

Ethnic disparities in Americans of European descent versus Americans of African descent related to polymorphic ERCC1, ERCC2, XRCC1, and PARP1

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Abstract

Nucleotide excision repair (NER) and base excision repair (BER) pathways are DNA repair pathways that are important in carcinogenesis and in response to DNA-damaging chemotherapy. ERCC1 and ERCC2 are important molecular markers for NER; XRCC1 and PARP1 are important molecular markers for BER. Functional polymorphisms have been described that are associated with altered expression levels of these genes and with altered DNA repair capability. We assayed genomic DNA from 156 Americans of European descent and 164 Americans of African descent for the allelic frequencies of specific polymorphisms of ERCC1 N118N (500C>T), ERCC1 C8092A, ERCC2 K751Q (2282A>C), XRCC1 R399Q (1301G>A), XRCC1 R194W (685C>T), and PARP1 V762A (2446T>C). Differences were observed between Americans of European descent and Americans of African descent in the allelic frequencies of the ERCC1 N118N polymorphism ($P < 0.000001$). Differences were also observed between these two ethnic groups for ERCC2 K751Q ($P = < 0.006675$), XRCC1 R399Q ($P < 0.000001$), and PARP1 V762A ($P = 0.000001$). The ERCC1 N118N polymorphic variant that is seen most commonly in Americans of European descent is associated with a measurable reduction in NER function. ERCC1-mediated reduction in NER functionality affects the repair of cisplatin-DNA lesions. [Mol Cancer Ther 2008;7(5):1246–50]

Introduction

Nucleotide excision repair (NER) is the DNA repair pathway that repairs bulky lesions that are covalently

bound to DNA bases. This includes DNA damage from UV light, polycyclic aromatic hydrocarbons, and selected anticancer pharmaceuticals such as the platinum compounds, e.g., cisplatin, carboplatin, and oxaliplatin (1, 2). ERCC1 and ERCC2 are 2 of the 16 proteins that participate in NER to excise the bulky lesion from the DNA strand (3, 4). ERCC1 performs several functions and, along with XPF, is essential for the 5' incision into the DNA strand that releases bulky DNA lesions (5, 6). ERCC2 is a 5'-3' helicase that participates in DNA strand separation before the 5' incision step done by the ERCC1-XPF heterodimer (7, 8). ERCC1 and ERCC2 are considered to be clinically useful molecular predictors for overall NER activity and have been studied in bladder, lung, ovarian, colorectal, and other cancers where platinum compounds are used (9–18).

Spontaneous DNA hydrolysis, oxidative damage to DNA, and simple alkylations to DNA bases are repaired by base excision repair (BER) pathway. BER has not been as well studied as NER in the setting of anticancer chemotherapy. However, data suggest that BER may play a role in clinical and cellular resistance to simple alkylating agents (19). The important enzymes involved in BER include XRCC1 and PARP1. XRCC1 stimulates endonuclease activities following the excision of a damaged nucleotide and acts as both a scaffold and a regulator for other BER proteins (20). PARP1 is required for XRCC1 function at sites of oxidative DNA damage (21).

There are several common diseases where there is a long history of ethnic differences in treatment outcomes and mortality. These include breast cancer, prostate cancer, lung cancer, and colorectal cancer as summarized in Table 1. Breast cancer is treated with Adriamycin and cyclophosphamide, drugs that cause oxidative damage to DNA (22) and alkylation of DNA, respectively (23). In these circumstances, BER may be of major importance. Lung cancer is commonly treated with cisplatin- or carboplatin-based regimens (24), whereas colorectal cancer is commonly treated with an oxaliplatin-based combination (25). In lung cancer and colorectal cancer, NER appears to be the most important DNA repair mechanism (1). Bladder cancer, cervical cancer, stomach cancer, and head and neck malignancies are also treated with DNA-damaging therapies and have had ethnic differences in disease outcome observed (26).

Ethnic disparity in treatment outcomes is a problem that is receiving increased recognition in clinical oncology but has been poorly studied. It is not completely clear whether differences noted between Americans of European descent (EA) and Americans of African descent (AA) in treatment outcomes are due to matters of patient access to care, differences in medical care delivery, differences in clinical

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response to the same therapies, or, most likely, a combination of all of these. The molecular causes of clinical resistance to chemotherapy have been elucidated for some of the commonly used anticancer agents. For cisplatin, carboplatin, and oxaliplatin, the NER DNA repair pathway appears to be of great importance (1), whereas agents that generate oxidative DNA damage within cells or produce simple alkylations to DNA are more influenced by the BER pathway (27, 28). This information led us to investigate the following: if ethnic differences exist in the clinical treatment outcomes of patients who are treated with drugs that may be affected by NER and/or BER, are these outcomes associated with ethnic differences in polymorphism frequency in genes that are involved in these DNA repair pathways.

