RESEARCH ARTICLE

XRCC1 and ADPRT Polymorphisms Associated with Survival in Breast Cancer Cases Treated with Chemotherapy

Sheng Ye¹*, Jian Rong²*, Shao-Hong Huang³, Zhou-San Zheng¹, Miao Yun¹, Shen-Ming Wang⁴*

Abstract

Aim: To investigate whether XRCC1 and ADPRT polymorphisms might be associated with outcomes of breast cancer. Methods: A prospective study was conducted with a total of 335 breast cancer patients undergoing chemotherapy consecutively collected from Jan. 2005 to Jan. 2008. Genotyping of XRCC1 and ADPRT polymorphisms was conducted by PCR-RFLP assay. Results: All 335 patients were followed up until death or the end of Jan. 2012, with a median follow-up period of 38.8 (2-64) months. It was shown that the variant genotype of XRCC1 399Gln/Gln was strongly significantly associated with a decreased risk of death from breast cancer, with an HR (95% CI) of 0.52 (0.28-0.91). Similarly, individuals carrying the ADPRT 762Ala/Ala demonstrated longer survival compared to ADPRT 762 Val/Val, with an HR (95% CI) of 0.58 (0.31-0.97). Individuals with combination genotypes of XRCC1 399Gln allele and ADPRT 762Ala/Ala presented with a longer survival, the HR (95% CI) being 0.56 (0.32-0.97). Conclusion: We found a significant association between XRCC1 399Gln/Gln and ADPRT 762Ala/Ala polymorphisms and clinical outcomes. These two genotypes could be used as a surrogate markers of clinical outcome in glioma cases receiving chemotherapy.

Keywords: Breast cancer - XRCC1 - ADPRT - polymorphism - outcome

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Introduction

Breast cancer is the most common cancer in women. It is estimated 1.38 million new cancer cases diagnosed in 2008 (23% of all cancers), and ranks second overall (10.9% of all cancers). It is now the most common cancer both in developed and developing regions with around 690000 new cases estimated in each region (population ratio 1:4) (IARC, 2008). In China, breast cancer is the most common type of cancer among women, with an incidence of 14.2/105, it is also one of the most leading causes of death in Chinese women (IARC, 2008). Although the major prognostic factors for breast cancer is the cancer stage, there are differences in survival among breast cancer patients with similar disease stages. Recently, a number of studies have revealed that polymorphisms in certain genes, especially DNA repair genes, have a role in tumor response to chemotherapy and thus survival variability among individual patients (Ang et al., 2011; Giovannetti et al., 2011; Liu et al., 2012; Wu et al., 2012). Therefore, better understanding of prognostic factors would be helpful for individualizing breast cancer treatment.

The DNA repair gene products can recognize and repair damaged DNA induced by autologous cells or environmental agents. Impaired DNA repair ability can increase genomic instability and tumorigenesis. Thus, single nucleotide polymorphisms in DNA repair genes can impair DNA repair mechanisms (Qiao et al., 2002). Studies have shown that DNA repair gene polymorphisms may promote cancer progression and thus develop more aggressive tumors (Kudo et al., 2012). These DNA Repair gene polymorphisms may lead to different responses to platinum-based chemotherapy by affecting the gene products’ capacity to remove anthracycline-DNA adducts (Kang et al., 2012). X-ray repair cross-complementing group 1 (XRCC1) and adenosine diphosphate ribosyl transferase (ADPRT) are two important genes in the DNA repair process. ADPRT specifically binds to DNA strand breaks, where it is autoactivated and recruits the XRCC1-Ligase IIIα complex to stimulate BER, causing XRCC1 to interact with ADPRT to recruit other partner proteins such as DNA polymerase β (Ploβ) to execute BER (Masson et al., 1998; Keith et al., 2003). For this reason, functional variants of XRCC1 and ADPRT may alter BER function and affect the outcome of breast cancer. Thus, we conducted a prospective study in 516 breast cancer patients to investigate whether XRCC1 and ADPRT polymorphisms were associated with outcomes of breast cancer.

Materials and Methods

Study Subjects

A prospective study design was conducted in our study.
Breast cancer patients were consecutively recruited at the First Affiliated Hospital of Sun-Yat Sen University from Jan. 2005 to Jan. 2008. All hospital patients with newly diagnosed primary breast cancer were asked to participate within one month after diagnosis, and all cases were histologically or clinically confirmed. Informed consent was obtained before each interview and blood draw. A total of 361 patients were included in our hospital, and only 335 patients agreed to participate in this study, with a participation rate of 92.8%.

