RESEARCH ARTICLE

Association Between *XRCC1* and *WRN* as Genetic Markers of Stability and Susceptibility to Cancer in Patients with HIV/AIDS and Cancer: a Cross-Sectional Study

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Abstract

Background: HIV-induced immunodeficiency has been implicated as a key factor for risk of cancer. Neoplasia is considered to result from accumulation of damage to the genome. Polymorphisms in repair genes, such as the *XRCC1* and *WRN*, have been associated with susceptibility to development of cancer in patients with HIV/AIDS. The aim of this study was to analyze the frequency of polymorphisms in *XRCC1* (Arg399Gln) and *WRN* (Cys1367Arg) in patients with HIV/AIDS with or without cancer. **Materials and Methods:** Genotyping for analysis of polymorphisms was carried out by PCR (Polymerase Chain Reaction) and RFLP (Restriction Fragment Length Polymorphism). Results: In the genotypic and allelic analysis, no increased risk of cancer was observed with any genotype or allele of *XRCC1* (Arg399Gln) singly (prevalence ratio 2.82; p-value= 0.24). However, with the *WRN* (Cys1367Arg) gene, the heterozygous genotype and arginine allele were associated with increased risk (prevalence ratio= 25.62; p-value= 0.0001). Correlation analysis showed no association between gender and the risk (male p-value= 0.639 and women p-value> 1); however, a positive association for the increased risk of cancer was shown with *XRCC1* (Arg399Arg) wild-type homozygous and WRN (Cys1367Arg) heterozygous (p-value< 0.001), with heterozygous *XRCC1* (Arg399Gln) and *WRN* (Cys1367Arg) (p-value< 0.001), and with variant homozygous *XRCC1* (Gln399Gln) and heterozygous WRN (Cys1367Arg) (p-value< 0.001). Conclusions: There is no increased risk of cancer in patients who are HIV/AIDS carriers of the *XRCC1* (Arg399Gln) gene singly. However, there is a high risk in patients with HIV/AIDS who have the heterozygous genotype and the arginine allele in the *WRN* (Cys1367Arg) gene singly. Those with *WRN* (Cys1367Arg) heterozygote genotype showed a high risk of cancer with all genotypes of the *XRCC1* (Arg399Gln) gene.

Keywords: HIV/AIDS- cancer- repair genes- polymorphisms

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Introduction

According to the data presented by the Joint United Nations Program on HIV/AIDS (2015) and World Health Organization (2013), there is a mean of 36.9 million people living with HIV (Human Immunodeficiency Virus) worldwide, leading to the deaths of over 1.2 million HIV carriers in 2014, representing one of the most devastating infections in history (WHO, 2013;UNAIDS, 2015).

HIV infection is characterized by the coexistence of immunodeficiency due to CD4 + cell depletion and systemic chronic activation of the innate and adaptive systems (Desai and Landay, 2010; Plaeger et al., 2012; Maldonado et al., 2015; Stein et al., 2016).

The antiretroviral therapy is highly effective in the survival of patients with AIDS (Acquired Immune Deficiency Syndrome). As a result, people with HIV/AIDS are living longer and reaching an advanced age. Consequently, the risk of chronic diseases associated with aging, specially, cancer . (CDC, 2007; CDC, 2011; Yanik et al., 2016).

There is a correlation between HIV/AIDS and the prevalence of specific types of cancer, namely Kaposi's sarcoma, non-Hodgkin lymphoma and, cervix uteri (CDC, 2007; CDC, 2011; Yanik et al., 2016). It is already known that more than 40% of HIV-infected people have some form of cancer (Biggar et al., 2007, Engels et al., 2008; Zlotorzynska et al., 2016). The neoplasm risk in AIDS patients is a hundred times greater than in the general population (Biggar et al., 2007; Engels et al., 200; Zlotorzynska et al., 2016).

The principal causes for the appearance of tumors

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are associated with genetic alterations caused by viral infections. For example, point mutations, deletions, duplications, insertions, translocations, chromosome aberrations, and epigenetic inactivation represent various types of potentially causative cancer events (Edwards et al., 2013; Liu et al., 2014). There are genes able to repair possible errors in DNA to maintain and promote genetic stability. Each type of error is removed by specific mechanisms (Sancar et al., 2004; Jackson and Bartek, 2009; Liu et al.,2014; Wyrick & Roberts SA, 2015).

Polymorphic variations and mutations in genes associated with DNA repair may affect the DNA repair capacity or inactivity of these genes. Therefore, it will positively affect the processes of mutagenesis and carcinogenesis (Goode et al., 2002; Bag et al., 2012; Karahalil et al., 2012).

