Genetic Variation in Immune Regulation and DNA Repair Pathways and Stomach Cancer in China

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Abstract

The incidence of stomach cancer is high in certain parts of the world, particularly in China. Chronic Helicobacter pylori infection is the main risk factor, yet the vast majority of infected individuals remain unaffected with cancer, suggesting an important role of other risk factors. We conducted a population-based case-control study including 196 incident stomach cancer cases and 397 matched controls to test the hypothesis that adverse single nucleotide polymorphism (SNP) genotypes and haplotypes within genes of the DNA repair and immune regulatory pathways are associated with increased stomach cancer risk. Genomic DNA isolated from blood samples was used for genotyping, and results were obtained for 57 putatively functional SNPs in 28 genes. Odds ratios (OR) and 95% confidence intervals (95% CI) were obtained from adjusted logistic regression models. For PTGS2, a gene involved in the inflammatory response, associations with stomach cancer risk were observed for TC genotype carriers of rs3279 (OR, 0.24; 95% CI, 0.08-0.73), CT genotype carriers of the T3′ untranslated region SNP rs689470 (OR, 7.49; 95% CI, 1.21-46.20), and CTTG haplotype carriers of rs3277, rs3278, rs3279, and rs689470 (OR, 0.41; 95% CI, 0.18-0.95). For ERCC5, a gene involved in nucleotide excision repair, TC genotype carriers of rs1047768 (OR, 0.65; 95% CI, 0.41-1.03), GC genotype carriers of the nonsynonymous SNP rs2227869 (OR, 0.30; 95% CI, 0.13-0.67), and CCG haplotype carriers of rs1047768, rs17655, and rs2227869 (OR, 0.45; 95% CI, 0.20-1.04) were associated with reduced stomach cancer risk. In conclusion, PTGS2 and ERCC5 were associated with stomach cancer risk in a Chinese population. (Cancer Epidemiol Biomarkers Prev 2009;18(8):2304–9)

Introduction

Over the last half century, the incidence of stomach cancer has fallen markedly in developed countries, whereas it remains common in China, Japan, eastern Europe, and Central and South America (1, 2). The decline in incidence in the developed areas can largely be attributed to the decline in prevalence of Helicobacter pylori (H. pylori) infection, widespread introduction of refrigeration, and dietary changes including decreased intake of salt preserved foods and increased access to fresh fruits and vegetables (3). Despite this decline in incidence, stomach cancer still poses a substantial public health burden; in 2002, it was the fourth most commonly diagnosed cancer worldwide with 934,000 new cases and the second leading cause of cancer-related deaths worldwide with 700,000 deaths (2). There is also a marked geographic variation in stomach cancer risk; China alone accounts for ~38% of the world’s stomach cancer burden (4). In Jiangsu Province of southeast China, where this study is based, the incidence of stomach cancer is nearly twice the national average, on the order of 55 per 100,000 individuals.

Stomach cancer has a multifactorial etiology. H. pylori is present in the stomachs of at least half of the world’s population, yet the vast majority of these individuals have no clinical signs, whereas only a small percentage develop neoplasias related to the infection (5). Diet and tobacco smoking are other established risk factors for stomach cancer, and there is increasing evidence that host genetics contribute to stomach cancer risk (6). In recent years, abnormal immune function has been linked to the development and progression of many common cancers, including stomach cancer. For example, chronic inflammation, on account of chronic H. pylori infection, environmental exposures, host genetic susceptibility, or some combination of these factors, can lead to increased
expression of cytokines, growth factors, and their receptors, which in turn promotes cellular proliferation (7, 8). In addition, free radicals are generated as byproducts of the inflammatory response. An important consequence of increased cellular proliferation and presence of free radicals is DNA damage, which can predispose an individual to cancer pathogenesis. Exogenous carcinogens, such as constituents of cigarette smoke, can also directly mutate cellular DNA in the gastric epithelium (9).

