Polymorphisms of XRCC1 AND XRCC3 Repair Genes and the Risk of Gastric Cancer in the Amazon Region – Brazil

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Introduction

The human XRCC1 gene is located in the chromosome 19q13.2, consists of 17 exons, and encodes the nuclear protein XRCC1. This protein is composed of 633 amino acids and is involved in base excision repair (BER). In this process, damaged DNA is identified and removed, including oxidized, desaminated or alkylated bases that may be produced spontaneously in the cell or as a result of exposure to exogenous agents such as radiation and UV light [1].

XRCC3 is considered to be one of the most important DNA repair genes. It consists of 7 exons located at 14q32.3 in the human chromosome and encodes a 346-amino acid protein of the same name. This protein, when interacting with Rad51, acts on the repair of double-stranded breaks (DSBs) by homologous recombination (HR), and can also participate in late recombination events, aiding the stabilization of the nucleoprotein complex and the formation of heteroduplex DNA [1-6].

Gastric cancer, despite a decreasing incidence since the 1950s, is still the fourth most common malignant neoplasm and the second largest cause of cancer death worldwide, as survival rates have not changed significantly in the last decades due to the high lethality of the disease [7-9]. The incidence of gastric cancer is higher in developing countries in people over 50 years of age, and men outnumber women by a ratio of 2 to 1. Despite declining rates in Brazil, gastric cancer still remains a disease of high mortality compared to other countries with the same epidemiological profile.

Given the high incidence rates of gastric cancer and mortality in Brazil, especially in the northern region of the country, the present study was aimed at analyzing the relationship of the XRCC1 Arg399Gln and XRCC3 Thr241Met polymorphisms in patients diagnosed with...
gastric cancer in the city of Macapá, in the Amazon region, northern Brazil.

Material and Methods
The case-control study was carried out in the city of Macapá, state of Amapá, Brazil. The total population consisted of 160 DNA samples, of which 100 were healthy individuals (controls) and 60 of patients diagnosed with gastric cancer and treated at the High Complexity Oncology Unit (Unidade de Alta Complexidade em Oncologia - UNACON) of Dr. Alberto Lima Clinical Hospital and the Institute of Hematology and Hemotherapy of Amapá (HEMOAP). The study was approved by the Research Ethics Committee (REC) of the Federal University of Amapá (UNIFAP) and was carried out in accordance with the Helsinki Principle Declaration. All individuals signed the Informed Consent Form (ICF).

Genotyping
DNA was isolated according to the manufacturer's instructions (Invitrogen). Samples were amplified and analyzed by PCR-RFLP. The amplification reaction of the Polymerase Chain Reaction (PCR) of the XRCC3 gene followed Shen, et al [4] and Cabral et al. [10]. The primers used to amplify the 208 bp fragment were 241F: 5-GCTGTTCGGGGCATGGTCTC-3 and 241R: 5 ACGAGCTCAGGGGTGCAACC-3 and the enzyme Nla III (New England Biolabs, Beverly, MA) was used. The identification of the XRCC1 polymorphism was carried out according to Vieira, (2010) and Rodrigues, et. al. (2015). The primers used to identify the 615pb fragment were 399F 5'TTGTGCTTTCTCTGTGTCCA3' and 399R 5'TCCTC-CAGCCTTTTCTGATA 3', and the restriction enzyme was Msp I. The amplified fragments were visualized by 2% agarose gel electrophoresis. The digestion of products followed the recommendation of the manufacturer of each enzyme.

Statistical Analysis
The comparison between genotype frequencies of the control and patients samples was performed using the statistical software Bio Estat 5.3 (Ayres, M. Pará, Brazil). where the was used the Fisher exact test and odds ratios (OR) with a 95% confidence interval (CI) were calculated.

Results and Discussion
The present study investigated the association between XRCC1 Arg399Gln and XRCC3 Thr241Met polymorphisms and gastric cancer in the city of Macapá, northern Brazil. Gastric cancer is the third most frequent type of cancer in the city of Macapá, the second most frequent in men, after prostate cancer, in Northern and Northeastern Brazil, and the fourth most frequent in these regions in women [11-14]. According to the Mortality Information System (MIS), the number of deaths reported in 2013 was 14,182, of which 9,142 were men and 5,040, women [12]. Table 1 and 2 shows our results.

