnosed, histologically confirmed lung cancer who were registered at the Departments of Thoracic Surgery and Thoracic Medical Oncology at The University of Texas M. D. Anderson Cancer Center. There were no age, sex, ethnic, or stage restrictions. We chose to study previously untreated patients to minimize the potential confounding influence of radiotherapy and chemotherapy on the chromosomal analyses. Patients were referred to our center for definitive treatment. The study coordinator conducted a daily review of computerized appointment schedules for the hospital outpatient clinics that serve lung cancer patients to enroll patients before initiation of therapy. Once a patient was determined to be eligible for the study, an appointment would be made for an in-person interview, to be conducted at the time of the next follow-up appointment.

Controls without prior history of cancer (except nonmelanoma skin cancer) were identified from a control pool database that has been described previously (11). Briefly, this potential control database was derived from subscribers to a large private multispecialty provider (Kelsey-Seybold Clinic), which includes a health-maintenance organization, capitated patients, and fee-for-service components in the Houston metropolitan area. Thus far, we have 39,264 respondents in our potential control database. After each case was identified, a list of five controls was generated from the potential control database by computer. The randomly selected control subject would be contacted by telephone to confirm his/her willingness to participate. If the person refused to participate or was deemed ineligible, another potential control would be selected from the potential control pool. Controls were frequency matched to the cases by sex, age (±5 years), ethnicity, and cigarette smoking status. An appointment would be scheduled at a Kelsey-Seybold clinic site that was convenient to the participant. Each participating control subject was given a $30.00 gift certificate for use at a local grocery store and parking validation.

Each participant was asked to sign an informed consent form for the blood drawing and for completion of a personal interview (conducted by M. D. Anderson Cancer Center staff) that lasted about 1 h. Epidemiological data, including demographic information, smoking status, and family history of cancer information, were collected by personal interview. The blood samples were delivered to the epidemiology laboratory by the interviewer.

BPDE Sensitivity Assay. (+/−)-anti-BPDE was purchased from Midwest Research Institute (Kansas City, MO). We used tetrahydrofuran (Sigma Chemical Co., St. Louis, MO) as the solvent. The 1 mM stock was aliquoted into microcentrifuge tubes (500 μl each) and stored at −20°C in the dark. Lymphocyte cultures were established as follows: whole blood (1 ml) was cultured in 9 ml of RPMI 1640 tissue culture medium (JRM Biosciences, Lenexa, KS) with 10% FCS and 1% phytohemagglutinin (Wellcome Research Laboratories, Research Triangle Park, NC) at 37°C for 72 h. BPDE was then added to each culture to a final concentration of 2 μM for 24 h. After routine blocking with colcemid, hypotonic treatment, and fixation, cell suspensions were stored at −20°C until they were processed for FISH experiments.

3p aberrations were detected by FISH with a 3p21.3-specific DNA probe for the human semaphorin IV gene (approximately 75 kb; Oncor Inc., Gaithers-

Received 12/4/97; accepted 3/2/98.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

[1] This work was supported by National Cancer Institute Grants 1RO3 70191, CA 55769, CA 68437, and SPORE P50 CA 70907.

[2] 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.

[3] The abbreviations used are: BPDE, benzo[*a*]pyrene diol epoxide; FISH, fluorescence *in situ* hybridization; OR, odds ratio; CI, confidence interval.

Downloaded from cancerres.aacrjournals.org on March 7, 2021. © 1998 American Association for Cancer Research.

burg, MD). A probe for chromosome 6q27 (Oncor Inc.) was used to detect the overall frequency of increased chromosome aberrations and as an internal control for hybridization efficiency. 6q27 was selected as the control locus because it has not been reported to be deleted in lung cancer and is located in a Giemsa-light region, as is the 3p21.3 test probe. The 6q27 probe also served as a control for differences in chromatin structure (which may affect hybridization) between 3p21.3 and the rest of the genome.