The fact that cancer is a relatively rare disease speaks to the important role of complex immune regulatory pathways in balancing the inflammatory response as well as specific DNA repair pathways in maintaining genome fidelity in the face of constant DNA damage by endogenous and environmental agents. In fact, rare germ-line mutations in genes involved in DNA repair have been linked to numerous inherited disorders, which predispose individuals to cancer, including xeroderma pigmentosum, human nonpolyposis colorectal cancer, familial breast/ovary cancers, and Nijmegen breakage syndrome (10); a variety of common single nucleotide polymorphisms (SNP) in genes involved in the immune response pathway have also been linked to cancer (11, 12), which underscores the sensitivity of normal function of these pathways to inherited genetic abnormalities and the ability of these abnormalities to affect cancer pathogenesis.

Several studies have reported significant associations between stomach cancer risk and SNPs in cytokine genes such as the interleukin-1 superfamily, interleukin-10, and tumor necrosis factor (13). To our knowledge, no prior genetic association study has comprehensively examined candidate genes in DNA repair pathways and stomach cancer risk. Thus, we conducted this study to examine the role of nucleotide variation in genes involved with two putatively important pathways in stomach cancer risk, immune regulation and DNA repair.

Materials and Methods

Study Population. The study population has been described in detail previously (14-16). Briefly, this population-based case-control study was set in Taixing City, located on the east bank of the Yangtze River in Jiangsu Province in southeast China. Taixing City has 23 townships (rural areas) and one central town (urban area). Although the original study included three cancer sites (esophagus, stomach, and liver) and one common population control group, the study population for this analysis only included patients with stomach cancer and population controls. Data collection consisted of in-person administered questionnaires and donated blood specimens.

Eligible cases were patients with newly diagnosed, and pathologically or clinically confirmed, stomach cancer from June 1, 2000 to December 30, 2000, reported to Taixing Tumor Registry at the Taixing Center for Disease Control. Eligible cases were ages ≥20 years, residents of Taixing for ≥10 years, in stable medical condition as determined by their physician, and willing and consented to participate. Of the 316 cases diagnosed in Taixing within the study recruitment period, 206 (65%) met our inclusion criteria and consented to participate. All cases included in this study completed the study questionnaire, and 196 (95%) donated a blood specimen from which DNA could be isolated.

Eligible controls were healthy individuals selected randomly from the general population in Taixing who were ages ≥20 years and residents of Taixing for ≥10 years. Controls were frequency matched to the combined case group (esophagus, stomach, and liver) on sex, age, and residential village or city block in a control-to-case ratio of 2:3. Due to the method of control selection, the distribution of controls were correspondent to all three cancer sites and thus do not exactly match the distribution of stomach cancer cases. For example, the higher proportion of younger controls is a result of liver cancers being diagnosed at a younger age compared with stomach cancer. Of the 464 eligible controls that were approached, 415 (89%) consented to participate. All controls included in this study competed the study questionnaire, and 397 (96%) donated a blood specimen from which DNA could be isolated.

Data Collection. All cases and controls completed a standardized questionnaire administered by an in-person interviewer in their home, hospital, or doctor’s office. The questionnaire elicited information on known or suspected risk or protective factors for alimentary cancers in the Chinese population. Specifically, information was collected on demographic factors, drinking water sources, dietary history, smoking history, alcohol drinking habits, green tea drinking habits, personal and family cancer history, occupational exposures, and physical activity. Blood specimens (8 mL) were collected using routine venipuncture procedures. Genomic DNA was isolated from the specimens using a modified phenol-chloroform protocol.

SNP Selection. Forty-two genes involved in the DNA repair and inflammation pathways were systematically selected for evaluation. When possible, known functional SNPs and potentially functional SNPs such as amino acid-changing (nonsynonymous) SNPs were selected. All selected SNPs had a minor allele frequency >5% reported in SNP databases, such as National Center for Biotechnology Information dbSNP, National Cancer Institute SNP 500 project (17), and National Institute of Environmental Health Sciences GeneSNPs (18), or in the published literature. A total of 121 SNPs in 42 genes involved in DNA repair and immune function were genotyped using the SNPlex platform.

The final set of SNPs used in this analysis was selected based on successful genotyping on at least 80% of the study population, resulting in the exclusion of 51 SNPs, and having genotype distributions among the controls compliant with Hardy-Weinberg equilibrium (P ≥ 0.001), resulting in exclusion of 13 additional SNPs. Thus, this analysis included a total of 57 SNPs in 28 genes (BRCAl, BRCA2, CDH1, PTGS2, ERCC1, ERCC5, ERCC6, IL10, IL1A, LIG1, LIG3, LIG4, MLHI, NBS1, NQ01, POLH, POLQ, RAD51, RAD52, REV1L, REV3L, TNFA, TNFB, XPC, XRCC1, XRCC3, XRCC4, and XRCC5).