Our results demonstrate that of the 60 samples of patients diagnosed with gastric cancer, 25 (41.6%) and 38 (63.8%) exhibited Arg399Gln and Thr241Met polymorphisms, respectively. Several studies have described the association of these two polymorphisms with malignant neoplasms [10,15,16].

Studies on these polymorphisms in specific populations are needed due to wide regional differences regarding the risk of developing cancer. Our research group previously found strong evidence that they may be associated with gastric cancer in this population [10, 15, 16].

Our results revealed that 58.3% of patients had the Thr/Met genotype, and 41.6% the Arg/Gln genotype. Our results confirm the involvement of these polymorphisms with this malignant disease [10,15,16].

Our findings support other studies already conducted on the association between XRCC3 polymorphism and the risk of gastric cancer. Although polymorphic genotype was found at a high frequency in the patients examined, further molecular studies are needed on the Thr241Met genotype and the risk of developing gastric cancer in this and other populations for greater reliability between the association of this polymorphism and the risk of gastric cancer.

Our results show that probably people with the Arg/Gln genotype show greater susceptibility to the development of some form of cancer. Thus, we can also consider the 399Gln polymorphism a possible genetic marker for use in can- cer prognosis, yet it is undoubtedly necessary to increase the number of cases and controls.

Given that gastric cancer is the third most frequent type in the state of Amapá (INCA, 2016), studies examining the association between molecular alterations and this disease may assist the description of the clinical picture of patients and the correct treatment. Our study demonstrated that most gastric cancer patient samples analyzed exhibited XRCC1 Arg399Gln and XRCC3 Thr241Met polymorphisms. Because of the small sample size, additional data are being gathered. Despite that, our findings revealed an early association between polymorphisms and gastric cancer in the study population.

Our goal is to apply these and additional results in the future and thus to benefit and assist in the treatment of each patient, since environmental factors of exposure as well as genetic alterations in other genes acting alone or interacting with each other may increase the risk of developing gastric cancer.

Consent
The author declare that written informed consent was obtained from all the patient.
Gastric cancer patients (n=60) | Control group (n=100)
---|---
Gene with SNP | % | Without SNP | % | with SNP | % | Without SNP | % | p-value
---|---|---|---|---|---|---|---|---|---
XRCC1 | 25 | 41.6 | 35 | 58.3 | 30 | 30 | 70 | 70 | 0.1828
XRCC3 | 38 | 63.3 | 22 | 36.6 | 10 | 10 | 90 | 90 | 0.0001

Table 1. Frequency of XRCC1 Arg399Gln and XRCC3 Thr241Met polymorphisms in the patients and controls samples

<table>
<thead>
<tr>
<th>Genotypes</th>
<th>Patients</th>
<th>%</th>
<th>Control</th>
<th>%</th>
<th>OR (CI 95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>XRCC1(G399A)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Reference</td>
</tr>
<tr>
<td>Arg/Arg</td>
<td>35</td>
<td>583</td>
<td>70</td>
<td>70</td>
<td>-</td>
</tr>
<tr>
<td>Arg/Gln</td>
<td>25</td>
<td>41.6</td>
<td>29</td>
<td>29</td>
<td>1.7241(0.8810-3.3741) p=0.1544</td>
</tr>
<tr>
<td>Arg/Gln</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td><strong>XRCC3(C241T)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Reference</td>
</tr>
<tr>
<td>Thr/Thr</td>
<td>22</td>
<td>36.6</td>
<td>83</td>
<td>83</td>
<td>-</td>
</tr>
<tr>
<td>Thr/Met</td>
<td>35</td>
<td>58.3</td>
<td>7</td>
<td>7</td>
<td>18.8636(7.3849-48.18433) p ≤ 0.0001</td>
</tr>
<tr>
<td>Met/Met</td>
<td>3</td>
<td>5</td>
<td>3</td>
<td>3</td>
<td>3.7727(0.7117-19.9998) p=0.2484</td>
</tr>
</tbody>
</table>

Table 2. Genotype frequency of XRCC1 and XRCC3 gene polymorphisms in the patients and controls

Ethical Approval
The author hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Reference

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