Polymorphisms of DNA repair genes \textit{XRCC1} and \textit{XRCC3}, interaction with environmental exposure and risk of chronic gastritis and gastric cancer

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INTRODUCTION

DNA repair pathways are responsible for maintaining the integrity of the genome in face of environmental insults and general DNA replication errors, playing a role in protecting it against mutations that lead to cancer[3]. So, polymorphisms of DNA repair enzymes, which may alter the function or efficiency of the DNA repair, may contribute to an increased risk of environmental carcinogenesis[3]. These low-penetrance susceptibility genes have common variants and interact with environmental factors, contributing as a major factor to the populational incidence of cancer[3]. Several polymorphisms in genes that participate in different DNA repair pathways, such as \textit{XRCC1}, \textit{XRCC2}, \textit{XRCC3}, \textit{hOGG1}, \textit{XRCC4}, \textit{XRCC5}, and \textit{XRCC6}, have been identified and related to cancer susceptibility.

The \textit{XRCC1} gene is responsible for a scaffolding protein that directly associates with other proteins such as DNA polymerase β, PARP (ADP-ribose polymerase) and DNA ligase III in a complex, to facilitate the processes of base excision repair (BER) or single-strand break repair[8]. The BER pathway repairs DNA damage caused by a variety of endogenous and exogenous factors, including oxidation, alkylating agents and ionizing radiations[9]. The \textit{XRCC1} protein can bind directly to both gapped and nicked DNA, as well as to gapped DNA associated with DNA

Abstract

AIM: To evaluate the association between polymorphisms \textit{XRCC1} Arg194Trp and Arg399Gln and \textit{XRCC3} Thr241Met and the risk for chronic gastritis and gastric cancer, in a Southeastern Brazilian population.

METHODS: Genotyping by PCR-RFLP was carried out on 202 patients with chronic gastritis (CG) and 160 patients with gastric cancer (GC), matched to 202 (C1) and 150 (C2) controls, respectively.

RESULTS: No differences were observed among the studied groups with regard to the genotype distribution of \textit{XRCC1} codons 194 and 399 and of \textit{XRCC3} codon 241. However, the combined analyses of the three variant alleles (194Trp, 399Gln and 241Met) showed an increased risk for chronic gastritis when compared to the GC group. Moreover, an interaction between the polymorphic alleles and demographic and environmental factors was observed in the CG and GC groups. \textit{XRCC1} 194Trp was associated with smoking in the CG group, while the variant alleles \textit{XRCC1} 399Gln and \textit{XRCC3} 241Met were related with gender, smoking, drinking and \textit{H pylori} infection in the CG and GC groups.

CONCLUSION: Our results showed no evidence of a relat-ionship between the polymorphisms \textit{XRCC1} Arg194Trp and Arg399Gln and \textit{XRCC3} Thr241Met and the risk of chronic gastritis and gastric cancer in the Brazilian population, but the combined effect of these variants may interact to increase the risk for chronic gastritis, considered a premalignant lesion. Our data also indicate a gene-environment interaction in the susceptibility to chronic gastritis and gastric cancer.
polymerase β, suggesting that this protein might be independently involved in DNA damage recognition. Two polymorphisms, more often found in XRCC1 conserved sites, lead to a C→T substitution at codon 194 in exon 6 and to a G→A substitution at codon 399 in exon 10 of the gene, leading to the amino acid alterations arginine (Arg) to tryptophan (Trp) and arginine (Arg) to glutamine (Gln), respectively. These changes in conserved protein sites may alter the BER capacity, increasing the chances of DNA damage.

The Arg399Gln variant is more frequent and has been associated mainly with head and neck, colorectal, gastric, esophageal, breast and lung cancers. The Arg194Trp polymorphism has been related to colorectal, gastric, head and neck and skin cancers.

Protein XRCC3 functions in the DNA double-strand break (DSB) and cross-link repair and interacts and stabilizes Rad51, one of the key components of the homologous repair (HR) pathway. The HR pathway uses a second intact copy of a homologous chromosome as a template to copy the information lost at the DSB site, generating a fragment of 615 and 491 bp, respectively. These changes in conserved protein sites may alter the BER capacity, increasing the chances of DNA damage.

