Polymorphisms in Nucleotide Excision Repair Genes, Polycyclic Aromatic Hydrocarbon-DNA Adducts, and Breast Cancer Risk

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Abstract

Genes involved in the nucleotide excision repair (NER) pathway, which removes bulky DNA adducts, are potential low-penetrance cancer susceptibility genes. We recently reported an association between detectable polycyclic aromatic hydrocarbon (PAH)-DNA adducts and breast cancer risk. Using a population-based breast cancer case-control study on Long Island, New York, we examined whether polymorphisms in NER genes modified the association between PAH-DNA adducts and breast cancer risk. We examined polymorphisms in *ERCC1* (3′-untranslated region 8092C/A), *XPA* (5′-untranslated region −4G/A), *XPD* (Asp^{312}Asn in exon 10), *XPF* (Arg^{415}Gln in exon 8), and *XPG* (Asp^{1104}His in exon 15) in 1,053 breast cancer cases and 1,102 population-based controls. The presence of at least one variant allele in *XPD* was associated with a 25% increase in the odds ratio [OR, 1.25; 95% confidence interval (95% CI), 1.04-1.50] for breast cancer. The increase associated with homozygosity of the variant alleles for *XPD* and *ERCC1* was stronger among those with detectable PAH-DNA adduct levels (OR, 1.83; 95% CI, 1.22-2.76 and OR, 1.92; 95% CI, 1.14-3.25 for detectable versus nondetectable adducts and homozygous wild-type genotype for *XPD* and *ERCC1*, respectively). We found no association between *XPA*, *XPF*, and *XPG* genotypes, PAH-DNA adducts, and breast cancer risk. When we combined genotypes for these NER pathway genes, there was a significant trend for increasing breast cancer risk with increasing number of putative high-risk alleles. Overall, this study suggests that the risk of breast cancer may be elevated among women with polymorphisms in NER pathway genes and detectable PAH-DNA adducts. (Cancer Epidemiol Biomarkers Prev 2007;16(10):2033–41)

Introduction

DNA is regularly damaged by both endogenous and exogenous mutagens. Because reduced DNA repair capacity may lead to genetic instability and carcinogenesis, genes involved in DNA repair have been proposed as candidate cancer susceptibility genes (1, 2). Suboptimal DNA repair has been associated with up to a 5-fold increased risk of breast cancer (3, 4).

The nucleotide excision repair (NER) pathway repairs a wide variety of DNA damage, including lesions from UV-induced photoproducts, cross-links, oxidative damage, and bulky chemical adducts, such as polycyclic aromatic hydrocarbon (PAH)-DNA adducts (5, 6). The first step involves damage recognition by a complex of bound proteins, including XPA (xeroderma pigmentosum group A). The next steps involve unwinding of the DNA by a complex including XPD and removal of the damaged single-stranded nucleotide fragment by molecules including ERCC1 (excision repair cross-complementing group 1), XPF, and XPG. The final step is DNA synthesis with polymerases.

Individuals with inherited defects in the NER pathway have xeroderma pigmentosum, a rare autosomal recessive disease characterized by an extreme sensitivity to sunlight and a >1,000-fold increased risk of skin cancer (7). Recent reports suggest that less dramatic reductions in DNA repair capacity occur at polymorphic frequencies in the general population and may be associated with increased susceptibility to breast, lung, and skin cancer (8). Common polymorphisms in DNA repair genes may alter an individual's DNA repair capacity and modify the effect of environmental exposures on cancer risk.

PAHs are ubiquitous in the environment and may be derived from exposure to combustion products of fossil fuels, cigarette smoking, and dietary intake of grilled and smoked foods (9). PAHs are potent mammary carcinogens in experimental animals (10). *In vitro* studies (11-13)

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show that PAHs are metabolized in human breast epithelial tissue to form PAH-DNA adducts. Previous epidemiologic studies (14, 15) noted that increased levels of aromatic DNA adducts in breast tissue were associated with breast cancer risk. Methods for measuring DNA adducts in humans have become more reliable in recent years, allowing detection of even background adduct levels in environmentally exposed individuals (16). PAH-DNA adduct levels reflect both exposure to PAH and possibly modulation of exposure by genetic factors, which affect carcinogen metabolism and DNA repair (15, 17-19).

The Long Island Breast Cancer Study Project (LIBCSP) was undertaken specifically to investigate environmental factors, including the role of PAH-DNA adducts in breast cancer, and reported an overall association of 1.32 [95% confidence interval (95% CI), 1.00-1.74] for detectable versus nondetectable adducts (20), a finding that was validated when we analyzed all samples available in the LIBCSP (21). However, the association between adduct levels and breast cancer risk did not vary when stratified by two of the main sources of PAHs among nonoccupationally exposed populations (i.e., cigarette smoking and consumption of grilled and smoked foods; ref. 21). Among controls, we did observe a modest increase in PAH-DNA adducts in current and former cigarette smokers [odds ratio (OR), 1.50; 95% CI, 1.00-2.24; OR, 1.46; 95% CI, 1.05-2.02, respectively; ref. 22]. These findings suggest that the metabolic response of the body to this carcinogenic exposure, rather than exposure level, may be more relevant in breast carcinogenesis.