Patients who received anthracycline-based chemotherapy were included in our study. Anthracycline-based chemotherapy included cyclophosphamide (C), the anthracycline agent (E or A), and/or 5-fluorouracil (F), (CEF and CAF regimens) combined with radiotherapy.

Genotyping

DNA samples were obtained from stored blood samples using Qiagen standard protocols (Shanghai, China). Genotyping for XRCC1 Arg194Trp, XRCC1Arg399Gln and ADPRT Val762Al polymorphisms was done by PCR-RFLP assay according to a previous study (Guo et al., 2008). The forwards and reverse primers of XRCC1 Arg194Trp were 5'-GCC AGG GCC CCT CCT TCA A-3' and 5'-TCC AGC CTT TTC TGA TA-3', respectively; For XRCC1 Arg399Gln, primers were 5'-TTG TGC TTT CTC TGT GTC CA-3' and 5'-TCC GAG GCC CCT CCT TCA T-3', respectively; For XRCC1 Arg394Trp, primers were 5'-CTA TCA TCT CCT GGC CCC TCC AGC CTT TTC TGA TA-3', respectively; For XRCC1 Arg399Gln, primers were 5'-CTA TCA TCT CCT GGC CCC TCC AGC CTT TTC TGA TA-3', respectively; For XRCC1 Arg394Trp, primers were 5'-TTG TGC TTT CTC TGT GTC CA-3' and 5'-TCC GAG GCC CCT CCT TCA T-3', respectively; For XRCC1 Arg399Gln, primers were 5'-CTA TCA TCT CCT GGC CCC TCC AGC CTT TTC TGA TA-3', respectively; For XRCC1 Arg394Trp, primers were 5'-TTG TGC TTT CTC TGT GTC CA-3' and 5'-TCC GAG GCC CCT CCT TCA T-3', respectively; For XRCC1 Arg399Gln, primers were 5'-CTA TCA TCT CCT GGC CCC TCC AGC CTT TTC TGA TA-3', respectively; For XRCC1 Arg394Trp, primers were 5'-TTG TGC TTT CTC TGT GTC CA-3' and 5'-TCC GAG GCC CCT CCT TCA T-3', respectively; For XRCC1 Arg399Gln, primers were 5'-CTA TCA TCT CCT GGC CCC TCC AGC CTT TTC TGA TA-3', respectively; For XRCC1 Arg394Trp, primers were 5'-TTG TGC TTT CTC TGT GTC CA-3' and 5'-TCC GAG GCC CCT CCT TCA T-3', respectively; For XRCC1 Arg399Gln, primers were 5'-CTA TCA TCT CCT GGC CCC TCC AGC CTT TTC TGA TA-3', respectively; For XRCC1 Arg394Trp, primers were 5'-TTG TGC TTT CTC TGT GTC CA-3' and 5'-TCC GAG GCC CCT CCT TCA T-3'.
outcome and longer survival compared to ADPRT 762 Val/Val, with HR (95% CI) of 0.58 (0.31-0.97). However, we did not find a significant decreased risk of death from breast cancer among patients with XRCC1 Arg280His allele and ADPRT Val762Ala polymorphism. We further identified the combination effect of XRCC1 Arg399Gln and ADPRT Val762Ala genotypes on the prognosis of breast cancer. The results showed individuals with combination genotypes of XRCC1 399Gln allele and ADPRT 762Ala/Ala presented decreased risk of death from breast cancer, with the HR (95% CI) of 0.56 (0.32-0.97).

### Discussion

There are increasing evidences that the DNA repair genes polymorphisms induce inter-individual variability in chemotherapy, and the reduced DNA capacity from DNA repair genes contributed to the longer survival after treatment with chemotherapy in various cancers, such as non-small cell lung cancer, colorectal cancer, pancreatic cancer, and head and neck squamous cell carcinoma (Ang et al., 2011; Giovannetti et al., 2011; Liu et al., 2012; Wu et al., 2012). Thus, the use of DNA repair gene polymorphisms as predictive or prognostic markers holds clinical promise. However, evidence linking DNA repair gene polymorphisms and breast cancer survival in Chinese populations is lacking. The current study demonstrated that breast cancer patients with XRCC1 399Gln/Gln polymorphisms had a longer survival time than XRCC1 399Arg/Arg genotype, carriers with and ADPRT 762Ala/Ala had relatively shorter survival times when compared with ADPRT 762Val/Val. However, no association was found between XRCC1 Arg280His and breast cancer prognosis.