There is a substantial interindividual variation in DNA repair capacity within a population. Individuals who have DNA repair deficiency, in particular patients with HIV, have a higher risk of developing some types of cancer. The relationship between polymorphisms and mutations in the repair genes *XRCC1* and *WRN* in a given population shows significant evidence of the trend that a population has to develop some kind neoplasm (Sharma et al., 2007; Sobti et al., 2009). The aim of this study was to analyze the frequency of polymorphisms in *XRCC1* and *WRN* genes in the development of malignancies in patients with HIV/AIDS and HIV/AIDS with cancer.

Materials and Methods

Study design

This was an observational study, which used a cross-sectional approach. It was conducted from 2013 to 2015 at the Department of Infectious and Parasitic Diseases of the Pedro Ernesto University Hospital, Rio de Janeiro State University (UERJ), RJ, Brazil.

Ethics

This study was approved by the Ethics Committee of the Pedro Ernesto University Hospital/UERJ, (CAAE:14189113.2.0000.5259). All samples were collected with written informed consent.

Subjects

All patients (groups HIV/AIDS and HIV/AIDSWC) included in this study were recruited by the Department of Infectious and Parasitic Diseases, Pedro Ernesto University Hospital, Rio de Janeiro State University, RJ, Brazil. Information regarding age, sex and medical history was gathered from the subjects in a structured form.

The inclusion criteria for the patient groups were having confirmed diagnosis of HIV/AIDS registered formally in their medical history; being 18 years of age or older and having started antiretroviral treatment , while for the HIV/AIDSWC group, the criteria also included having confirmed diagnosis of cancer registered formally in their medical records and having started antiretroviral treatment.

The exclusion criteria were opportunistic infections within 6 months, history of hereditary cancers, history of previous cancer diagnosis of HIV/AIDS, genetic syndromes, mental disorder diseases, syndromes associated with deficiency in DNA repair mechanisms, and a prior history of bone marrow transplantation. To ensure that such conditions were not included in the groups, of the medical history of all patients captured for study was analyzed. No exclusion criteria were considered from the point of view of the medicines used for the treatment of HIV/AIDS and cancer.

The samples from the groups HIV/AIDS and HIV/AIDSWC were obtained from peripheral blood at the Nucleic Acids Laboratory of the University Hospital Pedro Ernesto, RJ, Brazil.

Peripheral blood samples (5 ml) of 40 HIV/AIDS patients and 24 HIV/AIDSWC patients were obtained from peripheral blood at the Nucleic Acids Laboratory of the University Hospital Pedro Ernesto, RJ, Brazil. DNA was isolated from peripheral blood by using the standard phenol-chloroform procedure and stored at -20°C. DNA samples were amplified to detect the polymorphisms in *XRCC1* Arg399Gln codon 399 and *WRN* Cys1637Arg codon 1637 to understanding the relationship how can vary between *XRCC1* and *WRN* as genetic markers of stability and susceptibility to cancer in patients with HIVAIDS and cancer.

Genotyping

XRCC1 (Arg399Gln) and *WRN* (Cys1367Arg) polymorphisms were determined by PCR restriction fragment length polymorphism (PCR-RFLP) assay. The primers for the XRCC1 (Arg399Gln) polymorphism were forward (5'- CAA GTA CAG CCA GGT CCT AG -3') and reverse (5' - CCT TCC CTC ATC TGG AGT AC -3') and the primers for the *WRN* (Cys1367Arg) polymorphism were forward (5'- GCC TAA TCA GAA TGT TAG TT -3') and reverse (5' - TCA GTA TTG ATG CCT ACC TC -3')(Eurofins, MWG Operon®).

The mix of 50 µl of the PCR reactions containing 0.1 µg of DNA, 5 mmol/l dNTPs, 250 nM of each primer, and 1 U of Taq polymerase was added to the PCR buffer containing 10 mmol/l Tris-HCL, 1.5 mmol/l MgCl2, and 50 mmol/l KCl (Invitrogen®).