So far, the investigations about interactions between XRCC1 and XRCC3 polymorphisms and environmental carcinogenesis have produced scarce and conflicting results, showing the functional complexity of these variants, that can include their interaction with environmental factors, thus modulating the susceptibility to cancer. Regarding gastric cancer, only a few studies were conducted to investigate its association with XRCC1 and XRCC3 variants.

In Brazil, gastric cancer is still one of the most frequent types of cancer. The estimate for 2005 points to the fourth place in incidence and mortality, with about 23,000 new cases and 12,000 deaths. However, multiple factors are thought to play a role in gastric carcinogenesis, including diet, lifestyle, pathological changes in the stomach such as chronic gastritis, and genetic alterations, besides the infection by Helicobacter pylori, the first bacterium to be termed as a definitive cause of cancer.

Thus, we conducted a study to evaluate the association between the polymorphisms XRCC1 Arg194Trp and Arg399Gln and XRCC3 Thr241Met and the risk of chronic gastritis and gastric cancer in a Brazilian population, as well as the interaction between these polymorphisms and environmental factors involved in gastric carcinogenesis.

MATERIALS AND METHODS

Subjects
This was a case-control study on chronic gastritis and gastric cancer. The case groups comprised 202 patients with a histopathologically confirmed diagnosis of chronic gastritis (100 men and 102 women), with a mean age of 52 years (range 19-86 years), and 160 patients with a histopathologically confirmed diagnosis of gastric adenocarcinoma (118 men and 42 women), with a mean age of 61 years (range 28-93 years). All subjects were recruited from the Hospital de Base in São José do Rio Preto, SP, and from the Pio XII Foundation in Barretos, SP, Brazil. Gastric adenocarcinomas were classified as diffuse or intestinal types, according to the classification proposed by Lauren, and the chronic gastritis cases according to the Sidney System. H pylori infection was histologically established by the Giemsa staining technique. Two cancer-free control groups with no previous history of gastric disease were matched to the case groups with respect to age, gender and ethnicity. The control groups were composed of 200 healthy individuals (100 men and 102 women) with a mean age of 51 years (range 20-85 years), and the control group for gastric cancer (C2) consisted of 150 healthy volunteers (108 men and 42 women) with a mean age of 59 years (range 22-93 years). Epidemiological data on the study population were collected using a standard interviewer-administered questionnaire, with questions about current and past occupation, smoking habits, alcohol intake and family history of cancer. This work was approved by the National Research Ethics Committee and written informed consent was obtained from all individuals.

DNA extraction and genotype analyses
About 5 mL of whole blood were collected from all study participants in sterile EDTA-coated vacutainers. The samples were assigned a unique identifier code. DNA was extracted according to Abdel-Rahman et al. and stored at -20 ºC until used for genotyping.

Genotypic analyses of the XRCC1 gene were carried out by multiple PCR-RFLP, using primers for codons 399 (F 5'-TGTGTCCTTCTGTTCCACA-3' and R 5'-CTCTTCACCTTTCTGATA-3') and 194 (F 5'-GCCCCGTCCCAGGTA-3' and R 5'-AGCCCCAAGTCCCTTTGACT-3'), which generate a fragment of 615 and 491 bp, respectively, as previously described with modifications. Briefly, PCR was performed in 25 μL reaction buffer containing 12.5 pmol each primer, 0.2 mmol/L of dNTPs, 3 mmol/L of MgCl₂, about 100 ng DNA and 1 U of Taq DNA polymerase. The PCR products were digested overnight with 10 U of MspI at 37 °C. The wild-type Arg allele for codon 194 is identified by the presence of a 293 bp band, and the mutant Trp allele by the presence of a 313 bp band (indicative of the absence of the MspI cutting site). For codon 399, the presence of two bands of 375 and 240 bp, respectively, identifies the wild-type Arg allele, while the uncut 615 bp band identifies the mutant Gln allele (indicative of the absence of the MspI cutting site). A 178 bp band, resulting from an additional invariant MspI cutting site in the 491 bp amplified fragment, is always present and serves as an internal control for complete enzyme digestion.

