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THE ROLE OF XRCC1 POLYMORPHISMS IN BASE EXCISION REPAIR OF ETHENO-DNA ADDUCTS IN FRENCH VINYL CHLORIDE WORKERS

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Abstract
Objectives: The purpose of this study was to examine whether polymorphisms in the XRCC1 DNA-repair protein can affect the base excision repair capacity to remove etheno-DNA adducts induced by vinyl chloride exposure that account for the occurrence of mutant biomarkers of effect seen in exposed workers. **Materials and Methods:** Using polymerase chain reaction-restriction fragment length polymorphism and fluorescence polarization techniques, we examined the effect of three x-ray cross complementing-1 protein polymorphisms, at codons 194, 280 and 399, on the occurrence of mutant biomarkers in ras-p21 and p53 induced by vinyl chloride exposure in a cohort of 211 French vinyl chloride workers to correlate differences in genotype with differences in the presence of these biomarkers. Also, cell cultures of lymphoblast lines from a pair of individuals, one homozygous wild-type and one homozygous variant for the codon 399 polymorphism, were exposed to the reactive intermediate of vinyl chloride, and, using an enzyme-linked immunosorbent assay, levels of etheno-DNA adducts generated and repaired were measured and compared. **Results**: After adjusting for age, smoking, alcohol drinking and cumulative vinyl chloride exposure, compared to workers who were homozygous wild-type for all alleles, the odds ratio for the presence of either biomarker increased to 2.0 (95% CI: 1.0–3.9) for workers with any one variant allele and to 2.4 (95% CI: 1.1–5.2) for workers with more than one variant allele. Data from the cell culture experiments indicating that repair of etheno-DNA adducts is considerably better in wild-type cells compared to polymorphic cells were supportive of the epidemiologic results. **Conclusions:** This study provides further evidence that polymorphisms in XRCC1 can be an important biomarker of susceptibility in populations exposed to agents that produce damage removed by base excision repair.

Key words:
Base excision repair; DNA adducts; Mutations; Gene-environment interaction

INTRODUCTION

Vinyl chloride (VC) is a known animal and human carcinogen associated with the sentinel neoplasm of angiosarcoma of the liver (ASL). VC is used in large quantities around the world primarily in the manufacture of polyvinyl chloride polymers. VC exposure occurs in the workplace environment during this manufacture and in the general environment from releases near plastic industries, hazardous waste sites and landfills [1].

Following exposure, VC is metabolized in the liver to the reactive intermediates chloroethylene oxide (CEO) and chloracetaldehyde (CAA) that can interact with DNA

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and generate pro-mutagenic DNA adducts including etheno-guanosine (εG) and etheno-adenosine (εA) [1]. Although these etheno-DNA adducts are capable of causing several different types of DNA mutations, they are known to be able to produce the particular types of K-*ras* oncogene mutations (G to A transitions) and *TP53* tumor suppressor gene mutations (A to T transversions) found in the ASLs of exposed workers [2,3]. We have previously shown that these mutations lead to the production of mutant oncoprotein biomarkers (mutant *ras*-p21 and mutant p53) that can be identified in the serum of VC-exposed individuals with ASLs as well as VC-exposed individuals without any detectable neoplastic disease in a highly statistically significant dose-response relationship with regard to estimated, cumulative VC exposure [4,5]. However, at any given VC exposure level there were individuals who were negative for both biomarkers, positive for one or the other biomarker, or positive for both biomarkers, suggesting that there might be some genetically determined susceptibility to VC mutagenesis that could account for different mutant biomarker outcomes with similar exposures. Recently, we have found that a polymorphism at codon 399 in the x-ray cross complementing-1 (XRCC1) protein is a potential contributor to this variable susceptibility [6]. This is consistent with the fact that the types of pro-mutagenic DNA adducts generated by VC exposure would be anticipated to be removed by base excision repair (BER), a process in which XRCC1 plays a key role [7]. Additional polymorphisms in XRCC1 at codons 194 and 280 have been identified, which could account for altered BER activity and thus contribute to the variability in mutagenic response in these workers [8]. Thus, the goal of the present study was to determine the contribution of all three of these XRCC1 polymorphisms to this variability.

MATERIALS AND METHODS

Subjects were selected from a previously described population of VC-exposed workers in France [4]. A cohort of 225 of these workers had been previously analyzed for circulating mutant *ras*-p21 and mutant p53 biomarkers in their serum [4,5]. A group of 211 of these workers with available lymphocytes for DNA extraction were selected for study. All of the workers were white males with the following characteristics: average age = 56 years (range = 35–74); average cumulative VC exposure = 5871 ppm-years (range = 6–46 702); 39.3% of current or former smokers; 19.9% of current alcohol drinkers; 62% positive for at least one mutant biomarker (44.5% positive for mutant p53, 36.5% positive for mutant *ras*-p21, 19% positive for both).