For XRCC1, PCR was performed under the following conditions: denaturation at 94°C for 4 min followed by 35 cycles of 30 s at 94°C, 30 s at 60°C and 30 s at 72°C, and then for 10 min at 72°C. Products of 248-bp length were then visualized on 1% agarose gel, digested with 0.2 µg of NciI restriction enzyme and incubated at 37°C overnight, and analyzed on 10% polyacrylamide gel. Individuals homozygous for 399Arg displayed 89 and 159 bp fragments. The Arg399Gln heterozygous individuals displayed 89, 159, and248 bp fragments, and homozygous variants for 399Gln showed only the 248 bp fragment. For *WRN*, PCR was performed under the following conditions: denaturation at 94 °C for 4 min followed by 40 cycles of 45 s at 94°C, 45s at 55 °C and 30 s at 72°C, and then for 10 min at 72°C. Products of 193-bp length were then visualized on 1% agarose gel, digested with 0.2 µg of PmaCI restriction enzyme and incubated at 37 °C overnight, and analyzed on 10 % polyacrylamide gel. Individuals homozygous for 1367Arg displayed

193 bp fragments. The *WRN* Cys1637Arg heterozygous individuals displayed 93, 101, and 193 bp fragments, and homozygous variants for 1367Gln showed only the 93 and 101 bp fragments.

Statistical Analysis

The G test was used to verify whether genotype distributions were in Hardy–Weinberg equilibrium. Observed genotype and allele frequencies in subjects with HIV/AIDS and HIV/AIDS and Cancer were compared using the Chi-square and Fisher's exact tests, respectively. The prevalence ratio (PR) and 95% confidence interval (CI) were calculated using a Poisson regression model. Statistical significance was set at p-value< 0.05. Statistical analyses were performed with software SPSS 22® (IBM) (Eyassu et al., 2016).

Results

Baseline Characteristics of Subjects

We studied 64 subjects with ages ranging from 23 to 62 years, with the median age of 45. Our study population was divided into two groups: HIV/AIDS patients with cancer (HIV/AIDSWC) (n=24) and HIV/AIDS patients (n=40). The patients characteristics are shown in Table 1.

The types of cancer that composed the HIV/AIDSWC group were Kaposi's sarcoma (8) non-Hodgkin lymphoma (9), cervix uteri (2), anal carcinoma (1), epidermoid (1) colon (1), mesenchymal cells (2) and Hodgkin lymphoma (1). At the time of collection, all patients were in treatment against the cancer.

Analysis of the *XRCC1*(Arg399Gln) and *WRN* (Cys1367Arg) polymorphism genes

The genotype and allele frequencies for the polymorphisms analyzed between the HIV/AIDS and HIV/AIDSWC groups are shown in Tables 2 and 3.

Table 2. Distribution of genotype frequency of the *XRCC1* (Arg399Gln) polymorphism and *WRN* (Cys1367Arg) in HIV/AIDSWC and HIV/AIDS groups.

Table 3. Distribution of allele frequency of the XRCC1 (Arg399Gln) polymorphism and *WRN* (Cys1367Arg) in HIV/AIDSWC and HIV/AIDS groups.

The genotypic frequencies of XRCC1 (Arg399Gln) wild-type homozygous for Arg399, heterozygous, and variant homozygous for 399Gln were 72.5%, 27.5% and 0.0%, respectively, in the HIV/AIDS group. The values were similar in the HIV/AIDSWC group 54.2%., 41.6%, and 4.2%, respectively, not showing an elevated risk developing of cancer at the frequencies individually (prevalence ratio= 2.82; p-value= 0.24).

The frequencies of *WRN* (Cys1367Arg) wild-type homozygous for Cys1367 were 100% in the HIV/AIDS group. The values were different for the HIV/AIDSWC group, wild-type homozygous Cys1367 54.2%, heterozygous 45.8%, and variant homozygous 1367Arg 0.0% (p-value= 0.001). Therefore, the Cys/Arg genotype had an elevated risk of developing cancer as compared to those with Cys/Cys or Arg/Arg (prevalence ratio= 25.62;

Table 1. Baseline Characteristics of Subjects

	HIV/AIDSWC	p-value		HIV/AIDS	p-value
	n (%); (max-min)			n (%); (max-min)	
Nº of males/females	18 (75.0) / 6 (25.0)	0.0001		30 (75.0) / 10 (25.0)	0.0001
Age in years	40 (23-60)			47 (23-62)	
Median CD4 cell count	230 (10- 683)			620 (142- 1028)	
Median days since HIV/AIDS diagnosis	3537 (88-10119)			4244 (419-10478)	
88.0 |— 2094.4	11 (45.83)		419.0 |— 2431.2	10 (25.00)	
2094.4 |— 4100.8	3 (12.50)		2431.2 |— 4443.4	10 (25.00)	
4100.8 |— 6107.2	4 (16.67)		4443.4 |— 6455.6	14 (35.00)	
6107.2 |— 8113.6	2 (8.33)		6455.6 |— 8467.8	3 (7.50)	
8113.6 |— 10120.0	4 (16.67)		8467.8 |— 10480.0	3 (7.50)	
HAART treated	Yes			Yes	
Median Interval in days of diagnosis of HIV/AIDS and Cancer	1582 (7-9920)			NA	
Median days since cancer diagnosis	1800 (40 - 7488)			NA	
Neoplasms without viral	5	0.007			
Mesenchymal cells	2(40.0)				
Hodgkin lymphoma	1(20.0)				
Colon	1(20.0)				
Epidermoid	1(20.0)				
Viral neoplasms	20	0.0001			
Non-Hodgkin lymphoma	9 (45.0)				
Kaposi's sarcoma	8 (40.0)				
Cervix uteri	2(10.0)				
Anal carcinoma	1(5.0)				