Laboratory Assays

H. pylori Determination. H. pylori exposure was determined by assaying for CagA. H. pylori antibodies in the sera of cases and controls using indirect enzyme immunoassay techniques implemented by kits from the Reagent Company of the Shanghai Biotechnology Industry Park. The testing was done according to the manufacturer’s instructions. Results were efficient when the average A
value for the positive controls was greater than the average A value for the negative controls +0.5; otherwise, the measurements were repeated. Samples were considered positive when the A value was greater than the average A value for the negative controls +0.30.

**Genotype Determination.** Genotypes were determined using the Applied Biosystems SNPlex assay (19). This method assays SNP genotypes in 48 SNP PCR multiplexes using an oligonucleotide ligation process. Each SNP allele was ligated to an allele-specific oligonucleotide and then hybridized with a Zipchute probe with a mobility modifier and a fluorescent label, allowing the probe to be separated and detected by capillary electrophoresis. Detection was done on an Applied Biosystems 3730 DNA Analyzer, and data interpretation was done with the Applied Biosystems Genemapper software version 4.0, which uses a clustering algorithm with stringent quality checks to call genotypes. Only genotypes with a Genemapper Quality Score of >95% passed. With the SNPlex genotyping assay, the University of California-Los Angeles Genotyping Core achieves an average call rate of 98%, a reproducibility rate of 99.7%, and a concordance rate of 99.8%. Genotype concordance is validated by allelic discrimination assay on an Applied Biosystems 7900HT Fast Real-time PCR System.

**Statistical Analysis.** We used logistic regression models to obtain odds ratios (OR) and 95% confidence intervals (95% CI) as measures of association and precision between SNP genotypes and stomach cancer. For genes with more than one SNP, we calculated ORs and 95% CIs for the association between haplotypes and stomach cancer, following a log-additive genetic model using H Putin software (20, 21). For all single SNP and haplotype models, in addition to estimating crude ORs, we adjusted for sex, age (continuous), body mass index (continuous), education (ordinal, four categories), cigarette smoking (ever versus never), alcohol drinking (ever versus never), very hot foods eating habits (ordinal, four categories), *H. pylori* CagA status (positive versus negative), and green tea drinking (ever versus never).

Associations were considered statistically significant if P ≤ 0.05 or if the 95% CI excluded 1.0 in the adjusted models. However, on account of the large number of SNPs explored in this study, some may be significantly associated with stomach cancer just by chance. Thus, we calculated an estimate of the probability of false discoveries for statistically significant results from the adjusted models (22). This methodology is based on a Bayesian framework and requires providing a subjective estimate of the prior probability that a result is really positive. This prior probability, combined with statistical power and α level of the test, determines the posterior probability, which is called the false-positive report probability (FPRP). Because all of the SNPs in our study are involved in candidate pathways in stomach cancer risk, and many have been shown previously to have functional effects, we used a prior probability of 0.1. We estimated statistical power based on the ability to detect an OR of 1.5 (or its reciprocal, 0.67), with an α level equal to the observed P value. To evaluate whether an association is noteworthy, we used a FPRP cutoff value of 0.70 because this is a small initial study (22). Thus, any FPRP value ≤ 0.70 was considered to be noteworthy.

For all nonsynonymous SNPs included in our study, we bioinformatically assessed potential functionality using the Polyphen algorithm, which uses information on sequence features, multiple alignments with homologous proteins and mammalian orthologues, physiochemical properties of the substituted amino acid, structural parameters, and empirically derived rules to make predictions on the functionality of the SNP (23).

**Results**

Select characteristics of the stomach cancer cases and controls are presented in Table 1. Compared with controls, on average, cases were older, had a lower body mass index, were less educated, smoked more pack-years, more likely to eat scalding hot food, and less likely to drink green tea. On average, cases and controls were similarly distributed with respect to sex, ever smoking status, alcohol drinking habits, and *H. pylori* infection.