DNA was extracted from the workers' lymphocytes by routine techniques. Each DNA sample was analyzed for the presence of the XRCC1 polymorphism at codon 399 by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) techniques, as previously described [9]. Briefly, the PCR conditions consist of 20 ng genomic DNA, PCR buffer (50 mM KCl, 10 mM Tris-HCl, pH 8.3),1.5 mM $MgCl_2$, 200 mM each dNTP, 0.25 U Taq polymerase, and 25 ng each primer (forward 5'-TTGTGCTTTCTCTGTGTCCA-3' and reverse 5'-TCCTCCAGCCTTTTCTGATA-3') in a total volume of 10 μL. Reaction mixtures underwent a 5 min denaturation step at 94°C followed by 32 cycles of 30 sec at 94°C, 30 sec at 61°C and 60 sec at 72°C. Then the PCR products were digested with 2 units of MspI at 37°C for 2 h, resolved on 1.6% agarose gels and stained with ethidium bromide. The bands were visualized under UV light and photographed. By this approach, individuals were classified for the codon 399 polymorphism as homozygous wild-type (Arg/Arg; product bands at 375 bp and 240 bp), heterozygous (Arg/Gln; product bands at 615 bp, 375 bp and 240 bp) or homozygous variant (Gln/Gln; product band at 615 bp).

The fluorescence polarization (FP) method was used for the detection of XRCC1 polymorphisms at codons 194 and 280 [10]. Briefly, each DNA sample was amplified by PCR in a reaction mixture containing 20 ng genomic DNA, PCR buffer, 1.5 mM $MgCl_2$, 200 mM each dNTP, 0.3 unit Taq polymerase and 2 pmol primer pairs (forward 5'-ATGAGAGCGCCAACTCTG-3' and reverse 5'-CTACCCTCCTCCCTCAGACC-3' for codon 194 and forward 5'-CCCCAGTGGTGCTAACCTAAT-3'

and reverse 5'-GGTCCAGTCTGGCCCATACCT-3' for codon 280) in a total volume of 10 μL. The reaction mixture was denatured at 94°C for 4 min and then subjected to 34 cycles of 94°C for 30 sec, 60°C for 30 sec for codon 194 or 61°C for 30 sec for codon 280, and 72°C for 50 sec, followed by a final extension at 72°C for 5 min. Then the PCR products were digested for clearing excess primers and deoxynucleotides with 1 unit of shrimp alkaline phosphatase and 1 unit of *E.coli* exonuclease I in digestion buffer at 37°C for 45 min followed by heating at 95°C for 15 min. In the final step, 5 pmol of the probe for XRCC1 codon 194 polymorphism (forward 5'-CGGGGGCTCTCTTCTTCAGC-3') or for XRCC1 codon 280 polymorphism (reverse 5'-ACTGGGGCTGTGGCTGGGGTA-3') and the mixture from the Acycloprime-FP SNP c/t detection kit (PerkinElmer Life Sciences, Boston, MA) were added to the cleaned PCR products according to the manufacturer's instructions. The mixture underwent a denaturation step at 95°C for 2 min followed by 50–70 cycles of 95°C for 15 sec and 55°C for 30 sec. Plates were read on a VICTOR 2 fluorescence polarization microplate reader (PerkinElmer, Boston, MA). By this approach, individuals were classified as homozygous wild-type (ArgArg), heterozygous (ArgTrp) or homozygous variant (TrpTrp) for the codon 194 polymorphism or homyzygous wild-type (ArgArg), heterozygous (ArgHis) or homozygous variant (HisHis) for the codon 280 polymorphism accordingly to clearly separate visual clustering of the genotypes.

On the basis of this analysis, individuals were grouped together as being wild-type at all alleles, having any one variant allele, or having two variant alleles (no one had more than two variant alleles), and the odds ratios (OR) and 95% confidence intervals (CI) were calculated (unadjusted and adjusted for age, smoking, alcohol drinking and cumulative VC exposure) for the presence of the mutant biomarkers, either alone or in combination.