Gene-environment interactions may contribute to interindividual differences in susceptibility to environmental carcinogens and cancer risk. We investigated the potential role of polymorphisms in NER pathway genes and PAH-DNA adduct levels in the development of breast cancer. We previously reported that a polymorphism within the *XPD* gene (Lys-to-Gln substitution at codon 751 in exon 23) modified the associations between PAH-DNA adducts and cigarette smoking and breast cancer risk (23). In this article, we go on to evaluate five other polymorphisms in the NER pathway to determine whether the combined effect of multiple genotypes in the same DNA repair pathway would modify the association between PAH-DNA adducts and breast cancer risk. The five single nucleotide polymorphisms (SNP) included *ERCC1* (3′-untranslated region 8092C/A, rs3212986), *XPA* (5′-untranslated region −4A/G at position −4 from the ATG start codon, rs1800975), *XPD* (Asp-to-Asn substitution in codon 312 of exon 10, rs1799793), *XPF* (Arg-to-Gln substitution in codon 415 of exon 8, rs1800067), and *XPG* (Asp-to-His substitution in codon 1104 of exon 15, rs17655). Evidence from recent reports suggests that these genetic polymorphisms alter DNA repair capacity and contribute to cancer susceptibility (24-34). We hypothesized that those with suboptimal DNA repair, as characterized by genotype, would have a greater breast cancer risk due to increased PAH-DNA adduct levels.

Materials and Methods

Study Population. Subjects of the LIBCSP are from a population-based case-control study conducted on Long Island, New York (35). Breast cancer cases were composed of women ages >20 years who were residents of Nassau and Suffolk counties, spoke English, and were newly diagnosed with *in situ* or invasive breast cancer between August 1, 1996 and July 31, 1997. For full details of case ascertainment, see the description of the parent study (35). Population-based controls were identified by random digit dialing for those ages <65 years and rosters from the Health Care Financing Administration (now called the Center for Medicare and Medicaid Services) for those ages ≥65 years. Controls were frequency matched to the expected age distribution of case women by 5-year age groups. In-person interviews were completed for 82.1% of cases (n = 1,508) and 62.8% of controls (n = 1,556). Of those who completed an interview, 73.1% of cases and 73.3% of controls donated a blood sample. Of those who donated a blood sample, we were unable to genotype 4.4% of cases and 3.4% of controls mainly due to lack of sufficient DNA to complete the assay. Thus, our final sample size was 1,053 cases and 1,102 controls.

Genotyping Assays. As described previously (20), genomic DNA was extracted from mononuclear cells in whole blood separated by Ficoll (Sigma Chemical Co.) and washed twice with PBS. Pelleted cells were frozen at −80°C until DNA isolation by standard phenol and chloroform isoamyl alcohol extraction and RNase treatment were done. Master DNA 96-well plates containing 10 ng/μL were used to make replica plates. Several high-throughput genotyping methods are available, and over the course of this study, the methods used in the laboratory changed. The FP method (used for *ERCC1*) has the advantage of not requiring specialty probes, whereas the Taqman assay (used for *XPA* and *XPD*) is a more robust genotyping method with well-established, commercially available assays. The Sequenom method (used for *XPF* and *XPG*) was switched to for its ability to multiplex.

For *ERCC1*, template-directed primer extension with detection of incorporated nucleotides by fluorescence polarization was used as described (36). For PCR amplification, the primers (forward, 5′-TAGTTCCT-CAGTTTCCCG-3′; reverse, 5′-TGAGCCAATTCAGC-CACT-3′) gave a 255-bp product. Conditions for amplification were 25 ng DNA, 0.2 μL (8 pmol/μL) forward and reverse primers, 0.2 μL of 25 mmol/L $MgCl_2$, 1 μL of 10× PCR buffer, 0.05 μL (5 units/mL) HotStar Taq polymerase (Roche Molecular Biochemicals), 0.25 μL (10 mmol/L) deoxynucleotide triphosphates (Roche Molecular Biochemicals), and 5.6 μL water. Denaturation at 95°C for 15 min was followed by 30 cycles of 95°C for 30 s, 56°C for 45 s, and 72°C for 1 min followed by 4 min at 72°C. Primers and deoxynucleotide triphosphates were digested with 1 unit of shrimp alkaline phosphatase (1 unit/μL; Roche Molecular Biochemicals) after the addition of 1 μL of 10× buffer and 1 unit *Escherichia coli* exonuclease I (10 units/μL; U.S. Biochemical) and 7.9 μL water for 45 min at 37°C followed by heating at 94°C for 15 min. The reverse extension primer was 5′-CTACACAGGCTG-CTGCTGCTGCT-3′. Acycloprime FP SNP Detection kit G/T contained the dideoxynucleotide triphosphates labeled either with R110 or TAMRA (Perkin-Elmer Life Sciences). To 7 μL of reaction mixture were added 0.05 μL acycloprimer enzyme, 1 μL G/T Terminator mix, 2 μL of 10× reaction buffer, 0.5 μL extension primer

(10 pmol/μL), and 9.45 μL water. Extension was carried out by heating at 95°C for 2 min followed by 20 cycles of 95°C for 15 s and 55°C for 30 s. Plates were read on a Perkin-Elmer Victor instrument.