Table 2. Distribution of Genotype Frequency of the *XRCC1* (*Arg399Gln*) Polymorphism and *WRN (Cys1367Arg)* in *HIV/AIDSWC* and *HIV/AIDS* Groups

XRCC1	HIV/AIDSWC (n=24)	HIV/AIDS (n=40)	Prevalence ratio	p-value
Arg/Arg	13 (54.2)	29 (72.5)	2.82	0.24
Arg/Gln	10 (41.6)	11 (27.5)		
Gln/Gln	1(4.2)	0 (0.0)		
WRN	HIV/AIDSWC (n=24)	HIV/AIDS (n=40)	Prevalence ratio	p-value
Cys/Cys	13 (54.2)	40 (100.0)	25.62	0.0001
Cys/Arg	11 (45.8)	0 (0.0)		
Arg/Arg	0 (0.0)	0 (0.0)		

Table 3. Distribution of Allele Frequency of the *XRCC1 (Arg399Gln)* Polymorphism and *WRN (Cys1367Arg)* in *HIV/AIDSWC* and *HIV/AIDS* Groups

XRCC1	HIV/AIDSWC (n=24)	HIV/AIDS (n=40)	Prevalence ratio	p-value
Arg	36(75.0)	69(86.25)	1.82	0.17
Gln	12(25.0)	11(13.75)		
WRN	HIV/AIDSWC (n=24)	HIV/AIDS (n=40)	Prevalence ratio	p-value
Cys	37(77.1)	80(100.0)	18.51	0.001
Arg	11(22.9)	0(0.0)		

p-value= 0.0001) genotype.

The present study also showed that allelic frequency does not increase the risk of cancer in *XCRR1* individually (prevalence ratio= 1.82; p-value= 0.17). Nevertheless, the allelic Arg frequency in *WRN* had an elevated risk of developing cancer (prevalence ratio= 18.51; p-value= 0.001) in the HIV/AIDS group.

Correlation Analysis

The correlation analysis showed no association in the elevated risk of cancer between polymorphisms of the genes *XRCC1* (Arg399Gln) and *WRN* (Cys1367Arg) in relation to sex, male (p-value= 0.63) and female (p-value>1), in the HIV/AIDSWC and HIV/AIDS groups, as shown in Table 4.

Regarding the genotyping polymorphisms of genes *XRCC1* (Arg399Gln) and *WRN* (Cys1367Arg) between the HIV/AIDS and HIV/ AIDSWC groups, a positive association was detected for the elevated risk of cancer in individuals with wild-type homozygous *XRCC1* (Arg399Arg) and heterozygous *WRN* (Cys1367Arg) (p-value< 0.001); heterozygous *XRCC1* (Arg399Gln) and *WRN* (Cys1367Arg) (p-value< 0.001); variant homozygous *XRCC1* (Gln399Gln) and heterozygous *WRN* (Cys1367Arg) (p-value< 0.001).

However, the genotyping heterozygous *XRCC1* (Arg399Gln) and wild-type homozygous *WRN* (Cys1367Cys) (p-value= 0.06); wild-type Homozygous *XRCC1* (Arg399Arg) and wild-type homozygous *WRN* (Cys1367Cys) (p-value> 1) did not show an association with an elevated risk of cancer between the HIV/AIDS and HIV/AIDSWC groups.

Discussion

In this cross-sectional study, HIV/AIDSWC and HIV/AIDS groups obtained the same absolute numbers of males in both groups (75%), with a median age of 45 years. These data are similar to the characteristics of the individuals studied by Fernandes (2012), Yang et al, (2016) and Terra Junior et al. (2016), which also converged data with the amount and types of viral neoplasm and neoplasm without viral found in this study.