In order to provide support for the biological plausibility of the molecular epidemiologic studies, *in vitro* studies of the effect of XRCC1 polymorphisms on DNA repair ability have been initiated. Initially, immortalized lymphoblast cell lines have been produced from a pair of age-matched individuals, one of whom was found to be homozygous wild-type and one of whom was found to be homozygous variant for the codon 399 XRCC1 polymorphism and both of whom were found to be homozygous wild-type for the other XRCC1 polymorphisms; the cells were originally identified from genotyped samples at Columbia collected as part of a clinic-based registry of family members with relatives who had cancer, which included 24 homozygous wild-type and 11 homozygous variant individuals for XRCC1 codon 399 who were wild-type for codons 194 and 280. From these, the age-matched pair (both 49 years old) was selected for study. The cells were immortalized with an Epstein-Barr virus producing cell line (marmoset line B95-8) obtained from the Coriell Institute (Camden, NJ), according to their routine protocol. For each line, approximately 10^7 cells, suspended in culture in RPMI 1640 medium containing 100 U/mL penicillin, 100 μg/mL streptomycin, 2mM L-glutamine and 10% heat-inactivated human serum, was incubated with CAA, the reactive intermediate of VC, at a concentration of 50 μg/mL for 1 h at 37°C (determined to be the optimum conditions for adduct generation). The cells were then washed with PBS and allowed to recover for 1 h in order to provide time for DNA repair (determined to be the optimum time for repair). Cell samples were harvested and lyzed to collect the DNA by standard phenol-chloroform extraction and ethanol precipitation at each phase of the treatment (baseline, after exposure, after recovery). The level of εA adducts in equal amounts of DNA extracts (30 μg) from each cell line at each phase of treatment was quantitated using an εA-specific enzyme-linked immunosorbent assay (ELISA) [11]. The ELISA is based on a mouse monoclonal antibody raised against εA coupled to a carrier and shows no cross-reactivity with non-modified DNA, normal nucleotides or other etheno-DNA adducts; adduct levels for the cell samples (run in duplicate) were derived by interpolation from a standard curve generated with known amounts of εA adducts. The efficiency of repair was calculated from the ratio of adducts removed during the recovery period to the amount of adducts formed during the exposure period, corrected for the baseline levels, and compared between the cell lines.

RESULTS AND DISCUSSION

Among the 211 workers, genotype distributions at codons 194, 280 and 399 are presented in Tables 1 and 2. All these genotype distributions were consistent with Hardy-Weinberg equilibrium. There were no statistically significant differences in terms of the distribution of VC exposure levels among the different genotypes.

The associations between genotypes and the presence of the mutant biomarkers are presented in Tables 3–5. In Table 3, the association of variant XRCC1 alleles with frequency of the mutant *ras*-p21 biomarker demonstrates an increase in the adjusted OR for the biomarker from 1.0 in the group with all wild-type alleles to 1.3 (95% CI: 0.7–2.6) in the group with any one variant allele to 1.3 (95% CI: 0.6–2.8) in the group with any two variant alleles with no statistically significant trend with increasing allele dosage (p = 0.5). In Table 4, the association of the variant XRCC1 alleles with frequency of the mutant p53 biomarkers demonstrates an increase in the adjusted OR for the biomarkers from 1.0 in the group with all wild-type alleles to 1.5 (95% CI: 0.8–3.0) in the group with any one variant allele to 3.1 (95% CI: 1.4–6.7) in the group with any two variant alleles with a statistically significant trend with increasing allele dosage (p = 0.005). In Table 5, the association of variant XRCC1 alleles with frequency of both mutant biomarkers demonstrates an increase in the adjusted OR for the biomarkers from 1.0 in the group with all wild-type alleles to 2.0 (95% CI: 1.0–3.9) in the group with any one variant allele to 2.4 (95% CI: 1.1–5.2) in the group with any two variant alleles with a statistically significant trend with increasing allele dosage (p = 0.02).

These results are consistent with allele frequencies found in comparable populations [9] and demonstrate that polymorphisms of XRCC1 are quite common with 71% of this cohort having at least one variant allele. Furthermore, the presence of variant alleles appears to have functional significance since there is an increase in biomarkers of VC-induced mutations with increasing variant allele dosage even after controlling for other potentially contributory factors such as age, smoking, alcohol consumption and cumulative VC exposure. Our previous results in this cohort [6] as well as similar results in a cohort of Taiwanese VC workers [12], suggested that the presence of the XRCC1 polymorphism at codon 399 can influence the generation of the mutant p53 biomarker following VC exposure. The present results extend these observations suggesting that any of the three common polymorphisms in XRCC1 can similarly influence the generation of the mutant p53 biomarker, and to a lesser extent the mutant *ras*-p21 biomarker, following VC exposure. The difference in the degree of effect of the polymorphisms on the two biomarkers may be attributable to the fact that εG adducts may not be as efficiently removed by BER as εA adducts [13].

