Null Results in Brief

No Association between hOGG1, XRCC1, and XPD Polymorphisms and Risk of Reflux Esophagitis, Barrett’s Esophagus, or Esophageal Adenocarcinoma: Results from the Factors Influencing the Barrett’s Adenocarcinoma Relationship Case-Control Study

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Abstract

Reflux of gastric contents can lead to development of reflux esophagitis and Barrett’s esophagus. Barrett’s esophagus is a risk factor for esophageal adenocarcinoma. Damage to DNA may lead to carcinogenesis but is repaired through activation of pathways involving polymorphic enzymes, including human 8-oxoguanine glycosylase 1 (hOGG1), X-ray repair cross-complementing 1 (XRCC1), and xeroderma pigmentosum group D (XPD). Of the single nucleotide polymorphisms identified in these genes, hOGG1 Ser326Cys, XRCC1 Arg399Gln, and XPD Lys751Gln are particularly common in Caucasians and have been associated with lower DNA repair capacity. Small studies have reported associations with XPD Lys751Gln and esophageal adenocarcinoma. XRCC1 Arg399Gln has been linked to Barrett’s esophagus and reflux esophagitis. In a population-based case-control study, we examined associations of the hOGG1 Ser326Cys, XRCC1 Arg399Gln, and XPD Lys751Gln polymorphisms with risk of esophageal adenocarcinoma, Barrett’s esophagus, and reflux esophagitis. Genomic DNA was extracted from blood samples collected from cases of esophageal adenocarcinoma (n = 210), Barrett’s esophagus (n = 212), reflux esophagitis (n = 230), and normal population controls frequency matched for age and sex (n = 248). Polymorphisms were genotyped using TaqMan allelic discrimination assays. Odds ratios and 95% confidence intervals were obtained from logistic regression models adjusted for potential confounding factors. There were no statistically significant associations between these polymorphisms and risk of esophageal adenocarcinoma, Barrett’s esophagus, or reflux esophagitis. (Cancer Epidemiol Biomarkers Prev 2008;17(3):736–9)

Introduction

Reflux of gastric contents can lead to development of reflux esophagitis and Barrett’s esophagus. Barrett’s esophagus is an important risk factor for esophageal adenocarcinoma, the incidence of which has increased in recent years (1, 2). Damage to DNA may lead to carcinogenesis (3) but is repaired through activation of pathways involving polymorphic enzymes (4). Human 8-oxoguanine glycosylase 1 (hOGG1) and X-ray repair cross-complementing 1 (XRCC1) act on the base excision repair pathway. Xeroderma pigmentosum group D (XPD) enzyme is involved in the nucleotide excision repair pathway (5). Various single nucleotide polymorphisms have been identified in these genes, but hOGG1 Ser326Cys, XRCC1 Arg399Gln, and XPD Lys751Gln are particularly common in Caucasians and have been associated with lower DNA repair capacity (6-8). Small studies have reported associations with XPD Lys751Gln and esophageal adenocarcinoma (9-11). XRCC1 Arg399Gln has been linked to Barrett’s esophagus and reflux esophagitis. We investigated associations between hOGG1 Ser326Cys, XRCC1 Arg399Gln, and XPD Lys751Gln and risk of esophageal adenocarcinoma, Barrett’s esophagus, and reflux esophagitis in a large case-control study.
Materials and Methods

**Design.** The study methods have been described previously in detail (12). In summary, the Factors Influencing the Barrett's Adenocarcinoma Relationship study was carried out in Ireland between March 2002 and July 2005. Data and samples were collected from Caucasians with (a) esophageal adenocarcinoma, (b) Barrett's esophagus, (c) reflux esophagitis, and (d) normal controls.

**Genotyping.** The Puregene DNA purification kit (Gentra Systems) was used to extract DNA from blood samples. The hOGG1 Ser326Cys (rs1052133), XRCC1 Arg399Gln (rs25487), and XPD Lys751Gln (rs13181) polymorphisms were genotyped using TaqMan allelic discrimination assays (Applied Biosystems). As a quality-control measure, genotyping was repeated for 10% of the samples, and the replicates were 100% concordant.