For *XPA* and *XPD*, genotyping assays were developed using the fluorogenic 5′-nuclease or Taqman assay (37). The Taqman assays were done using a Taqman PCR Core Reagent kit (Applied Biosystems) according to the manufacturer's instructions. The fluorogenic oligonucleotide reverse probes used to detect each of the alleles were 5′-AAGCCCCGTCGGCCGCCGCCATCTC[C/T]GGCCCACTCCGAGGACCTAGCTCCC-3′ and 5′-CGGGGCTCACCCTGCAGCACTTCGT[C/T]GGCCCACTCCGAGGACCTAGCTCCC-3′ for *XPA* and *XPD*, respectively. PCR amplification using 15 ng of genomic DNA was done in a thermal cycler (ABI 7500, Applied Biosystems) with an initial step of 95°C for 10 min followed by 40 cycles of 95°C for 25 s and 65°C for 1 min. The fluorescence profile of each well was measured in an ABI 7500HT Sequence Detection System and the results were analyzed with Sequence Detection Software (Applied Biosystems).

For *XPF* and *XPG*, genotyping was done by BioServe Biotechnologies using high-throughput matrix-assisted laser desorption/ionization time-of-flight mass spectrometry of Sequenom, as described previously (38), using primers (5′-GGAAACTAGGAGGACAAGTGAG-3′ and 5′-GACTTCTTCAGCTTTGCTATCC-3′ for *XPF* and 5′-CAGCTGTTCTCCTTTGTACATTC-3′ and 5′-AAACCCAGAAGAGAGGCATAAC-3′ for *XPG*).

Controls for genotype at each locus and two no DNA controls were included on each plate. Any samples that were outside the variables defined by the controls were identified as noninformative and were retested. In addition, 10% of samples were distributed throughout the DNA samples for quality control purposes. Laboratory personnel were blinded to case/control status. Concordance based on the κ statistic was >90% for all five SNPs.

Exposure Data. Exposure information comes from two sources: the parent study questionnaire that was administered by trained interviewers in the subject's home and laboratory analyses using blood samples to measure PAH-DNA adducts (20). As part of the structured questionnaire (http://epi.grants.cancer.gov/LIBCSP/projects/Questionnaire.html), respondents were asked about their pregnancy, occupational, and residential history; their use of pesticides in their home or on a farm; electrical appliance use; lifetime history of consumption of smoked or grilled foods; medical history; family history of cancer; body size changes by decade; recreational physical activities; cigarette smoking; alcohol use; menstrual history; use of exogenous hormones; and demographic characteristics (35).

We limited our assessment of interactions to an exposure marker of bulky adduct formation, a direct measure of PAH-DNA adducts, and to cigarette smoking. The PAH-DNA analyses were conducted on the subset of participants who donated sufficient blood samples (≥25 mL; ref. 21), which included 873 (79.2%) breast cancer cases and 941 (82.5%) controls. PAH-DNA adduct levels were assessed using a competitive ELISA with a polyclonal antiserum generated against benzo(*a*)pyrene diol epoxide–modified DNA, but which recognized the diol epoxide adducts of several other PAHs as described previously (18). We analyzed the data on PAH-DNA adducts first by assessing differences between those with detectable versus nondetectable adducts. Among those with detectable adducts, we categorized subjects into categories based on the median value among controls and by quartiles (23). The PAH-DNA adduct assays were conducted as two separate batches; therefore, the cutoff values for the two rounds differed. In addition to never/former/current cigarette smoking status, we examined interactions with duration of cigarette smoking (<10 years, 11-20 years, and >20 years) as well as with passive and active cigarette smoking (39).

Statistical Methods. We first compared differences between genotypes in each exposure category using the χ^2 test for categorical variables (40). Tests for Hardy-Weinberg equilibrium were conducted using observed genotype frequencies and a χ^2 test with 1 degree of freedom (41). Unconditional logistic regression was used to estimate ORs and 95% CI adjusting for potential confounding variables (40). All models were adjusted for age at reference (defined as age at diagnosis for cases and age at identification for controls). We examined potential confounding by the following factors: race, first-degree family history of breast cancer, history of benign breast disease, age at menarche, age at first pregnancy, parity, fertility problems, menopausal status, oral contraceptives, hormone replacement therapy, body mass index, lifetime alcohol intake, and active smoking status. Confounders were included in the final model if their inclusion changed the exposure estimate by >10% (40). None of these covariates confounded the estimates on exposure by >10%.