Our findings are entirely consistent with the proposed carcinogenic pathway for VC and with the role of XRCC1 in BER of VC-induced DNA adducts. As noted above, the reactive intermediates of VC, CEO and CAA, generate pro-mutagenic etheno-DNA adducts that can cause the types of mutations seen in the K-*ras* oncogene and *TP53* tumor suppressor gene found in ASLs of exposed workers,

Table 1. Distribution of polymorphisms in XRCC1 at codons 194, 280 and 399 in vinyl chloride (VC) workers

Codon	Homozygous wild-type N (%)	Heterozygous N (%)	Homozygous variant N (%)
194	187 (89)	24 (11)	0
280	193 (91)	18 (9)	0
399	86 (41)	90 (43)	35 (16)

Table 2. Distribution of combinations of XRCC1 polymorphisms at codons 194, 280 and 399 vinyl chloride (VC) workers

No variant alleles N (%)	One variant allele			Two variant alleles		
	Heterozygous at 194 only N (%)	Heterozygous at 280 only N (%)	Heterozygous at 399 only N (%)	Heterozygous at 194 and 399 N (%)	Heterozygous at 280 and 399 N (%)	Homozygous variant at 399 N (%)
	15 (7)	9 (4)	72 (34)	9 (4)	9 (4)	35 (17)
62 (29)		96 (46)			53 (25)	

Table 3. Association between polymorphisms in XRCC1 at codons 194, 280 and 399 and the mutant *ras*-p21 biomarker in vinyl chloride (VC) workers

XRCC1 codons 194, 280 and 399	p21 biomarker		Odds ratio (95% CI)	Adjusted odds ratio* (95% CI)
	–	+		
All wild-type	42 (68%)	20 (32%)	1	1
One variant allele	59 (62%)	37 (38%)	1.3 (0.7–2.6)	1.3 (0.7–2.6)
Two variant alleles	33 (62%)	20 (38%)	1.3 (0.6–2.8)	1.3 (0.6–2.8)

* Adjusted for age, smoking, drinking and cumulative VC exposure; for trend, p = 0.52; CI – confidence interval.

Table 4. Association between polymorphisms in XRCC1 at codons 194, 280 and 399 and the mutant p53 biomarkers in vinyl chloride (VC) workers

XRCC1 codons 194, 280 and 399	p53 biomarker		Odds ratio (95% CI)	Adjusted odds ratio* (95% CI)
	–	+		
All wild-type	41 (66%)	21 (34%)	1	1
One variant allele	55 (57%)	41 (43%)	1.5 (0.8–2.8)	1.5 (0.8–3.0)
Two variant alleles	21 (40%)	32 (60%)	3.9 (1.4–6.3)	3.1 (1.4–6.7)

* Adjusted for age, smoking, drinking and cumulative VC exposure; for trend, p = 0.005; CI – confidence interval.

Table 5. Association between polymorphism in XRCC1 polymorphisms at codons 194, 280 and 399 and the mutant *ras*-p21 and mutant p53 biomarkers in vinyl chloride (VC) workers

XRCC1 codons 194, 280 and 399	p21 and p53 biomarker		Odds ratio (95% CI)	Adjusted odds ratio* (95% CI)
	both –	any +		
All wild-type	31 (50%)	31 (50%)	1	1
One variant allele	33 (34%)	63 (66%)	1.9 (1.0–3.7)	2.0 (1.0–3.9)
Two variant alleles	16 (30%)	37 (70%)	2.3 (1.1–5.0)	2.4 (1.1–5.2)

* Adjusted for age, smoking, drinking and cumulative VC exposure; for trend, p = 0.02; CI – confidence interval.

thus accounting for the presence of the mutant biomarkers in exposed workers. The etheno adducts produced by VC should be removed by the BER pathway, which, as noted, may be more efficient for the εA adduct than for the εG adduct. The BER machinery contains several proteins, including a methyl purine glycosylase, an endonuclease (APE1), a DNA polymerase (Polβ), a ligase (LigIII) and poly(ADP-ribose)polymerases (PARP1 and PARP2), and is coordinated by XRCC1, which acts as a scaffold for these proteins and regulates their functions through interactions with them [7]. Specific domains of XRCC1 are the sites of interaction with these other proteins. For example, the XRCC1 N-terminal domain (approximately amino acid residues 1–195) has been observed to mediate the interaction with the palm-thumb domain of Polβ [14,15]. Amino acid residue 194 lies within this N-terminal domain, and, hence, polymorphisms here might be expected to have some effect on the structure and function of this domain and its ability to interact with Polβ. The XRCC1 central BRCT1 domain (approximately amino acid residues 315–403) has been associated with the functioning of PARP1, PARP2 and APE1 [16,17]. Amino acid residue 399 lies within this central BRCT1 domain, and, hence, polymorphisms here might be expected to have some effect on the structure and function of this domain and its ability to interact with these proteins. The third polymorphic site in XRCC1 occurs at amino acid residue 280 in a domain of unknown function; however, since this domain lies between the N-terminal domain and the central BRCT1 domain and is also close to the nuclear localization signal site, it is possible that amino acid residues in this domain could affect the relationship between these two other domains or its localization, and thus the functional ability of the protein.