**Statistical Analysis.** Departures from Hardy-Weinberg equilibrium were tested for using the goodness-of-fit test. Genotype frequencies among cases of esophageal adenocarcinoma, Barrett's esophagus, and reflux esophagitis were compared with controls using the \( \chi^2 \) test for association while adjusting for potential confounding factors by logistic regression. Statistical significance was set at \( P < 0.05 \). Analyses were done using SPSS for Windows version 13.0 (SPSS).

Results

The Factors Influencing the Barrett’s Adenocarcinoma Relationship study recruited a total of 227 esophageal adenocarcinoma patients, 224 Barrett’s esophagus patients, 230 reflux esophagitis patients, and 260 population controls. The demographic characteristics of each group are presented in Table 1. The participation rates of Barrett’s esophagus and reflux esophagitis patients and control subjects were 82.4%, 68.7%, and 41.8%, respectively. The participation rate of eligible, alive esophageal adenocarcinoma patients was 74.2% and the overall esophageal adenocarcinoma response rate was 63.9%. DNA samples were available for analysis from 210 (92.5%) esophageal adenocarcinoma patients, 212 (94.6%) Barrett’s esophagus patients, 230 (100%) reflux esophagitis patients, and 248 (95.4%) controls.

The distribution and frequency of genotypes for cases and controls are shown in Table 2. There were no significant departures from Hardy-Weinberg equilibrium for any of the polymorphisms in any of the subject groups. For controls, the frequency of polymorphic variants was 0.24 (hOGG1 Ser326Cys), 0.36 (XRCC1 Arg399Gln), and 0.38 (XPD Lys751Gln). These were similar to frequencies reported in Caucasians in the SNP500 Database (http://snp500cancer.nci.nih.gov).

There were no statistically significant associations between the hOGG1 Ser326Cys, XRCC1 Arg399Gln, and XPD Lys751Gln polymorphisms and the risk of esophageal adenocarcinoma, Barrett’s esophagus, or reflux esophagitis.

Discussion

To date, this is the largest case-control study to explore the association between DNA repair gene polymorphisms and risk of esophageal adenocarcinoma. In addition, it is the first population-based study to evaluate the role of these polymorphisms in Barrett’s esophagus and reflux esophagitis. All three polymorphisms were in Hardy-Weinberg equilibrium and had sufficient statistical power (>80%) to detect an odds ratio (OR) of >2.0. Further strengths of our study include the population-based design and clear characterization of phenotypes to minimize misclassification bias. Detailed interview data allowed us to control for a range of potential confounding factors, and DNA was available for analysis in almost all subjects.