ERCC1, ERCC2, XRCC1, and PARP1 have been reported to have polymorphic variants that appear to affect the functioning of the respective gene. Also, for ERCC1, ERCC2, and XRCC1, the polymorphic variants have been associated with clinically important endpoints. The aim of this study is to assess the allelic frequency of the note polymorphisms in the genes ERCC1, ERCC2, XRCC1, and PARP1.

Materials and Methods

Whole-blood samples ($n = 320$) from healthy male volunteers (Valley Biomedical) were analyzed. All volunteers had signed informed consent to allow their samples to be used for genotyping, and none had a diagnosis of cancer.

Plasma was used to isolate genomic DNA according to the manufacturer's instructions using the UltraSens Virus Kit (Qiagen). PCR was done using the Platinum Taq PCR Kit (Invitrogen) with gene-specific primers. PCR was denatured at 94°C for 5 min followed by denaturation at 94°C for 30 s, annealing at optimal temperature for each pair of primers for 30 s, and synthesis for 30 s at 72°C for 40 cycles; the final extension was carried out at 72°C for 7 min. Primers and PCR conditions used in this study will be provided per request.

Direct nucleotide sequencing PCR was conducted using the Big Dye Terminator Cycle Sequencing Ready Reaction kit V3.1 (Applied Biosystems) and an ABI Prism 3130 Genetic Analyzer using the manufacturer's instructions.

For each SNP, P values were calculated by χ^2 test with 1 df based on allele frequency using Number Cruncher Statistical Software.

Table 1. Summary of previous studies on racial disparity of mortality and treatment outcome in cancer

Cancer type	Treatment	Ethnic groups (no. samples)	Major findings	OR (95% CI)/ P	Ref.
Breast cancer	Not defined	AA* (185) and EA (10,937)	Overall survival significantly favored EAs	2.27 (1.82-2.84)	(46)
	Surgery, radiation, and adjuvant chemotherapy	AA (771) and EA (5,651)	Increased risk of death in AA patients	1.57 (1.18-2.10)*	(47)
	Surgery, cyclophosphamide, methotrexate, and 5-fluorouracil	AA (543) and EA (7,582)	Increased death in AA patients	1.21 (1.01-1.46) [†]	(48)
Prostate cancer	Orchiectomy or LHRH analogue therapy	AA (55) and EA (90)	No difference	1.18 (1.03-1.34) [†]	(49)
	Surgery, radiation, hormone therapy, and others	AA (14,307) and EA (108,067)	Increased risk of death in AA patients	1.61 (1.50-1.72) [§]	(50)
Lung cancer	Not defined	AA and EA, numbers not defined	Lower 5-y survival rate in AA patients	0.99 (0.92-1.06)	(51)
Colorectal cancer	Surgery	AA (199) and EA (292)	Lower 5- and 10-y survival rate in AA	1.67 (1.21-2.33) [¶]	(26)
				1.52 (1.12-2.07)**	
Rectal cancer	Methyl-lomustine, vincristine, fluorouracil, leucovorin, and/or radiation therapy after surgery	AA (104) and EA (1,070)	Higher mortality in AA patients	1.45 (1.09-1.93)	(52)
Colon cancer	Not defined	AA (454) and EA (521)	Higher risk of death among AA patients after adjusted for stage	1.2 (1.1-1.5)	(53)

*Breast cancer-specific survival adjusted for tumor characteristics and major treatments.

[†]Lymph node-negative disease.

[‡]Lymph node-positive disease.

[§]Adjusted only for age.

^{||}Adjusted for stage, treatment, grade, socioeconomic status, and year of diagnosis.

[¶]Within 5 y of surgery.