The results of the *in vitro* exposure studies are presented in Table 6. In the homozygous wild-type cells, the amount of εA adducts increased from a baseline level of 0.31 ng to 2.19 ng following exposure and then decreased to 0.47 ng after recovery. In contrast, in the homozygous variant cells, the amount of εA adducts increased from a baseline level of 0.41 ng to 2.46 ng following exposure and then decreased to 1.50 ng after recovery. Thus, in the homozygous wild-type cells, of the 1.88 ng of adducts generated during exposure, 1.72 ng were repaired during the recovery for a repair efficiency of 91%, whereas, in the homozygous variant cells, of the 2.05 ng of adducts generated during exposure, only 0.55 ng were repaired during the recovery for a repair efficiency of 22%. Thus, the efficiency of repair of εA DNA adducts in the homozygous wild-type cells was 4 times greater than the efficiency of repair in the homozygous variant cells. Although limited in scope, these preliminary results are entirely consistent with the epidemiologic results from the VC worker cohort, which

showed an increased OR of 4 for the presence of the mutant p53 biomarker (which, as noted, results from the εA DNA adducts) in individuals who are homozygous variant at codon 399 compared to those who are homozygous wild-type [6].

Prior studies in the literature have reported positive, negative and null relationships between XRCC1 polymorphisms and both cancer risk or the formation of cancer biomarkers such as DNA adducts, DNA mutation frequency and the occurrence of chromosomal aberrations [8]. For example, in terms of cancer risk, a study of esophageal cancer found the 194 variant genotype to be at significantly increased risk; a study of gastric cancer found the 194 variant and the 399 variant genotypes to be at significantly increased risk; a study of colorectal cancer found the combined heterozygotes and homozygotes for the 399 variant allele to be at significantly increased risk; and several studies of lung cancer have found the 280 variant or 399 variant genotypes to be at significantly increased risk [18–21]. Other studies have found no significant associations for these genotypes and cancers of the lung or breast, and still other studies have found a significant protective effect against cancer for these genotypes, including for head and neck cancer when confined to certain ethnic groups, esophageal cancer, bladder cancer and skin cancer [22–26]. Furthermore, in terms of cancer biomarkers, Taiwanese maternity subjects with the 399 variant genotype were found to have increased placental aflatoxin-DNA adducts; a study of healthy, nonsmoking Italians with the 399 variant genotype were found to have increased bulky DNA adducts; three other studies found no association between XRCC1 genotype and bulky adducts or the ability to repair UV photoproducts; glycophorin A variant frequency was increased in healthy adults with the 399 variant genotype, although no change was observed in newborns with that genotype; the 399 polymorphism, but not the 194 polymorphism, has been associated with an increase in sister chromatid exchanges; and length of mitotic delay in lymphocytes with the 399 or 194 polymorphism after exposure to ionizing radiation was similar to wild-type cells [9,27–32]. However, most of these prior studies had potential design flaws and were not based on such a well-defined carcinogenic pathway with such a strong mechanistic rationale as in this study.

Table 6. εA adduct levels in lymphoblast DNA during treatment with chloroacetaldehyde (CAA)

XRCC1 codon 399	Treatment	Adduct level (ng)
Homozygous wild-type	Baseline	0.31
	After exposure	2.19
	After recovery	0.47
Homozygous variant	Baseline	0.41
	After exposure	2.46
	After recovery	1.50

CONCLUSIONS

In summary, the results of this study support the hypotheses that XRCC1 is involved in the repair of VC-induced lesions and that polymorphisms in XRCC1 contribute significantly to an increased risk for mutagenic damage from VC and to the variability in susceptibility for such damage among exposed individuals. These findings may have more general significance as well. For example, etheno-DNA adducts are known to be generated by exposures other than VC that contribute to environmental carcinogenesis, including other industrial chemicals, oxidative stress and cigarette smoke. Also, XRCC1 participates in BER with many other glycosylases for repair of a range of different DNA damage. Finally, these XRCC1 polymorphisms are quite common in many populations. Therefore, the overall contribution of XRCC1 polymorphisms to susceptibility differences for mutagenesis and carcinogenesis could be substantial.

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