Of the 28 genes examined in this study, 8 genes showed statistically significant (or marginally significant) associations in either the single SNP or haplotype models or both (Tables 2 and 3). For genes with multiple SNPs, the r² statistic for correlation of genotypes was calculated for all SNPs with the same gene. None of the SNPs displayed in Table 2 had a r² value exceeding 0.80 with any other SNPs in the same gene. Notable FPRPs, which we describe as those below our preset value of 0.7, were observed for the CTTCT haplotype of PTGS2 (FPRP = 0.69), ERCC5 rs2227869 (FPRP = 0.54), and the TG haplotype of RAD51 (FPRP = 0.65).

The two synonymous SNPs of PTGS2, rs5277 and rs5278, were not significantly associated with stomach cancer risk; however, TC genotype carriers of the synonymous SNP rs5279 were associated with a significantly reduced risk of stomach cancer compared with TT genotype carriers (OR, 0.24; 95% CI, 0.08-0.73), and CT genotype carriers of the 3’-untranslated region SNP rs694770 were associated with a significantly increased risk of stomach cancer.

### Table 1. Selected characteristics of cases and controls

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Controls</th>
<th>Cases</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>n</td>
<td>397</td>
<td>196</td>
<td></td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>69.2</td>
<td>67.0</td>
<td>0.56</td>
</tr>
<tr>
<td>Age (mean)</td>
<td>57.7</td>
<td>61.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Body mass index (mean)</td>
<td>22.3</td>
<td>21.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Education (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Illiterate</td>
<td>17.6</td>
<td>32.0</td>
<td></td>
</tr>
<tr>
<td>Primary school</td>
<td>34.2</td>
<td>51.9</td>
<td></td>
</tr>
<tr>
<td>Middle school</td>
<td>29.9</td>
<td>14.6</td>
<td></td>
</tr>
<tr>
<td>Senior middle school</td>
<td>15.9</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Bachelor or higher degree</td>
<td>2.4</td>
<td>0.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Cigarette smoking (% ever)</td>
<td>47.6</td>
<td>54.2</td>
<td>0.12</td>
</tr>
<tr>
<td>Pack-years (mean)</td>
<td>23.6</td>
<td>27.4</td>
<td>0.01</td>
</tr>
<tr>
<td>Alcohol drinking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>50.2</td>
<td>55.2</td>
<td></td>
</tr>
<tr>
<td>Occasionally</td>
<td>17.5</td>
<td>15.4</td>
<td></td>
</tr>
<tr>
<td>Often</td>
<td>18.2</td>
<td>15.9</td>
<td></td>
</tr>
<tr>
<td>Everyday</td>
<td>14.1</td>
<td>13.4</td>
<td>0.70</td>
</tr>
<tr>
<td>Very hot foods eating habits</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scalding</td>
<td>7.3</td>
<td>15.1</td>
<td></td>
</tr>
<tr>
<td>Hot</td>
<td>56.0</td>
<td>49.3</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>34.2</td>
<td>32.7</td>
<td></td>
</tr>
<tr>
<td>Cool</td>
<td>2.4</td>
<td>3.0</td>
<td>0.03</td>
</tr>
<tr>
<td><em>H. pylori</em> (% CagA+)</td>
<td>31.2</td>
<td>35.3</td>
<td>0.32</td>
</tr>
<tr>
<td>Green tea drinking (% ever)</td>
<td>45.6</td>
<td>32.1</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>
cancer compared with CC genotype carriers (OR, 7.49; 95% CI, 1.21-46.20). Compared with carriers of the wild-type GTTC haplotype of PTGS2, carriers of the CTTC haplotype were associated with a significantly reduced risk of stomach cancer (OR, 0.30; 95% CI, 0.12-0.76).