Several studies have associated the XRCC1 Gln399Gln genotype with the high risk of specific types of cancer in the general population, such as breast, lung, thyroid,

Table 4. Prevalence Ratio by Poisson Regression with Interaction Model

Factors	Prevalence ratios	Confidence intervals	p-value
[sex=Male]	0.86	0.48 - 1.56	0.63
[sex=Female]	1	ns	ns
[xrcc1=3.00] * [wrn=2.00]	6.13	2.98 - 12.63	<0.001
[xrcc1=2.00] * [wrn=2.00]	5.84	2.81 - 12.10	<0.001
[xrcc1=2.00] * [wrn=1.00]	2.36	0.94 - 5.94	0.067
[xrcc1=1.00] * [wrn=2.00]	5.88	2.85 - 12.10	<0.001
[xrcc1=1.00] * [wrn=1.00]	1	ns	ns

*Interaction; *[XRCC1=1.00]*, Wild-type homozygous; *[XRCC1=2.00]*, Heterozygous; *[XRCC1=3.00]*, Variant homozygous; *[WRN=1.00]*, Wild-type homozygous; *[WRN=2.00]*, Heterozygous

gastric, and prostate cancers, based on the fact that allele 399Gln has more chromosomal breaks per cell than other genotypes that have a greater capacity for DNA repair (Shen et al., 2000; Divine et al., 2001; Wang et al., 2003; Rybicki et al., 2004;. Liu et al., 2013; Yi et al., 2013; Shkarupa et al., 2015). However, our study showed no association between the genotype of XRCC1 (Arg399Gln) and the risk of cancer in individual patients with HIV/AIDS. This result can be explained in the context of the cancers in this study, which are different from those found in the literature and that are common in patients with HIV/AIDS.

The *WRN* gene is associated with the process of genetic stability and DNA repair. Research involving the *WRN* gene for the development of cancer has shown that inactivation or malfunction of the *WRN* gene increases the risk of developing non-Hodgkin lymphomas and sarcomas, since they are the major neoplasms found in patients with HIV/AIDS in the literature and this study (Hill et al., 2006; Shen et al.,2006; Skibola et al., 2007; Fernandes, 2012; Yang et al.,2016;Terra Junior et al.,2016).

In this study the heterozygous genotype polymorphism *WRN* (Cys1367Arg) showed an increased risk of cancer in patients with HIV/AIDS, and the wild-type homozygous genotype showed resistance to the neoplastic process. These data corroborate the results described by Smith et al. (2005), in which the Cys1367 allele and the wild-type homozygous genotype confer a better function of the *WRN* protein, in the process of genetic stability in DNA repair and catalytic activity.

The relation of the proportion of the number of male and female patients with HIV/AIDS and cancer risk is complex, since most studies of this scope have a larger population of men compared to women (Fernandes., 2012; Yang et al., 2016; Terra Junior et al., 2016). In this study, the data were obtained through the interaction of the HIV/AIDSWC and HIV/AIDS groups with sex distribution, and *XRCC1* and *WRN* genes not associated with the increased risk of cancer. In 2015, Castel et al. in their study of the prevalence of cancer in patients with HIV/AIDS no relationship between the sex distribution and the onset of cancer in patients with HIV/AIDS, unlike Yang et al.'s (2016) study, which did find such a relationship.

Previous research showed that the wild-type homozygous *XRCC1* and *WRN* genotypes are less likely to develop cancer (Smith et al., 2005; Jacobs & Bracken, 2012), converging with our data obtained through the statistical interaction model, being the most protective combination of the genotypes. However, the heterozygote *WRN* gene genotype had the highest risk of developing cancer when interacted with all genotypes, which can be explained by the presence of the arginine allele, which has been shown to be associated with the risk of cancer in studies on the polymorphism (Cys1367Arg of the *WRN* gene (Khayat et al., 2005).

The main limitations of the study include a single base hospital for the study. Due to the limited sample, it was not possible to stratify the study population by viral subtype of HIV/AIDSWC and HIV/AIDS groups.

The study associated polymorphisms and DNA repair through *XRCC1* (Arg399Gln) and *WRN* (Cys1367Arg) genes in patients with HIV/AIDS and in patients with HIV/AIDS with cancer. We speculate that there is no increased risk of cancer in patients with HIV/AIDS carriers of the *XRCC1* (Arg399Gln) gene individually. It is speculated that there is a high risk of cancer in patients with HIV/AIDS who have the heterozygous genotype and arginine allele in the *WRN* (Cys1367Arg) gene individually. When the Poisson regression model statistical for interaction was performed between the two genes in this study, patients with HIV/AIDS with the heterozygous genotype in the *WRN* (Cys1367Arg) gene showed a high risk of cancer when it was associated with all genotypes of the *XRCC1* (Arg399Gln) gene.

It is essential to determine the impact of different polymorphisms in the *XRCC1* and *WRN* genes in the process on carcinogenesis in patients with HIV/AIDS.

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Competing Interests

The authors have no conflicts of interest that are directly relevant to the content of this article.

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