We evaluated for potential interaction (both additive and multiplicative) by using indicator terms for those with the genotype only, exposure only, and both the genotype and exposure of interest (42). To evaluate interaction on a multiplicative scale, the likelihood ratio test comparing a model with and without the interaction terms was used (43). If the relative risk, as approximated by the OR, for both genotype and exposure was greater than the relative risk of either factor alone added together minus 1, we concluded that there was a positive additive interaction.

For the haplotype analysis of *XPD* genetic polymorphisms ($Lys^{751}Gln$ and $Asp^{312}Asn$), breast cancer risk was analyzed by calculation of adjusted ORs for specific combinations. For the analysis of gene*gene interactions in the NER pathway, adjusted ORs were calculated based on the number of ''high-risk'' alleles. By collapsing together the variant alleles across NER pathway-related genes, we may have inadvertently combined possible high-risk and ''protective'' alleles. First, we calculated individual age-adjusted ORs for breast cancer risk based on number of high-risk alleles. Then, we generated low-, intermediate-, and high-risk categories with cutpoints determined by similar ORs of breast cancer risk.

All analyses were conducted using Statistical Analysis System version 9.1.

[7] http://epi.grants.cancer.gov/LIBCSP/projects/Questionnaire.html

Results

Genotype frequencies for genetic polymorphisms in *ERCC1, XPA, XPD* ($Asp^{312}Asn$), *XPF*, and *XPG* are reported in Table 1. The genotypes are in Hardy-Weinberg equilibrium [χ^2 = 0.75, 0.75, 0.68, 0.83, and 0.87 with 1 degree of freedom for *ERCC1, XPA, XPD* ($Asp^{312}Asn$), *XPF*, and *XPG*, respectively]. Frequencies of the variant allele for *ERCC1* were 27.3% and 25.4% in breast cancer cases and controls, respectively. Variant allele frequencies for *XPA, XPD* ($Asp^{312}Asn$), *XPF*, and *XPG* were 31.9% and 34.1%, 36.6% and 33.8%, 8.0% and 8.8%, and 25.2% and 26.2% among cases and controls, respectively. The presence of at least one variant *XPD* $Asp^{312}Asn$ allele was associated with a 25% increase in risk of breast cancer (OR, 1.25; 95% CI, 1.04-1.50) after adjusting for age. The presence of two variant *XPF* $Arg^{415}Gln$ alleles was associated with reduced breast cancer risk (OR, 0.27; 95% CI, 0.07-1.00); however, the number of subjects with this genotype was small. Because of the low prevalence of the homozygous variant genotype for *XPF*, the risk associated with having at least one variant allele (*GA* and *AA* combined) was computed in reference to having the homozygous wild-type *GG* genotype.

Age-adjusted estimates stratified by PAH-DNA adduct levels are presented in Table 2. The increase in breast cancer risk for homozygosity of the *XPD* $Asp^{312}Asn$ variant allele was more pronounced among those with detectable PAH-DNA adduct levels (OR, 1.83; 95% CI, 1.22-2.76 for detectable versus nondetectable PAH-DNA adduct levels and homozygous wild-type genotype; multiplicative *P* for interaction = 0.02). The OR for the homozygous variant genotype was higher among those with detectable PAH-DNA adduct levels above the median (OR, 2.19; 95% CI, 1.32-3.61) than the estimate for those with adducts below the median (OR, 1.50; 95% CI, 0.89-2.53; multiplicative *P* for interaction = 0.01). For those with detectable PAH-DNA adduct levels above the median, we observed a dose-response relationship with the presence of the variant $Asp^{312}Asn$ allele (OR, 1.22; 95% CI, 0.84-1.75 for Asp/Asp; OR, 1.60; 95% CI, 1.10-2.31 for Asp/Asn; OR, 2.19; 95% CI, 1.32-3.61 for Asn/Asn; *P* for trend = 0.01). We further examined whether the association increased with increasing quartiles of PAH-DNA adduct levels. The association between *XPD* $Asp^{312}Asn$ genotype and breast cancer risk was more pronounced among those in the highest quartile of PAH-DNA adduct levels: OR, 2.07 (95% CI, 1.33-3.24) for those with Asp/Asn genotype and OR, 2.59 (95% CI, 1.31-5.11) for those with the Asn/Asn genotype (*P* for trend = 0.01; data not shown).

The OR for the association between breast cancer and the homozygous *ERCC1* variant genotype (AA) was increased among those with detectable PAH-DNA adducts (OR, 1.92; 95% CI, 1.14-3.25; *P* for interaction = 0.43). The effect of the genotype was more pronounced among those with detectable PAH-DNA adducts below the median (OR, 2.21; 95% CI, 1.12-4.38) than among those with adducts above the median (OR, 1.63; 95% CI, 0.79-3.36), and the multiplicative interaction term was not statistically significant (*P* = 0.58).