For the ERCC5 synonymous SNP rs1047768, compared with TT genotype carriers, TC genotype carriers were associated with a marginally significant reduced risk of stomach cancer in the adjusted model (OR, 0.65; 95% CI, 0.41-1.03), and GC genotype carriers of the ERCC5 nonsynonymous SNP rs2227869 were associated with a significantly reduced risk of stomach cancer in the adjusted model compared with individuals with the GG genotype (OR, 0.30; 95% CI, 0.13-0.67). The ERCC5 nonsynonymous SNP rs17655 was not associated with stomach cancer in the single SNP model. However, in the haplotype model, carriers of all three ERCC5 variant alleles (CCG haplotype) were associated with a marginally significant reduced risk of stomach cancer in the adjusted model (OR, 0.45; 95% CI, 0.20-1.04) compared with carriers of all three common alleles (TGC haplotype). Polyphen predicts that the ERCC5 rs2227869 Cys>Ser substitution is benign and that the ERCC5 rs17655 His>Asp substitution possibly affects protein function.

For RAD51, neither the synonymous SNP rs3092981 nor the 3’-untranslated region SNP rs12593359 were significantly associated with stomach cancer risk in the single SNP models; however, carriership of the TG haplotype was associated with a significant increased risk of stomach cancer compared with the CG haplotype (OR, 1.95; 95% CI, 1.02-3.74). The RAD51 TT haplotype was associated with a marked decreased risk of stomach cancer in the adjusted model, but the association was not statistically significant (OR, 0.40; 95% CI, 0.04-3.86).

### Discussion

We identified several SNPs and haplotypes in the candidate pathways of immune regulation and DNA repair that were significantly associated with stomach cancer risk in the Chinese population, even after correction for multiple comparisons. Mounting epidemiologic evidence highlights an important role of inflammation and SNPs in
immune regulatory genes in stomach cancer risk, and our results suggest that SNPs in PTGS2 be added to the growing list of immune-related stomach cancer susceptibility markers (12, 24-26). Although exogenous and endogenous DNA-damaging agents have long been suspected of increasing stomach cancer risk, no previous population-based study has thoroughly examined the role of SNPs in multiple DNA repair pathways and stomach cancer risk despite the critical role of these pathways in reversing this damage. Our findings lend support to the notion that SNPs in ERCC5 [involved in nucleotide excision repair (NER)] and RAD51 (involved in homologous recombination) play a role in determining one’s susceptibility profile to stomach cancer.

Chronic gastric inflammation, which is characterized by secretion of proinflammatory molecules, such as PTGS2, and infiltration of the gastric epithelium by chronic inflammatory cells, such as lymphocytes, plasma cells, and macrophages, can result from persistent gastric H. pylori infection. There is increasing evidence linking this chronic inflammatory state to increased stomach cancer risk (9, 11, 27). It is plausible that SNPs in PTGS2 could exacerbate this inflammatory response and further increase an individual’s susceptibility to stomach cancer as has been seen for other proinflammatory cytokines (24).

PTGS2 codes for an enzyme that is responsible for the conversion of arachidonic acid to prostaglandins in response to inflammation, resulting in increased cellular proliferation and angiogenesis. In a previous study, a 5′-SNP in PTGS2 was significantly associated with transcriptional activity and stomach cancer in a Chinese population (28), whereas another study in a Polish population did not identify any significant associations with PTGS2 SNPs and stomach cancer (29). None of the SNPs examined in these two prior studies were genotyped in our study population. However, in our haplotype models, we found a reduced risk of stomach cancer associated with the PTGS2 SNP rs5277; this SNP was previously genotyped by the International HapMap Project (30). Interestingly, in the 45 unrelated individuals of Han Chinese descent who were genotyped in the HapMap, rs5277 was not in high linkage disequilibrium ($r^2 \geq 0.80$) with any other SNPs, including those SNPs genotyped in the two previous studies of PTGS2 and stomach cancer (28, 29). Taken together, results from our study and previous research suggest that PTGS2 SNPs predispose individuals to the development of stomach cancer.

The NER pathway predominantly targets bulky lesions. Chemical adducts due to constituents of common environmental and dietary exposures, such as cigarette smoke and well-cooked meats (risk factors for stomach cancer), are among the bulky lesions repaired by NER. The importance of NER genes in the development of cancer is evident from cancer-prone syndromes, such as xeroderma pigmentosum, which result from rare inherited mutations in NER genes (31). Although no previous studies have reported on the association between SNPs in ERCC5 (involved in NER) and stomach cancer, several studies have reported on associations between ERCC5 SNPs and cancer at other sites. For example, carriership of the C allele of the synonymous SNP rs1047765, which was associated with a reduced stomach cancer risk in our study, has been associated with increased survival from head and neck cancer (32) and colorectal cancer (33) in prior studies, although the molecular mechanisms for these associations remain largely unknown.