Polymorphism of the XRCC3 gene was deter-
mained by PCR-RFLP, using codon 241 primers (F - 5' GCCTGGTGGTCATCGACTC 3' e R - 5' ACAGGGCTCTGGAAGGCACT GCTCAGTCTACGACC 3'), as previously described by David-Beabes et al.[42]. The 25 μL PCR mixture contained about 100 ng of DNA, 12.5 pmol of each primer, 0.2 mmol/L of dNTPs, 2 mmol/L of MgCl₂ and 1 U of Taq DNA polymerase. The 552 bp amplified product was digested overnight with 5 U of NlaIII at 37 ºC. The wild-type allele Thr was identified by the presence of two 239 and 313 bp bands, while the mutant allele Met was represented by 105, 208, and 239 bp bands.

Statistical analysis
Chi-square or Fisher's exact tests were utilized to compare the groups with regard to genotype frequencies and putative risk factors such as age, gender, ethnicity, smoking, drinking, H pylori infection and histological type of adenocarcinoma. To investigate the gene-environment interactions, the odds ratios (OR) and their 95% confidence intervals (95% CI) were calculated, according to a combination of the XRCC1 and XRCC3 polymorphisms with putative risk factors. The statistical analyses were performed using Statdisk and GraphPad InStat computer software programs. A probability level (P) of less than 0.05 was used as criterion of significance.

RESULTS
Cases and controls did not show any statistically significant difference with regard to age, gender and ethnicity, indicating a well-matched study population. Gastric cancer (GC) patients were more likely to be cigarette smokers or alcohol drinkers than chronic gastritis (CG) patients and controls (C2), and this difference was statistically significant (P<0.05), the same occurring with CG patients when compared to controls (C1).

The XRCC1 and XRCC3 genotypes and the allele frequency distributions among cases and controls are presented in Table 1. The allele frequencies of polymorphisms 194Trp, 399Gln and 241Met were similar in cases and controls, not showing any statistically significant

| Table 1 | XRCC1 and XRCC3 allele frequencies in patients with chronic gastritis (CG) and gastric cancer (GC) and in the respective control groups C1 and C2 |
|---------|-------------------------------------------------|-------------------------------------------------|----------|-------------------------------------------------|-------------------------------------------------|----------|
| Genotypes | CG (n = 202) | C1 (n = 202) | P | GC (n = 160) | C2 (n = 150) | P |
| XRCC1 | | | | | | |
| Codon 194 | | | | | | |
| Arg/Arg | 176 (87.1) | 183 (90.6) | 140 (87.5) | 130 (86.7) | | |
| Trp/Trp | 26 (12.9) | 19 (9.4) | 0.2683 | 20 (12.5) | 20 (13.3) | 0.8269 |
| Allele frequency | 0.07 | 0.05 | 0.06 | 0.07 | | |
| XRCC3 | | | | | | |
| Codon 399 | | | | | | |
| Arg/Arg | 98 (48.5) | 95 (47) | 73 (45.6) | 70 (46.7) | | |
| Arg/Gln | 91 (45.0) | 82 (40.6) | 67 (41.9) | 57 (38.0) | | |
| Gln/Gln | 13 (6.5) | 25 (12.4) | 0.7651 | 20 (12.5) | 23 (15.3) | 0.5035 |
| Allele frequency | 0.29 | 0.33 | 0.33 | 0.34 | | |
| XRCC3 | | | | | | |
| Codon 241 | | | | | | |
| Thr/Thr | 92 (45.5) | 84 (41.6) | 84 (52.5) | 67 (44.7) | | |
| Thr/Met | 81 (40.1) | 89 (44.1) | 53 (33.1) | 60 (40.9) | | |
| Met/Met | 29 (14.4) | 29 (14.3) | 0.4221 | 23 (14.4) | 23 (15.3) | 0.1679 |
| Allele frequency | 0.34 | 0.36 | 0.31 | 0.35 | | |