We also assessed whether there were additive interactions between genotype and PAH-DNA adduct levels by creating indicator variables and using a common reference group. The joint effect of both Asn/Asn genotype for *XPD* and detectable adducts was 1.8 (OR, 1.83; 95% CI, 1.22-2.76) versus those with nondetectable adducts and the Asp/Asp genotype. The separate effects of Asn/Asn genotype and detectable adducts relative to a common reference group of Asp/Asp genotype and nondetectable adducts were 0.7 (OR, 0.71; 95% CI, 0.39-1.29) and 1.5 (OR, 1.45; 95% CI, 1.05-2.00), respectively. Thus, the joint additive effect was 1.8 versus the effects of either alone minus 1 (0.7 + 1.5 − 1 = 1.2). Similarly, the joint effect of both AA genotype for *ERCC1* and detectable PAH-DNA adducts relative to those with nondetectable adducts and the wild-type CC genotype was 1.9 (OR, 1.92; 95% CI, 1.14-3.25). The separate effects of AA genotype and detectable PAH-DNA adducts versus those with CC genotype and nondetectable adducts were 0.9 (OR, 0.89; 95% CI, 0.43-1.85) and 1.2 (OR, 1.21; 95% CI, 0.91-1.61), respectively. Thus, the joint additive effect was 1.9 versus the effects of either alone minus 1 (0.9 + 1.2 − 1 = 1.1). These models supported the presence of an additive interaction

Table 1. Genotype frequency for polymorphisms in NER pathway genes, Long Island breast cancer study project, 1996-1997

Gene	Genotype	Cases, *N* (%)	Controls, *N* (%)	Odds Ratio* (95% CI)
ERCC1	CC †	551 (52.1)	606 (54.9)	1.00
	CA	434 (41.1)	436 (39.5)	1.09 (0.92-1.30)
	AA	72 (6.8)	62 (5.6)	1.29 (0.90-1.85)
XPA	GG †	488 (46.1)	488 (44.3)	1.00
	GA	466 (44.0)	477 (43.3)	0.97 (0.81-1.17)
	AA	105 (9.9)	137 (12.4)	0.77 (0.58-1.02)
XPD	GG (Asp/Asp) †	415 (40.2)	490 (45.2)	1.00
	GA (Asp/Asn)	478 (46.4)	454 (41.9)	1.25 (1.04-1.50)
	AA (Asn/Asn)	138 (13.4)	139 (12.8)	1.16 (0.89-1.52)
XPF	GG (Arg/Arg) †	859 (84.4)	888 (83.4)	1.00
	GA (Arg/Gln)	156 (15.3)	167 (15.7)	0.99 (0.78-1.26)
	AA (Gln/Gln)	3 (0.3)	10 (0.9)	0.27 (0.07-1.00)
XPG	GG (Asp/Asp) †	562 (56.3)	571 (54.3)	1.00
	GC (Asp/His)	371 (37.1)	409 (38.9)	0.94 (0.78-1.13)
	CC (His/His)	66 (6.6)	71 (6.8)	0.98 (0.69-1.41)

*Adjusted for age.
† Referent group.

between both *XPD* and *ERCC1* genotype and PAH-DNA adducts.

We found no association between variant alleles in *XPA, XPF*, and *XPG* and breast cancer risk when stratified by PAH-DNA adduct levels. Adjusting for genotype in the remaining four NER genetic polymorphisms did not significantly alter the point estimates stratified by PAH-DNA adduct levels. We also

Table 2. Age-adjusted odds ratios (OR) and 95% confidence intervals (CI) for polymorphisms in NER pathway genes stratified by PAH-DNA adducts, Long Island breast cancer study project, 1996-1997