For the FISH procedure, 10 μl of the cosmid probe were added to each interphase smear, which had been pretreated with 2× SSC (pH 7.0) at 37°C for 30 min; dehydrated in 70, 80, 95, and 100% ethanol for 2 min each at room temperature; denatured with 70% formamide and 2× SSC (pH 7.0), at 70–72°C for 2 min; dehydrated in a series of concentrations of ice-cold ethanol; and then air-dried. Hybridizations were performed at 37°C for at least 16 h. Because stringency conditions can affect hybridization efficiency, we hybridized cases and controls concurrently. The posthybridization wash was in 2× SSC (pH 7.0) for 5 min at 72°C without agitation. Signals were detected by incubating the slides for 10 min at 37°C in FITC-conjugated avidin (Oncor Inc.) and then washing the slides in 1× BST buffer [0.5 M $NaHCO_3$, 1.5 M NaCl, and 0.25% Tween 20 (pH 8.0)] three times for 3 min each time. If a signal was weak, it was amplified by incubation with antiavidin antibody for 10 min at 37°C. Then the slides were washed in 1×BST again, incubated with FITC-antiavidin antibody for 10 min at 37°C, and then washed in 1× BST buffer again. Finally, the slides were counterstained with propidium iodide/antifade, the cells were viewed through a fluorescent microscope (Leeds Inc., Irving, TX) with individual FITC filters, and the images were captured with an Image System (PSI, Houston, TX).

The following scoring criteria were applied to the FISH signals: (*a*) nuclei did not overlap; (*b*) signal intensity was about the same; (*c*) minor hybridization spots, which are smaller and less intense than real signals, were excluded; (*d*) signals were only counted when they were completely separate from each other; and (*e*) paired or close signals were counted as one signal. The laboratory personnel who scored the 3p aberrations did not know the samples' case-control status. The most common abnormal signals were one signal and three signals, which may reflect deletion and translocation, respectively.

Statistical Analysis. Laboratory and questionnaire data for this project were merged and edited, and clean system files were created by using SAS statistical software packages. We examined the association between 3p BPDE sensitivity, assessed as the number of chromosome 3p21.3 aberrations in 1000 interphases, and risk of lung cancer in the case-control study. Our analytic approach was to dichotomize 3p BPDE sensitivity at the median value for controls and also to study it as a continuous variable. Crude and adjusted ORs and 95% CIs for BPDE sensitivity at 3p21.3 were calculated. Logistic regression analysis was used to adjust for multiple covariates.

Results

This study comprised 40 lung cancer cases and 54 controls (Table 1). The cases and controls were well matched with respect to ethnicity, sex, and age. There were no significant differences between cases and controls in terms of smoking status or other smoking variables. In terms of histological distribution, there were 3 patients (7.5%) with small cell lung cancer, 6 (15.0%) with squamous cell lung cancer, 21 (52.5%) with adenocarcinoma, 1 (2.5%) with large cell lung cancer carcinoma, and 9 (22.5%) with nondifferentiated small cell lung cancer. Stage information was only available for 30 cases. Among these cases, about 27% were stage I and II.

The number of BPDE-induced chromosome 3p21.3 aberrations ranged from 15 per 1000 to 54 per 1000 (mean: 34.1 ± 9.7 per 1000) for cases and from 5 per 1000 to 57 per 1000 (mean: 22.1 ± 10.7 per 1000) for controls ($P < 0.0001$). In contrast, no difference in BPDE-induced chromosome aberrations was observed at 6q27, a control locus: the number of BPDE-induced chromosome 6q27 aberrations ranged from 6 per 1000 to 18 per 1000 (mean: 10.9 ± 3.8 per 1000)