The XRCC1 Arg399Gln and XRCC1 Arg194Trp polymorphisms are the two most common sequence variants among the three polymorphisms. Our study showed the XRCC1 Arg399Gln and XRCC1 Arg194Trp could affect the clinical outcome in breast cancer patients. The possible explanation is that they enhance DNA repair capacity. XRCC1 gene is thought to be involved in DNA single-strand break repair, and also plays an important role in the BER pathway (Brem et al., 2005; Nazarkina et al., 2007). The gene polymorphism in codon 399 may be related to DNA repair, and likely has an effect on protein function (Savas et al., 2004). Several studies have found an association of XRCC1-399 with the risk of various cancers, such as breast cancer, colorectal cancer, lung cancer, thyroid carcinoma, gastric cancer and breast cancer (Engin et al., 2011; Fard-Esfahani et al., 2011; Xu et al., 2011; Raabe et al., 2012; Zhao et al., 2012). Previous study showed an improved survival rate for breast cancer patients with XRCC1-399 Gln/Gln receiving chemotherapy (Bewick et al., 2009; Rodrigues et al., 2011). One study conducted in Canada reported XRCC1 Arg399Gln was an independent predictor for progression (Bewick et al., 2009), and another study showed a non-significant decreased risk of survival for breast cancer (Rodrigues et al., 2011). Similar results were found for the survival of non-small-cell lung cancer, colorectal cancer, gastric cancer and ovarian cancer (Khrunin et al., 2010; Engin et al., 2011; Tahara et al., 2011; Liao et al., 2012).

We found a light decreased survival of breast cancer among patients with ADPRT 762Ala/Ala genotypes, which were consistent with a previous analysis (Gonçalves et al., 2011). This Meta-analysis showed the over-expression of PARP1 may be associated with tumor sensitivity to cytotoxic treatment, essentially cyclophosphamide and/or anthracycline-based chemotherapy (Gonçalves et al., 2011). Our study is consistent with the recently reported positive correlation between PARP1 protein expression and response to neoadjuvant chemotherapy (Loibl et al., 2010; Von et al., 2010). Moreover, ADPRT polymorphism is reported to have a significant association with the prognosis of various human cancers, such as ovarian cancer, lung cancer and glioma (Nowsheen et al., 2011; Kase et al., 2011; Wysham et al., 2012). Further larger studies are needed to validate the association between ADPRT Val762Ala polymorphism and breast cancer prognosis.

In conclusion, this study is the first one to evaluate the associations between XRCC1 and ADPRT and breast cancer outcomes in a Chinese population. We found a significant association between XRCC1 399Gln/Gln and ADPRT Val762Ala polymorphisms and clinical outcomes. Further prospective studies incorporating larger numbers of patients are needed to validate these associations.

### References


### Table 3. Association of Combination of XRCC1 Arg399Gln and ADPRT Val762Ala Genotypes with Breast Cancer Survival

<table>
<thead>
<tr>
<th>Genotypes</th>
<th>No. of patients N=335</th>
<th>% Patient deaths N=159</th>
<th>% Median overall survival (months)</th>
<th>HR (95% CI)¹</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>XRCC1Arg399Gln and ADPRT Val762Ala</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arg/Arg and Val/Val</td>
<td>73</td>
<td>21.8</td>
<td>51</td>
<td>32.1</td>
<td>31.5</td>
</tr>
<tr>
<td>Arg/Arg and Ala allele</td>
<td>79</td>
<td>23.6</td>
<td>32</td>
<td>20.1</td>
<td>34.2</td>
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<tr>
<td>Gln allele and Val/Val</td>
<td>63</td>
<td>18.8</td>
<td>25</td>
<td>15.7</td>
<td>33.9</td>
</tr>
<tr>
<td>Gln allele and Ala allele</td>
<td>120</td>
<td>35.8</td>
<td>51</td>
<td>32.1</td>
<td>39.8</td>
</tr>
</tbody>
</table>

¹Adjusted for age, lymph node metastasis (UICC) and tumor size.