| Table 2 | Association between XRCC1 and XRCC3 genotype profiles and risk for chronic gastritis (CG) and gastric cancer (GC) |
|---------|-------------------------------------------------|-------------------------------------------------|----------|-------------------------------------------------|-------------------------------------------------|----------|
| XRC1XRC3 | | | | | | |
| Codon 194 | | | | | | |
| Arg/Thr | 33 | 32 | 1.0 (reference) | 33 | 34 | 1.0 (reference) | 32 | 23 | 1.0 (reference) | | |
| One variant polymorphism | | | | | | |
| Arg/Thr | 5 | 8 | 0.6 (0.17-2.04) | 0.5469 | 5 | 6 | 1.2 (0.32-4.16) | 1.0000 | 8 | 6 | 1.1 (0.32-3.44) | 1.0000 |
| Arg/Gln | 51 | 38 | 1.4 (0.68-2.50) | 0.5124 | 51 | 42 | 0.8 (0.42-1.51) | 0.5234 | 38 | 34 | 1.2 (0.63-2.50) | 0.5918 |
| Arg/Met | 50 | 27 | 2.0 (0.91-3.57) | 0.1237 | 50 | 49 | 1.0 (0.51-1.75) | 1.0000 | 27 | 34 | 2.0 (0.83-3.70) | 1.0426 |
| Two variant polymorphisms | | | | | | |
| Arg/Gln | 3 | 5 | 0.6 (0.13-2.63) | 0.7106 | 3 | 2 | 0.6 (0.1-4.16) | 1.0000 | 5 | 4 | 1.1 (0.16-5.45) | 1.0000 |
| Arg/Met | 4 | 3 | 1.0 (0.50-1.85) | 1.0000 | 43 | 58 | 1.4 (0.69-2.43) | 0.4309 | 43 | 39 | 1.2 (0.63-2.50) | 0.5389 |
| Three variant polymorphisms | | | | | | |
| Arg/Gln | 6 | 10 | 0.6 (0.17-2.04) | 0.0372 | 8 | 5 | 0.6 (0.17-2.04) | 0.5400 | 1 | 3 | 5.0 (0.40-50.0) | 0.3113 |
differences ($P>0.05$). However, a combined analysis of the XRCC1 Arg194Trp and Arg399Gln polymorphisms and the XRCC3 Thr241Met polymorphism (Table 2), and the assessment of the inter- and intra-gene interactions of these three polymorphisms revealed a statistically significant ($P = 0.0372$) association when the three variant alleles interacted in the chronic gastritis group, as compared to the gastric cancer group. Other combinations did not show any significant difference. The banding patterns of XRCC1 Arg194Trp and Arg399Gln and of XRCC3 Thr241Met are represented in Figure 1.

Table 3 shows the associations of the different genotypes with the variables gender, smoking, drinking and H pylori infection, among the groups. For this analysis, we combined the heterozygous and mutant homozygous genotypes. Allele 194Trp was associated with smoking, with an increased OR for chronic gastritis (4.16, 95%CI = 1.16-16.66), when we compared the CG and C1 groups. The comparison between the CG and GC groups revealed that in men who were smokers and drinkers there was an association with increased OR’s for gastric cancer in the individuals with the alleles XRCC1 399Gln (3.03,

Table 3  Association of heterozygous and mutant homozygous to the polymorphisms of codons 194 and 399 of the XRCC1 gene and to the codon 241 of the XRCC3 gene with demographic and environmental risk factors in chronic gastritis (CG) and gastric cancer (GC) patients and the respective control groups C1 and C2