**Within 10 y of surgery.

Table 2. Genotype distribution

Gene	Genotype	EA	AA	Allele	EA	AA	<i>P</i>
ERCC1* N118N (500C>T)	CC	23 (0.21) [†]	96 (0.76)	C	99 (0.46)	219 (0.86)	<0.000001
	CT	53 (0.49)	27 (0.21)	T	117 (0.54)	35 (0.14)	
	TT	32 (0.30)	4 (0.03)				
	Total	108	127	Total	216	254	
ERCC1 C8092A	CC	77 (0.53)	74 (0.52)	C	213 (0.73)	204 (0.72)	0.870913
	AC	59 (0.40)	56 (0.40)	A	79 (0.27)	78 (0.28)	
	AA	10 (0.07)	11 (0.08)				
	Total	146	141	Total	292	282	
ERCC2 K751Q (2282A>C)	AA	49 (0.42)	81 (0.56)	A	154 (0.65)	219 (0.76)	0.006675
	AC	56 (0.47)	57 (0.40)	C	82 (0.35)	69 (0.24)	
	CC	13 (0.11)	6 (0.04)				
	Total	118	144	Total	236	288	
XRCC1 R399Q (1301G>A)	GG	49 (0.46)	113 (0.80)	G	145 (0.68)	252 (0.89)	<0.000001
	AG	47 (0.44)	26 (0.19)	A	67 (0.32)	30 (0.11)	
	AA	10 (0.10)	2 (0.01)				
	Total	106	141	Total	212	282	
XRCC1 R194W (685C>T)	CC	120 (0.87)	133 (0.90)	C	257 (0.93)	280 (0.95)	0.460941
	CT	17 (0.12)	14 (0.09)	T	19 (0.07)	16 (0.05)	
	TT	1 (0.01)	1 (0.01)				
	Total	138	148	Total	276	296	
PARP1 V762A (2446T>C)	TT	80 (0.67)	108 (0.91)	T	192 (0.81)	227 (0.95)	0.000001
	CT	32 (0.27)	11 (0.09)	C	46 (0.19)	11 (0.05)	
	CC	7 (0.06)	0 (0)				
	Total	119	119	Total	238	238	

P value is calculated by χ^2 test with 1 *df* based on allelic frequency.

*Gene name, amino acid change and position, and nucleotide change and position.

[†]Count (frequency).

Results

A summary of the six polymorphisms studied is provided in Table 2. The genotype distribution of each SNP is in Hardy-Weinberg equilibrium ($P > 0.05$). No genotype frequency differences were observed between EAs and AAs for the ERCC1 C8092A polymorphism. However, significant differences in genotype frequency were noted for the ERCC1 N118N (500C>T) transition ($P < 0.000001$). The CC genotype occurred more frequently in AAs (76%) compared with EAs (21%). However, the TT genotype is seen in only 3% of AAs and in 30% of EAs. The CT genotype is seen in 21% and 49% of the respective groups. Reed et al. have shown that the TT genotype is associated with reduced expression of ERCC1, reduced cisplatin-DNA adduct repair, and increased sensitivity to cisplatin (27, 28).

For the ERCC2 K751Q (2282A>C) polymorphism, there were differences between EAs and AAs in the distribution of the AA, AC, and CC genotypes ($P = 0.006675$).

The AA genotype was seen more frequently in AAs (56% versus 42%), but the other two genotypes were observed more frequently in EAs: AC (47% versus 40%) and CC (11% versus 4%).

For the XRCC1 R399Q (1301G>A) polymorphism, substantial differences between ethnic groups were also noted ($P < 0.000001$). The GG genotype occurred in 80% of AAs but only in 46% of EAs. The other two genotypes occurred more frequently in EAs: AG (44% versus 19%) and AA

(10% versus 1%). The XRCC1 R194W (685C>T) polymorphism did not differ in genotype frequency between ethnic groups.

The TT genotype of PARP1 V762A (2446T>C) occurred more frequently in AAs than EAs (91% versus 67%; $P = 0.000001$). The other genotypes occurred more frequently in EAs: CT (27% versus 9%) and CC (6% versus 0%).

Discussion

We assessed genomic DNA from 156 EAs and 164 AAs for allelic frequency of the noted polymorphisms in the genes ERCC1, ERCC2, XRCC1, and PARP1. Our data suggest a profound difference between these two ethnic groups in three genes: ERCC1, XRCC1, and PARP1.

Of the differences shown between ethnic groups, one of the most interesting is the difference observed for the N118N polymorphism of ERCC1. The polymorphism of AAC to AAT at codon 118 of ERCC1 was first reported by Reed et al. (27, 28).