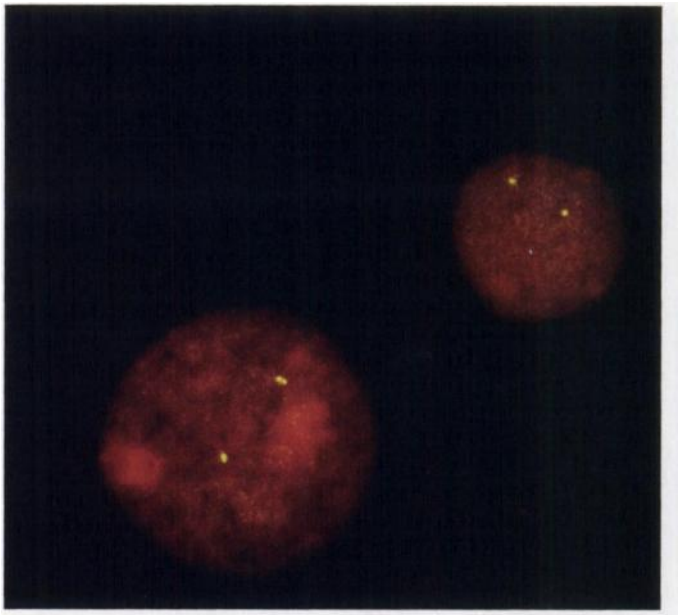

Fig. 1. Two lymphocyte interphases from a healthy control. Each interphase has two copies of the 3p21.3 signal.

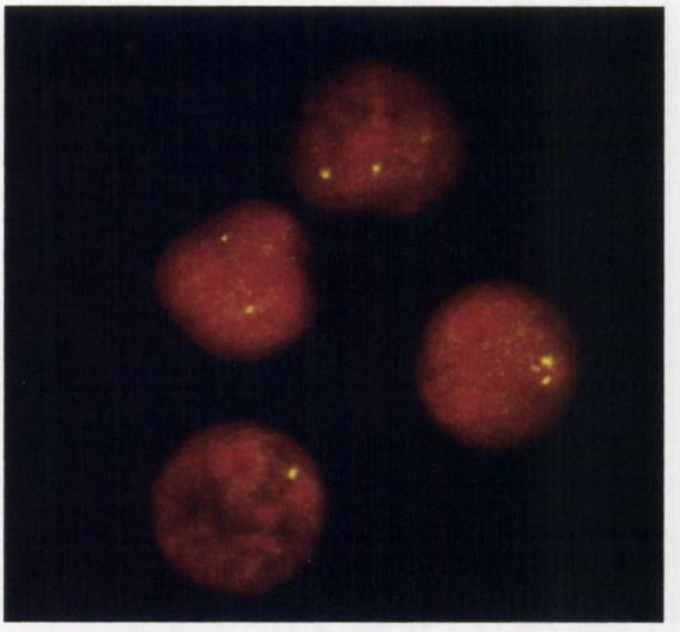

Fig. 2. Four lymphocyte interphases from a lung cancer patient. The top three interphases each have two copies of the 3p21 signal, and the interphase at the bottom has one copy.

Table 1 *Distribution of selected characteristics of lung cancer cases and controls*

Characteristic	Cases[a]	Controls[a]	*P*
Ethnicity			
Non-Hispanic white	33 (82.50)	43 (79.63)	
Mexican-American	2 (5.00)	6 (11.11)	
African-American	5 (12.50)	5 (9.26)	0.53
Sex			
Male	17 (42.50)	28 (51.85)	
Female	23 (57.50)	26 (48.15)	0.37
Mean age, yr (SD)	62.70 (9.44)	60.48 (9.64)	0.27
Smoking status			
Never	1 (2.50)	3 (5.88)	
Former	20 (50.00)	22 (43.14)	
Current	19 (47.50)	26 (50.98)	0.65
Number of cigarettes/day (SD)	26.79 (16.63)	23.44 (13.97)	0.37
Years smoked (SD)	33.82 (14.83)	33.03 (15.33)	0.83
Pack-years smoked (SD)	50.33 (37.15)	43.38 (34.47)	0.43

[a] Values are no. (%), unless otherwise noted.

Downloaded from cancerres.aacrjournals.org on March 7, 2021. © 1998 American Association for Cancer Research.

Table 2 *Association of 3p21.3 BPDE sensitivity with lung cancer risk*

3p21.3 BPDE sensitivity	No. (%)		OR (95% CI)	
	Cases	Controls	Univariate	Adjusted[a]
Nonsensitive	3 (7.50)	26 (48.15)	1	1
Sensitive[b]	37 (92.50)	28 (51.85)	11.45 (3.32, 38.90)	14.10 (3.54, 56.19)
Dose response[c]				
0–19	3 (7.50)	26 (48.15)	1	1
20–28	11 (27.50)	14 (25.93)	6.81 (1.63, 28.52)	7.68 (1.65, 35.82)
≥29	26 (65.00)	14 (25.93)	16.10 (4.13, 62.73)	20.83 (4.79, 90.62)