Genotype	PAH-DNA adducts	Cases, *N*	Controls, *N*	Odds Ratio* (95% CI)
ERCC1 8092C/A				
CC †	Non-Detectable	119	151	1.00
CA	Non-Detectable	90	119	0.95 (0.66-1.38)
AA	Non-Detectable	14	20	0.89 (0.43-1.85)
CC	Detectable	340	356	1.21 (0.91-1.61)
CA	Detectable	251	258	1.24 (0.92-1.67)
AA	Detectable	45	30	1.92 (1.14-3.25)
CC	Detectable (<Median)	170	184	1.18 (0.86-1.63)
CA	Detectable (<Median)	129	122	1.35 (0.96-1.91)
AA	Detectable (<Median)	26	15	2.21 (1.12-4.38)
CC	Detectable (≥Median)	170	172	1.24 (0.90-1.72)
CA	Detectable (≥Median)	122	136	1.14 (0.81-1.61)
AA	Detectable (≥Median)	19	15	1.63 (0.79-3.36)
XPA -4G/A				
GG †	Non-Detectable	93	130	1.00
GA	Non-Detectable	114	124	1.32 (0.91-1.91)
AA	Non-Detectable	17	37	0.70 (0.37-1.32)
GG	Detectable	308	278	1.60 (1.17-2.19)
GA	Detectable	262	276	1.36 (0.99-1.87)
AA	Detectable	67	87	1.08 (0.71-1.64)
GG	Detectable (<Median)	145	134	1.58 (1.11-2.26)
GA	Detectable (<Median)	143	137	1.49 (1.04-2.12)
AA	Detectable (<Median)	40	46	1.24 (0.75-2.05)
GG	Detectable (≥Median)	163	144	1.62 (1.14-2.30)
GA	Detectable (≥Median)	119	139	1.23 (0.86-1.77)
AA	Detectable (≥Median)	27	41	0.91 (0.52-1.58)
XPD $Asp^{312}Asn$(G/A)				
GG †	Non-Detectable	84	133	1.00
GA	Non-Detectable	111	109	1.57 (1.07-2.30)
AA	Non-Detectable	20	44	0.71 (0.39-1.29)
GG	Detectable	259	279	1.45 (1.05-2.00)
GA	Detectable	270	276	1.56 (1.13-2.15)
AA	Detectable	92	78	1.83 (1.22-2.76)
GG	Detectable (<Median)	138	125	1.74 (1.21-2.51)
GA	Detectable (<Median)	143	151	1.53 (1.07-2.18)
AA	Detectable (<Median)	39	40	1.50 (0.89-2.53)
GG	Detectable (≥Median)	121	154	1.22 (0.84-1.75)
GA	Detectable (≥Median)	127	125	1.60 (1.10-2.31)
AA	Detectable (≥Median)	53	38	2.19 (1.32-3.61)
XPF $Arg^{415}Gln$(G/A)				
GG †	Non-Detectable	170	237	1.00
GA+AA	Non-Detectable	43	45	1.38 (0.87-2.19)
GG	Detectable	529	520	1.44 (1.14-1.82)
GA+AA	Detectable	87	109	1.13 (0.80-1.60)
GG	Detectable (<Median)	276	261	1.51 (1.16-1.96)
GA+AA	Detectable (<Median)	43	53	1.14 (0.73-1.79)
GG	Detectable (≥Median)	253	259	1.38 (1.06-1.79)
GA+AA	Detectable (≥Median)	44	56	1.12 (0.72-1.75)
XPG $Asp^{1104}His$(G/C)				
GG †	Non-Detectable	123	163	1.00
GC	Non-Detectable	70	97	0.98 (0.66-1.46)
CC	Non-Detectable	14	19	1.04 (0.48-2.23)
GG	Detectable	353	329	1.46 (1.10-1.93)
GC	Detectable	218	255	1.18 (0.88-1.59)
CC	Detectable	41	39	1.48 (0.90-2.44)
GG	Detectable (<Median)	174	173	1.37 (1.00-1.88)
GC	Detectable (<Median)	120	114	1.46 (1.03-2.07)
CC	Detectable (<Median)	22	21	1.44 (0.75-2.75)
GG	Detectable (≥Median)	179	156	1.56 (1.09-2.13)
GC	Detectable (≥Median)	98	141	0.95 (0.67-1.36)
CC	Detectable (≥Median)	19	18	1.52 (0.76-3.04)

*Adjusted for age.
† Referent group.

calculated age-adjusted estimates stratified by smoking exposure. There was no significant association between breast cancer risk and these genetic polymorphisms based on smoking status (never, former, or current smokers), smoking duration, and active versus passive smoking (data not shown). Genotype frequencies for each of the genetic polymorphisms evaluated were unrelated to the level of PAH-DNA adducts in the control group even after adjustment for smoking status (Table 3).

In terms of gene*gene interactions, we first conducted haplotype analysis of two polymorphisms in the *XPD* gene (Asp^{312}Asn and Lys^{751}Gln). We previously reported that the presence of at least one variant allele within the *XPD* gene (Lys^{751}Gln) was associated with a 20% increase in risk of breast cancer (OR, 1.21; 95% CI, 1.01-1.44; ref. 23). We observed an association of the combination of *XPD*-312Asp/Asn and *XPD*-751Lys/Gln genotypes with increased breast cancer risk (OR, 1.33; 95% CI, 1.08-1.64). We also found linkage disequilibrium between the *XPD*-312Asp and *XPD*-751Lys wild-type alleles as well as for the *XPD*-312Asn and *XPD*-751Gln variant alleles.

When we combined genotypes for these NER pathway genes, there was a significant trend for increasing breast cancer risk with an increasing number of putative high-risk alleles. Because the two *XPD* polymorphisms were in linkage disequilibrium, we only included *XPD* (Asp^{312}Asn) in the combined analysis. The *XPG* polymorphism (Asp^{1104}His) was excluded due to equivocal breast cancer risk associated with the wild-type and variant alleles. There were a total of four polymorphisms in four genes included in the combined analysis (Table 4). Low-, intermediate-, and high-risk categories were defined based on similar point estimates of breast cancer risk for each number of putative high-risk alleles. Compared with carriers with three or fewer risk alleles (low risk), those with four to six risk alleles (intermediate risk) had an OR of 1.29 (95% CI, 1.07-1.56) and those with seven or more risk alleles (high risk) had an OR of 1.47 (95% CI, 0.97-2.24; P for trend = 0.02).