<table>
<thead>
<tr>
<th>Groups</th>
<th>Gender</th>
<th>Smoke</th>
<th>Drink</th>
<th>H pylori infection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male n (%)</td>
<td>Female n (%)</td>
<td>n (%)</td>
<td>Yes n (%)</td>
</tr>
<tr>
<td>XRCC1</td>
<td>Arg194Trp *</td>
<td>C1</td>
<td>10 (52.6)</td>
<td>9 (47.4)</td>
</tr>
<tr>
<td></td>
<td>Trp194Trp</td>
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<td>P = 0.0250</td>
<td>P = 0.4355</td>
</tr>
<tr>
<td>XRCC3</td>
<td>Arg399Gln *</td>
<td>CG</td>
<td>55 (52.9)</td>
<td>49 (47.1)</td>
</tr>
<tr>
<td></td>
<td>C1</td>
<td>52 (48.9)</td>
<td>55 (51.1)</td>
<td>68 (63.6)</td>
</tr>
<tr>
<td></td>
<td>P = 0.0005</td>
<td>P = 0.0084</td>
<td>P = 0.0001</td>
<td>P = 0.004</td>
</tr>
<tr>
<td></td>
<td>Met241Met</td>
<td>CG</td>
<td>57 (51.8)</td>
<td>53 (48.2)</td>
</tr>
<tr>
<td></td>
<td>C1</td>
<td>59 (77.6)</td>
<td>17 (22.4)</td>
<td>21 (27.6)</td>
</tr>
<tr>
<td></td>
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<td>P = 0.0494</td>
<td>P = 0.0019</td>
<td>P = 0.0175</td>
</tr>
<tr>
<td>XRCC3</td>
<td>Thr241Met</td>
<td>CG</td>
<td>57 (51.8)</td>
<td>53 (48.2)</td>
</tr>
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<td></td>
<td>C1</td>
<td>59 (77.6)</td>
<td>17 (22.4)</td>
<td>21 (27.6)</td>
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<td></td>
<td>P = 0.0738</td>
<td>P = 0.0010</td>
<td>P = 0.0110</td>
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</tr>
<tr>
<td></td>
<td>Met241Met</td>
<td>CG</td>
<td>57 (51.8)</td>
<td>53 (48.2)</td>
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<tr>
<td></td>
<td>C1</td>
<td>59 (77.6)</td>
<td>17 (22.4)</td>
<td>21 (27.6)</td>
</tr>
<tr>
<td></td>
<td>P = 0.3458</td>
<td>P = 0.0031</td>
<td>P = 0.0000</td>
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</table>

Figure 1 PCR-RFLP of XRCC1 and XRCC3 genes. A: XRCC1 gene. Lane 1: molecular weight marker. Lane 2: wild-type homozygous codons 194 and 399. Lane 3: wild-type homozygous codon 194 and heterozygous codon 399. Lane 4: mutant homozygous codon 194 and wild-type homozygous codon 399. Lane 5: heterozygous codon 194 and wild-type homozygous codon 399. Lane 6: wild-type homozygous codon 194 and mutant homozygous codon 399. B: XRCC3 gene. Lane 1: molecular weight marker. Lanes 2 and 5: heterozygous codon 241. Lane 3: wild-type homozygous codon 241. Lane 3: wild-type homozygous codon 241. Lane 4: mutant homozygous codon 241.
that investigated the role of the allele with regard to gastric antral cancer. The only study suggested that the 194Trp allele might be a protective risk of gastric cancer in a Korean population, but the differences observed in these reports may be due to the presence of variants of the common susceptibility polymorphisms, not just a single one, but DNA repair genes or activation and detoxification genes may jointly contribute to the susceptibility of gastric and other cancers. Thus, it is important to include more gene polymorphisms for the same or other DNA repair pathways to verify the gene-gene interactions, as well as the gene-environment interactions that may be important in the etiology of the disease.

When we assessed the association of XRCC1 Arg194Trp and Arg399Gln and XRCC3 Thr241Met with the risk of chronic gastritis and gastric cancer, we found an increased risk for chronic gastritis when all three variant alleles were present at the same time, supporting the hypothesis of an additive effect of these three polymorphisms. There are no studies on chronic gastritis regarding its association with DNA repair gene polymorphisms, as there are for several metabolizing genes, such as GSTM1, GSTT1 and CYP2E1, in Brazilian and Chinese populations. Chronic gastritis, a frequent inflammation of the stomach, is considered a premalignant lesion. Gastritis may start after an H pylori infection and progress over time from an initially superficial form to more severe forms, including severe atrophic gastritis with intestinal metaplasia. About 10% of patients with gastric atrophy develop gastric cancer within a time period of 15 years. Therefore, a reduced DNA repair capacity due to variant alleles may allow mutations to accumulate in the DNA of the epithelial cells of the stomach, resulting from the inflammatory process caused by H pylori or from environmental factors such as dietary habits and lifestyle, increasing the risk of gastric cancer.