[a] Adjusted for age (as a continuous variable), sex, ethnicity, and smoking status.
[b] Dichotomized at the median value of sensitivity (20 aberrations per 1000) in the controls.
[c] The number of aberrations was expressed per 1000 interphases. Twenty and 29 aberrations are the median and 75th percentile values, respectively, of sensitivity in the controls.

for 9 cases and from 2 per 1000 to 19 per 1000 (mean: 11.9 ± 4.6 per 1000) for 11 controls ($P > 0.05$). The two lymphocyte interphases from a healthy control (Fig. 1) have two copies of the 3p21.3 signal. Four lymphocyte interphases from a lung cancer patient are shown in Fig. 2. There is only one copy of the 3p21.3 signal in the interphase, at the bottom. Normally, each cell should have two copies of the 3p21.3 signal. A cell's having only one copy of the signal suggests deletion, and three or more copies of the signal suggest breaks, translocations, or other aberrations. Using the median value in the controls (20 per 1000) as a cutoff point to classify 3p21.3 BPDE-induced sensitivity, 37 of the 40 cases (92.5%) but only 28 of the 54 controls (51.9%) were sensitive to BPDE (Table 2), resulting in an OR of 11.5 (95% CI: 3.3, 38.9) for lung cancer. After adjustment for age, sex, ethnicity, and smoking status, the OR for BPDE sensitivity at 3p21.3 was 14.1 (95% CI: 3.5, 56.2).

When we categorized the subjects by the median value and 75th percentile distribution of 3p21.3 aberrations in the controls, there was a significant gradient of increasing risk of lung cancer with increasing number of 3p21.3 aberrations (Table 2). We also assessed the relationship between the 3p21.3 aberration profile and age, sex, ethnicity, smoking status, and pack-years smoked. There were no significant associations (data not shown).

Discussion

Benzo[*a*]pyrene has been reported to be one of the most potent *in vivo* and *in vitro* carcinogenic compounds in tobacco smoke. Previously, we have demonstrated that bleomycin sensitivity is an excellent cancer risk predictor (12–14). Our data further suggest that sensitivity to BPDE may be a more relevant and more important lung cancer susceptibility marker than is bleomycin sensitivity (4). BPDE sensitivity was associated with a significantly elevated risk for lung cancer, with an OR (95% CI) of 7.26 (3.00, 17.58; Ref. 4). The ORs were even higher for lighter smokers and younger patients, supporting our hypothesis that mutagen sensitivity is associated with lung cancer susceptibility. However, there is still little information on the molecular targets of the carcinogens in tobacco smoke.

Deletion of 3p may be a particularly useful genetic marker, because several studies have reported that it occurs in the early stages of lung carcinogenesis, such as bronchial dysplasia (15). Furthermore, it is the most frequently reported chromosomal aberration in lung cancer (6–10). However, because the deletions in lung cancer are large, the putative lung tumor suppressor gene or genes at 3p have not been definitely identified. Candidate loci have been identified, including the *von Hippel-Lindau* gene, located at 3p25, which was subsequently found to be rarely mutated in lung cancer cell lines. 3p21 is another site of recurrent homozygous deletions in small cell lung carcinoma. Transfer of DNA fragments from 3p21.3–3p21.2 into tumor cell lines suggested that the region has tumor suppressor activity (16, 17). Deletions in 3p12–3p14 have also been reported in lung tumors (9). Tumors associated with carcinogenic exposure may be especially susceptible to breakage at 3p (9, 10, 18–20). Very recently, Sozzi *et al.* (10) reported that loss of heterozygosity affecting at least one locus of the *FHIT* gene at 3p was observed in 41 of 51 tumors in smokers (80%) but in only 9 of 40 tumors in nonsmokers (22%). The difference between the frequency of losses in *FHIT* in smokers and nonsmokers was statistically significant, whereas no difference in loss of heterozygosity was observed at *D10S197*, a control locus. Notably, an accurate history of smoking exposure in six of eight nonsmoking patients with *FHIT* abnormalities revealed a significant exposure to passive smoke, either at home or at work. Therefore, 3p may be the molecular target of tobacco smoke. Our data support this notion: we found more BPDE-induced chromosome 3p21.3 aberrations in cases than we did in controls. No difference in BPDE-induced chromosome aberrations was observed at 6q27, which further supports the hypothesis that 3p is a specific target of BPDE. Furthermore, there was a dose-response relationship between the degree of BPDE sensitivity at 3p21.3 and lung cancer risk. 3p may, therefore, harbor a gene for susceptibility to tobacco exposure. However, there are some limitations in this study, including the small sample size, which prevented us from performing histology-specific and stage-specific analyses. Nevertheless, the findings are provocative and warrant more definitive studies.