Table 3. PAH adduct levels by genotype among controls, Long Island breast cancer study project, 1996-1997

Genotype	Nondetectable PAH levels	Detectable PAH levels	Adjusted OR* (95% CI)
ERCC1			
CC	151	356	1.00
CA	119	258	1.07 (0.80-1.43)
AA	20	30	1.60 (0.88-2.91)
XPA			
GG	130	278	1.00
GA	124	276	0.97 (0.72-1.31)
AA	37	87	0.92 (0.59-1.43)
XPD			
GG	133	279	1.00
GA	109	276	0.82 (0.61-1.11)
AA	44	78	1.19 (0.77-1.82)
XPF			
GG	237	520	1.00
GA+AA	45	109	0.92 (0.63-1.34)
XPG			
GG	163	329	1.00
GC	97	255	0.76 (0.56-1.03)
CC	19	39	0.93 (0.52-1.67)

*Adjusted for age and smoking status.

Table 4. Combined effects of polymorphisms in NER pathway genes on breast cancer risk, Long Island breast cancer study project, 1996-1997

Number of high risk alleles*	Cases	Controls	Odds Ratio † (95% CI)
Low risk (0-3) ‡	268	335	1.00
Intermediate risk (4-6)	742	728	1.29 (1.07-1.56)
High risk (7-8)	57	48	1.47 (0.97-2.24)

*Includes *ERCC1* (variant *A* allele), *XPA* (wild-type *G* allele), *XPD* (variant Asn^{312} allele), and *XPF* (wild-type Arg^{415} allele). The polymorphism for *XPD* (Lys^{751}Gln) was excluded due to strong linkage disequilibrium with *XPD* (Asp^{312}Asn), and *XPG* (Asp^{1104}His) was excluded due to equivocal breast cancer risk associated with the wild-type and variant alleles.
† Adjusted for age.
‡ Referent group.

Discussion

Overall, we found a modest, 25% statistically significant increase in the OR for the association between those subjects with at least one *XPD* Asp^{312}Asn variant allele and breast cancer risk, but the estimate for the homozygous variant genotype was further increased to 83% among the subsample of women with detectable PAH-DNA adduct levels. We recently reported that another polymorphism within the *XPD* gene (Lys^{751}Gln) modified the associations between PAH-DNA adducts, cigarette smoking, and breast cancer risk (23). The *XPD* Asp^{312}Asn and Lys^{751}Gln polymorphisms are in linkage disequilibrium, as supported by our study and pedigree analysis of four families from Utah (44). A group from Germany reported that the *XPD*-312Asp/Asp wild-type genotype was associated with a 2-fold increase in breast cancer risk (45), which is inconsistent with the results we observed in this study. The German study only examined *XPD* genotype in relation to breast cancer risk, whereas we evaluated gene-environment interactions using an exposure marker of bulky adduct formation, PAH-DNA adducts measured in blood. We found that the association between breast cancer risk and *XPD* Asp^{312}Asn genotype was more pronounced among those with increasing PAH-DNA adduct levels. Several studies have supported an association between the *XPD* Asp^{312}Asn variant allele and increased risk for lung cancer (29), upper aerodigestive tract cancers (46), and prostate cancer (31). However, other studies have not supported a higher risk for the Asp^{312}Asn variant allele of the *XPD* gene for lung cancer (44), skin cancer (30), and esophageal cancer (47). These conflicting results may be explained by differences in study size, ethnic background of study participants, and type of controls (i.e., hospital based versus population based).

XPD encodes a DNA helicase, which is involved in NER, basal transcription, cell cycle control, and apoptosis (48-50). The Asp amino acid at codon 312 in exon 10 of the *XPD* gene is located in the seven-motif helicase

domain of the RecQ family of DNA helicases and is evolutionarily conserved. Several studies have examined the functional significance of the *XPD* Asp^{312}Asn polymorphism. One study reported higher levels of PAH-DNA adducts in malignant breast tissue associated with *XPD* Asp^{312}Asn variant allele (15). Another study reported that *XPD* Asp^{312}Asn variant allele was associated with reduced repair of aromatic DNA adducts detected in peripheral lymphocytes and increased lung cancer risk among nonsmokers (51). Other studies showed that the *XPD* Asp^{312}Asn variant allele was associated with a 2.5-fold increased apoptotic response in lymphoblastoid cell lines after UV exposure (52) and a >2.5-fold increased risk of lymphocyte chromosome aberrations *in vivo* using a mutagen sensitivity assay with the tobacco-specific nitrosamine 4-(methylnitrosamino)-I-(3-pyridyl)-1-butanone (53). Thus, higher levels of DNA adducts in individuals carrying the *XPD* Asp^{312}Asn variant allele suggest that they have lower DNA repair capacity. In our findings reported here, we did not observe an association between polymorphisms in these NER pathway genes and PAH-DNA adduct levels among controls, although we did observe a statistically significant interaction between *XPD* genotype, PAH-DNA adducts, and breast cancer risk.