This codon change results in the same amino acid, but the C>T transition decreases the translation rate from mRNA to protein by 50% (29). This polymorphism was noted to be associated with reduced mRNA expression of ERCC1, reduced repair of platinum-DNA adduct, and greater sensitivity to platinum compounds (29, 30). Codon 118 of ERCC1 has also been studied in several malignancies, such as lung cancer, ovarian cancer, colorectal cancer, and other

malignancies (1, 9–18). Our data suggest the possibility that reduced NER capacity may occur more commonly in EAs that carry the variant T allele more frequently, and this might result in greater sensitivity to platinum compounds in EAs or AAs. This would be consistent with the observed improved survival rates in EAs compared with AAs in malignancies where platinum compounds are important components of therapy, including lung, colorectal, head/neck, and ovarian cancers.

Although several studies also suggested C8092A mutation in the 3'-untranslated region of ERCC1, an indicator of altered chemosensitivity (29) or cancer risk (31), we did not observe differences in genotype distribution of this polymorphism between EAs and AAs. Therefore, this polymorphism may be important to risk and clinical outcome in a similar fashion in both populations but is likely not associated with health disparities between EAs and AAs.

ERCC2 is a DNA helicase subunit of the transcription factor IIH and catalyzes a local unwinding around DNA lesion in a 5' to 3' direction. The transcription factor IIH-mediated opening generates junctions between duplex and single-stranded DNA that in turn could be cleaved by ERCC1-XPF heterodimer. ERCC2 has a polymorphism at codon 751, K751Q, which is of particular interest. The codon 751 wild-type of A/A has been associated with suboptimal DNA repair (13). Also, the A/A genotype has been seen with greater frequency in patients with colorectal cancer that respond to oxaliplatin-based chemotherapy (18). These patients also show longer median survival time. However, the C/C variant homozygote is associated with reduced DNA repair capacity in patients with lung cancer (32), is significantly associated with risk and outcome in acute myeloid leukemia (33), and is overrepresented in patients with lung cancer of Chinese extraction (34). The interethnic variance of ERCC2 polymorphisms was reported previously among European, African, and Asian populations (35). The lowest variant allele frequency occurred in Asian and the highest in European, with African having a median variance rate. However, the mixed clinical picture for ERCC2 makes it difficult to interpret the ethnic differences in allelic frequencies that we observed in this report. We reported here that significantly low frequency of variant ERCC2 K751Q was detected in AAs.

BER pathway protects cells from endogenous DNA damage induced by spontaneous hydrolysis and/or reactive oxygen species. Meanwhile, it is also important to resist lesions caused by ionizing radiation and alkylating agents. A critical component of BER is XRCC1, for which one relevant polymorphism is at codon 399. This point mutation is in the BRCT1 domain, which provides binding site for PARP1 polymerase (20). The wild-type G/G genotype appears to be associated with increased sensitivity to platinum-based chemotherapy in Asian populations (36) and in one study of 112 patients with non-small cell lung cancer (37), whereas the variant allele showed improved survival in one Spanish population (38) and in

bladder cancer (17). The A/A genotype is associated with smoke-induced pancreatic cancer (39) and is associated with breast cancer risk in AAs (40).

Another prevalent SNP in XRCC1 is at codon 194, which is in a possible binding site for several protein partners in BER and the positively charged arginine is changed to a hydrophobic tryptophan. This polymorphism is susceptible to affect binding and DNA repair efficiency (20) and the variant allele was associated to better response to platinum-based chemotherapy in patients with advanced non-small cell lung cancer (41). Our data indicated significantly low frequency of XRCC1 R399Q, but not R194W, in AAs. Thus, the polymorphism of XRCC1 R399Q may be informative in health disparity between the two populations.

PARP1 plays various roles in molecular processes including DNA damage detection and repair. A common PARP1 polymorphism at codon 762 results in the substitution of valine by alanine in the catalytic domain. This change was proven to dramatically reduce the enzymatic activity (42). The variant genotype contributes to prostate cancer susceptibility and altered DNA repair function to oxidative damage (43), association with risk of esophageal squamous cell carcinoma in Chinese population (44), and increased risk of smoking-related lung cancer (45). The prevalence of variant genotype is extremely low in AAs (0% in our samples), which may indicate better protein function of PARP1 in this population.

Our data suggest the possibility that a comparatively modest reduction in BER may occur more commonly in EAs. This would imply greater sensitivity to chemotherapy agents that alkylate DNA, such as cyclophosphamide, and/or to agents that generate free radicals that damage DNA, such as Adriamycin. This would be consistent with observed differences in response to therapy in breast cancer, comparing EAs and AAs.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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