Acknowledgments

We thank Dr. Walter N. Hittelman for his invaluable suggestions and Dr. Maureen Goode for editorial assistance.

References

1. Davila, D. G., and Williams, D. E. The etiology of lung cancer. Mayo Clin. Proc., *68:* 170–182, 1993.
2. Sellers, T. A., Potter, J. D., Bailey-Wilson, J. E., Rich, S. S., Rothschild, H., and Elsta, R. C. Lung cancer detection and prevention: evidence for an interaction between smoking and genetic predisposition. Cancer Res., *52:* 2696–2697, 1992.
3. Phillips, D. H. Fifty years of benzo(*a*)pyrene. Nature (Lond.), *303:* 468–472, 1983.
4. Wu, X., Gu, J., Hsu, T. C., Hong, W. K., Shi, H., and Spitz, M. R. Differential sensitivity to benzo[*a*]pyrene-diol-epoxide (BPDE) as a marker of lung cancer susceptibility. Proc. Am. Assoc. Cancer Res., *38:* 618, 1997.
5. Wu, X. F., Hsu, T. C., Annegers, J. F., Amos, C. I., Fueger, J. J., and Spitz, M. R. A case-control study of nonrandom distribution of bleomycin-induced chromatid breaks in lymphocytes of lung cancer patients. Cancer Res., *55:* 557–561, 1995.
6. Whang-Peng, J., Kao, S. C., Lee, E. C., Bunn, P. A., Carney, D. N., Gazdar, A. F., and Minna, J. D. A specific chromosome defect associated with human small cell lung cancer. Science (Washington DC), *215:* 181–185, 1982.
7. Kok, K., Hosfra, R., Pilz, A., van den Berg, A., Terpstra, P., Buys, C. H., and Carrit, B. A gene in the chromosomal region 3p21 with greatly reduced expression in lung cancer is similar to the gene for ubiquitin activating enzyme. Proc. Natl. Acad. Sci. USA, *90:* 6071–6075, 1993.
8. Roche, J., Boldog, F., Robinson, M., Robinson, L., Varella-Garcia, M., Swanton, M., Waggoner, B., Fishel, R., Franklin, W., Gemmill, R., and Drabkin, H. Distinct 3p21.3 deletions in lung cancer and identification of a new human semaphorin. Oncogene, *12:* 1289–1297, 1996.
9. Sozzi, G., Veronese, M. L., Negrini, M., Baffa, R., Cotticelli, M. G., Inoue, H., Tornielli, S., Pilotti, S., Gregorio, L. D., Pastorino, U., Pierotti, M. A., Ohta, M., Huebner, K., and Croce, C. M. The *FHIT* gene at 3p14.2 is abnormal in lung cancer. Cell, *85:* 17–26, 1996.
10. Sozzi, G., Sard, L., De Gregorio, L., Marchetti, A., Musso, K., Buttitta, F., Tornielli, S., Pellegrini, S., Veronese, M. L., Manenti, G., Incarbone, M., Chella, A., Angeletti, C. A., Pastorino, U., Huebner, K., Bevilaqua, G., Pilotti, S., Croce, C. M., and Pierotti,

Downloaded from cancerres.aacrjournals.org on March 7, 2021. © 1998 American Association for Cancer Research.