We found a statistically significant increase of 92% in the OR for the association between the homozygous variant genotype (AA) for the *ERCC1* polymorphism (3′-untranslated region 8092C/A) and breast cancer risk but only among those women with detectable PAH-DNA adduct levels. To our knowledge, this is the first study to examine these associations for breast cancer, but other studies have supported an association between *ERCC1* genotype and risk of adult glioma (24) and head and neck cancer (25). This polymorphism located within the 3′-untranslated region of the *ERCC1* gene may affect mRNA stability and alter mRNA levels (24). One study found that reduced *ERCC1* mRNA expression was associated with more than a 2-fold increased risk of squamous cell carcinoma of the head and neck (26).

We did not find an association between polymorphisms in *XPA, XPF*, and *XPG* and breast cancer risk even after stratification for PAH-DNA adduct levels. In the NER pathway, XPA is involved in DNA damage recognition, whereas XPF and XPG contribute to the removal of the damaged single-stranded nucleotide fragment. Other population studies have shown that these *XPA, XPF*, and *XPG* polymorphisms may be associated with increased susceptibility to lung, bladder, and breast cancer (27, 28, 32-34). However, no studies to date have evaluated the functional effect of these genetic variants on DNA repair capacity. It is possible that these SNPs have no effect or only a modest effect on DNA repair capacity or that redundancy in the DNA repair system may compensate for deficiencies in a single pathway.

The LIBCSP was undertaken specifically to investigate environmental factors, including the role of PAH-DNA adducts in breast cancer, and reported an overall association of 1.32 (95% CI, 1.00-1.74) for detectable versus nondetectable adducts (20), a finding that was validated when we analyzed all samples available in the LIBCSP (21). However, the association between adduct levels and breast cancer risk did not vary when stratified by two of the main sources of PAHs among nonoccupationally exposed populations (i.e., cigarette smoking and consumption of grilled and smoked foods; ref. 21). These findings suggest that the metabolic response of the body to this carcinogenic exposure, rather than exposure level, may be more relevant in breast carcinogenesis.

This is the first study to examine the interaction between polymorphisms in multiple genes in the NER pathway and PAH-DNA adducts on breast cancer risk. Most studies that look at individual effects show no association between the SNP and breast cancer risk (54-57). We addressed associations between individual polymorphisms and the combined effect of multiple polymorphisms and found that examining multiple SNPs in combination showed a dose-response relation. When Gu et al. (58) analyzed the combined effects of eight polymorphisms in NER genes on risk of bladder cancer recurrence, they found a significant trend for an increased recurrence risk with an increasing number of putative high-risk alleles. Mechanic et al. (59) recently reported that polymorphisms in NER genes modified the relationship between breast cancer and smoking only among African-American women. In our sample, which consisted predominantly of white women, we found no association between breast cancer risk and NER polymorphisms based on smoking status. However, we are the first group to examine the joint effects of NER SNPs on breast cancer risk in relation to a direct exposure marker, PAH-DNA adducts. We observed a ~2-fold increase in breast cancer risk among those with variant alleles for *XPD* and *ERCC1* and detectable PAH-DNA adduct levels.

Potential sources of bias in our study design include subject selection, recall bias on smoking exposure history, and measurement error on genotype and PAH-DNA adducts. In terms of subject selection, response rates were lower among controls compared with cases, especially among women over the age of 75 years (35). Therefore, these results may not be generalizable to older women. In addition, blood donors differed from those who did not donate blood on several factors (35). However, all models included the frequency matching factor age at reference, and adjustment for other known breast cancer risk factors did not appreciably change the effect estimates, and was therefore not included in our final models. Recall bias may have occurred if exposure information on cigarette use may have been differentially recalled. Overreporting of exposure among cases and underreporting among controls could result in bias away from the null. However, it is unlikely that such differential recall would vary by genotype status and, therefore, is unlikely to explain the patterns we observed. Measurement error is limited in this study because of the high reliability (>90%) in the measurement of genotype. Unlike questionnaire exposure data, measurement of PAH-DNA adduct levels is not subject to recall bias, although laboratory error is possible. However, this measurement error in PAH-DNA adduct levels is unlikely to differ by genotype status and, thus, cannot explain the observed associations between DNA adducts and genotype.

This study combined several end point measurements, including adduct formation and genetic markers of cancer susceptibility. We addressed associations between individual polymorphisms and the combined effects of

multiple polymorphisms in the same DNA repair pathway on breast cancer risk. Analysis of haplotype and gene*gene interactions between multiple genes provides a more comprehensive assessment of the NER pathway. This information may enhance our ability to identify high-risk populations and preventable environmental risk factors for breast cancer.

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Polymorphisms in Nucleotide Excision Repair Genes, Polycyclic Aromatic Hydrocarbon-DNA Adducts, and Breast Cancer Risk

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