Gastric cancer has a complex etiology in which genetic and environmental factors play an important role. In this study, we observed a statistically significant association between variant alleles and demographic and environmental factors such as gender, smoking, drinking and H pylori infection.

It is known that H pylori infection has a very important role in the development of chronic gastritis and in its development into gastric cancer. Various mechanisms were proposed for H pylori-associated carcinogenesis, such as the formation of DNA adducts, the generation of free radicals, and a dysregulation of the gastric epithelial cell cycle. So, these factors, associated with a decreased DNA repair capacity, may increase the risk for gastric cancer. Differently from these findings, we found a high frequency of variants 399Gln and 241Met
in *H. pylori*-negative gastric cancer patients, as compared to
chronic gastritis patients. However, these data must have been
influenced by the great number of *H. pylori*-negative
individuals, as compared to the *H. pylori*-positive individuals
found in the gastric cancer group, probably due to an
underestimate of the histological diagnosis in these
patients.

In smokers, the presence of *XRCC1* 194Trp was more
frequent in chronic gastritis cases, while polymorphisms
*XRCC1* 399Gln and *XRCC3* 241Met were more frequent
in both the chronic gastritis and the gastric cancer groups,
compared with healthy controls. Whether the mechanisms
of tobacco carcinogens act in human gastric cancer is
currently uncertain. The main carcinogens contained
in tobacco smoke include polyaromatic hydrocarbons
(PAH), N-nitrosamines and aromatic amines. Cigarette
smoking increases the number of single-strand breaks and
dNA adducts, which, if left unrepaired, can lead to
gene mutation[51]. These DNA damages can be repaired
by BER, in which the *XRCC1* protein has an important
role. Functional studies of *XRCC1* variants observed a
significantly elevated level of sister chromatid exchange
(SCE) in peripheral blood lymphocytes after in vitro
exposure to the tobacco-specific NNK in carriers of the
399Gln allele, but the same was not observed for the
194Trp polymorphism[52]. Duell et al.[53] reported higher
frequencies of SCE for current smokers with the 399Gln
polymorphism than for smokers with the Arg/Arg
genotype.

Protein *XRCC3* participates in the DSB repair by the
homologous repair pathway and the 241Met variant may
lead to biological implications for the enzyme’s function
and/or the interaction with other proteins involved in
dNA damage repair. Matullo et al.[54] associated the 241Met
polymorphism with 3’-DNA adduct levels, indicating a
possible role of the *XRCC3* gene in the repair of bulky
dNA adducts. Thus, variations in DNA repair capacity
caused by polymorphisms of DNA repair genes may
modulate the genotoxic effect of tobacco smoking.

Excessive alcohol consumption can also lead to
dNA damage through the production of free radical
intermediates, such as reactive oxygen species, which are
produced during the ethanol metabolism[55]. The frequency
of DNA single-strand breaks also increases with chronic
exposure to alcohol[56]. We observed an association with
alcohol consumption in the patients with chronic gastritis
and gastric cancer, and found an increased risk for these
diseases when polymorphisms *XRCC1* 399Gln and
*XRCC3* 241Met were present.

In conclusion, in the Brazilian population studied,
we did not find evidence of a relationship between the
polymorphisms *XRCC1* Arg194Trp and Arg399Gln and
*XRCC3* Thr241Met and the development of chronic
gastritis and gastric cancer. However, intra- and
inter-gene interactions may contribute to the development
of chronic gastritis, a precursor lesion of stomach cancer.
We also verified a gene-environment interaction between
the *XRCC1* and *XRCC3* polymorphisms, mainly with the
habits of smoking and drinking, in the chronic gastritis
and gastric cancer patients. Our study is an important
addition to the small number of previously published
reports on DNA repair gene variants in gastric cancer
and shows the need for further studies in different
populations, to elucidate the role of these polymorphisms
in carcinogenesis.

ACKNOWLEDGMENTS

We thank Prof. Dr. Antonio José Manzato for assistance
with the statistical analysis.

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