M. A. Association between cigarette smoking and FHIT gene alterations in lung cancer. Cancer Res., *57:* 2121–2123, 1997.
11. Hudmon, K. S., Honn, S. E., Jiang, H., Chamberlain, R. M., Xiang, W., Ferry, G., Gosbee, W., and Spitz, M. R. Identifying and recruiting healthy control subjects from a managed care organization: a methodology for molecular epidemiological case-control studies of cancer. Cancer Epidemiol. Biomarkers Prev., *6:* 565–572, 1997.
12. Wu, X., Delclos, G. L., Annegers, J. F., Bondy, M. L., Honn, S. E., Henry, B., Hsu, T. C., and Spitz, M. R. A case-control study of wood dust exposure, mutagen sensitivity, and lung cancer risk. Cancer Epidemiol. Biomarkers Prev., *4:* 583–588, 1995.
13. Spitz, M. R., Hoque, A., Trizna, Z., Schantz, S. P., Amos, C. I., King, T. M., Bondy, M. L., Hong, W. K., and Hsu, T. C. Mutagen sensitivity as a risk factor for second malignant tumors following upper aerodigestive tract malignancies. J. Natl. Cancer Inst. (Bethesda), *86:* 1681–1684, 1994.
14. Spitz, M. R., Fueger, J. J., Beddingfield, N. A., Annegers, J. F., Hsu, T. C., Newell, G. R., and Schantz, S. P. Chromosome sensitivity to bleomycin-induced mutagenesis, an independent risk factor for upper aerodigestive tract cancers. Cancer Res., *49:* 4626–4628, 1989.
15. Hung, J., Kishimoto, Y., Sugio, K., Virmani, A., McIntire, D. D., Minna, J. D., and Gazdar, A. F. Allele-specific chromosome 3p deletions occur at an early stage in the pathogenesis of lung carcinoma. J. Am. Med. Assoc., *273:* 558–563, 1995.
16. Daly, M. C., Xiang, R. H., Buchhagen, D., Hensel, C. H., Garcia, D. K., Killary, A. M., Minna, J. D., and Naylor, S. L. A homozygous deletion on chromosome 3 in a small cell lung cancer cell line correlates with a region of tumor suppressor activity. Oncogene, *8:* 1721–1729, 1993.
17. Killary, A. M., Wolf, M. E., Giambemardi, T. A., and Naylor, S. L. Definition of a tumor suppressor locus within human chromosome 3p21–p22. Proc. Natl. Acad. Sci. USA, *89:* 10877–10881, 1992.
18. Ohta, M., Inoue, H., Cotticelli, M. G., Kastury, K., Baffa, R., Palazzo, J., Siprashvili, Z., Mori, M., McCue, P., Druck, T., Croce, C. M., and Huebner, K. The *FHIT* gene, spanning the chromosome 3p14.2 fragile site and renal carcinoma-associated t(3;8) breakpoint, is abnormal in digestive tract cancers. Cell, *84:* 587–597, 1996.
19. Virgilio, L., Shuster, M., Gollin, S. M., Veronese, M. L., Ohta, M., Huebner, K., and Croce, C. M. *FHIT* gene alterations in head and neck squamous cell carcinoma. Proc. Natl. Acad. Sci. USA, *93:* 9770–9775, 1996.
20. Akihiko, G., Hagiwara, K., Ke, Y., Burke, L. M., Khan, M. A., Nagashima, M., Bennett, W. P., and Harris, C. C. FHIT mutations in human primary gastric cancer. Cancer Res., *57:* 1435–1437, 1997.

Downloaded from cancerres.aacrjournals.org on March 7, 2021. © 1998 American Association for Cancer Research.

AACR American Association for Cancer Research

Cancer Research

The Journal of Cancer Research (1916–1930) | The American Journal of Cancer (1931–1940)

Benzo[*a*]pyrene Diol Epoxide-induced 3p21.3 Aberrations and Genetic Predisposition to Lung Cancer

Xifeng Wu, Ying Zhao, Susan E. Honn, et al.

Cancer Res 1998;58:1605-1608.

Updated version	Access the most recent version of this article at: http://cancerres.aacrjournals.org/content/58/8/1605

E-mail alerts	Sign up to receive free email-alerts related to this article or journal.
Reprints and Subscriptions	To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.
Permissions	To request permission to re-use all or part of this article, use this link http://cancerres.aacrjournals.org/content/58/8/1605. Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.

Downloaded from cancerres.aacrjournals.org on March 7, 2021. © 1998 American Association for Cancer Research.