Table 1. Characteristics of controls, reflux esophagitis, Barrett’s esophagus, and esophageal adenocarcinoma patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>Controls, n (%)</th>
<th>Reflux esophagitis, n (%)</th>
<th>P (reflux esophagitis vs controls)</th>
<th>Barrett’s esophagus, n (%)</th>
<th>P (Barrett’s esophagus vs controls)</th>
<th>Esophageal adenocarcinoma, n (%)</th>
<th>P (esophageal adenocarcinoma vs controls)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>220 (84.6)</td>
<td>189 (82.2)</td>
<td>0.468</td>
<td>185 (82.6)</td>
<td>0.548</td>
<td>192 (84.6)</td>
<td>0.992</td>
</tr>
<tr>
<td>Female</td>
<td>40 (15.4)</td>
<td>41 (17.8)</td>
<td></td>
<td>39 (17.4)</td>
<td>35 (15.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean (y)</td>
<td>63.0</td>
<td>61.7</td>
<td>0.219</td>
<td>62.4</td>
<td>0.567</td>
<td>64.2</td>
<td>0.276</td>
</tr>
<tr>
<td>Education</td>
<td>12.0</td>
<td>10.8</td>
<td>&lt;0.001</td>
<td>11.3</td>
<td>0.013</td>
<td>10.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(full-time), mean (y)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrosophageal reflux symptoms*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>211 (81.2)</td>
<td>140 (60.9)</td>
<td>&lt;0.001</td>
<td>60 (26.8)</td>
<td>&lt;0.001</td>
<td>117 (51.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ever</td>
<td>49 (18.8)</td>
<td>90 (39.1)</td>
<td></td>
<td>164 (73.2)</td>
<td></td>
<td>110 (48.5)</td>
<td></td>
</tr>
<tr>
<td>Smoking status †</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>102 (40.2)</td>
<td>109 (48.4)</td>
<td>0.026</td>
<td>87 (39.2)</td>
<td>0.400</td>
<td>45 (20.4)</td>
<td>&lt;0.001</td>
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<tr>
<td>Ex-smoker</td>
<td>107 (42.1)</td>
<td>68 (30.2)</td>
<td></td>
<td>85 (38.3)</td>
<td>0.399</td>
<td>99 (44.8)</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>45 (17.7)</td>
<td>48 (21.3)</td>
<td></td>
<td>50 (22.5)</td>
<td>0.306</td>
<td>77 (34.8)</td>
<td></td>
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<tr>
<td>Alcohol, mean (g/d)</td>
<td>26.1</td>
<td>22.0</td>
<td>0.151</td>
<td>22.3</td>
<td>0.214</td>
<td>19.2</td>
<td>0.012</td>
</tr>
<tr>
<td>Body mass index, mean (kg/m²)</td>
<td>27.0</td>
<td>27.8</td>
<td>0.047</td>
<td>27.0</td>
<td>0.895</td>
<td>28.7</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Symptoms of heartburn or acid reflux experienced at least once a week or ≥50 times per year, ≥5 y before the interview date.
†“Never smoker” is defined as those subjects who had never smoked, who had smoked <100 cigarettes in their lifetime, or who had smoked <1 cigarette per day for ≥6 mo. “Ex-smoker” is defined as smokers who had stopped ≥5 y before the interview date. “Current smoker” is defined as smokers who had smoked at least 1 cigarette per day for ≥6 mo, 5 y before the interview date.
In keeping with our results, all three previous studies have reported no association between the hOGG1 Ser326Cys polymorphism and risk of esophageal adenocarcinoma, Barrett’s esophagus, or reflux esophagitis. No previous study has investigated this polymorphism in relation to these conditions.

However, association studies in esophageal squamous cell carcinoma have produced conflicting results (13, 14). A limitation of our study was inadequate power to detect a modest excess risk (OR < 2.0) or to examine the role of possible gene-environment interactions.

In summary, we found no significant associations between the hOGG1 Ser326Cys, XRCC1 Arg399Gln, and XPD Lys751Gln polymorphisms and the risk of esophageal adenocarcinoma, Barrett’s esophagus, or reflux esophagitis.

Our findings are in contrast to results from a Swedish case-control study, which suggested that the XPD Lys751Gln polymorphism was associated with a significantly increased risk of esophageal adenocarcinoma (10). This study also had a population-based design, strict definition of phenotypes, and detailed interview data. However, DNA was available for analysis in only 50% of interviewed subjects, questioning the internal validity of the study. In addition, the present study included over two times the number of esophageal adenocarcinoma subjects. Liu et al. also reported an increased risk of esophageal adenocarcinoma in association with the XPD Lys751Gln polymorphism (9). Although this study was a case-control study, which suggested that the XPD Lys751Gln polymorphism was associated with both reduced risk of esophageal adenocarcinoma (11). This study was limited by its hospital-based design and small sample size, including only 56 esophageal adenocarcinoma subjects.}

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polymorphisms: effects on aflatoxin B1-DNA adducts and glyco-
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