In the HapMap Project, rs1047768 was in high linkage disequilibrium with >20 other SNPs in ERCC5. Although none of these other SNPs were located in exons and the vast majority were located in introns, we cannot rule out the possibility that the association we observed with rs1047768 is truly due to one of these correlated SNPs through unknown mechanisms. The decreased association we observed between stomach cancer and rs2227869, a nonsynonymous SNP of ERCC5, fell within our preset cutoff for the FPRP. Although this SNP was predicted by Polyphen to be benign, there is evidence from the literature that it may be associated with bladder cancer risk (34, 35). This SNP is in linkage disequilibrium with two ERCC5 SNPs also genotyped by the HapMap project: a 3′-untranslated region SNP (rs2296148) and an intronic SNP (rs4150275).

RAD51 is involved in homologous recombination, which operates on double-stranded DNA breaks. Double-stranded breaks can be produced by replication errors, by reactive oxygen species, and by exogenous agents such as ionizing radiation and cigarette smoking. A recent article reported that a RAD51 5′-untranslated

### Table 3. The association between haplotypes in immune regulatory and DNA repair pathways and stomach cancer

<table>
<thead>
<tr>
<th>Gene</th>
<th>Haplotype*</th>
<th>Frequencies</th>
<th>Controls</th>
<th>Cases</th>
<th>OR (95% CI)</th>
<th>P</th>
<th>Adjusted†</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTGS2</td>
<td>GAGGTG</td>
<td>0.93 0.96</td>
<td>1.00 1.00</td>
<td></td>
<td>0.41 (0.81-0.95) 0.038</td>
<td>0.30 (0.12-0.76) 0.011</td>
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<tr>
<td></td>
<td>CTCT</td>
<td>0.04 0.02</td>
<td>0.85 (0.27-2.56) 0.750</td>
<td></td>
<td>0.92 (0.27-3.16) 0.894</td>
<td></td>
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<tr>
<td></td>
<td>GCCG</td>
<td>0.02 0.01</td>
<td>1.00 1.00</td>
<td></td>
<td>0.41 (0.02-0.86) 0.018</td>
<td>0.45 (0.20-1.04) 0.062</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ERCC5</td>
<td>TG</td>
<td>0.30 0.32</td>
<td>1.00 1.00</td>
<td></td>
<td>0.30 (0.27-3.16) 0.894</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>GG</td>
<td>0.40 0.43</td>
<td>1.00 1.00</td>
<td></td>
<td>1.09 (0.61-1.42) 0.770</td>
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<td></td>
<td>CC</td>
<td>0.18 0.18</td>
<td>1.00 1.00</td>
<td></td>
<td>0.41 (0.20-0.86) 0.018</td>
<td>0.45 (0.20-1.04) 0.062</td>
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<tr>
<td></td>
<td>CG</td>
<td>0.07 0.03</td>
<td>0.93 (0.61-1.42) 0.744</td>
<td></td>
<td>0.45 (0.20-1.04) 0.062</td>
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<tr>
<td>RAD51</td>
<td>TG</td>
<td>0.08 0.04</td>
<td>0.93 (0.61-1.42) 0.744</td>
<td></td>
<td>0.45 (0.20-1.04) 0.062</td>
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<tr>
<td></td>
<td>CG</td>
<td>0.07 0.03</td>
<td>0.85 (0.45-1.95) 0.827</td>
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<td>0.84 (0.36-1.91) 0.670</td>
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<tr>
<td></td>
<td>GG</td>
<td>0.14 0.14</td>
<td>0.97 (0.71-1.44) 0.728</td>
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<td>0.84 (0.36-1.91) 0.670</td>
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<tr>
<td></td>
<td>TT</td>
<td>0.06 0.11</td>
<td>1.98 (1.15-3.41) 0.013</td>
<td></td>
<td>1.07 (0.71-1.62) 0.731</td>
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<tr>
<td></td>
<td>TT</td>
<td>0.06 0.03</td>
<td>0.44 (0.07-2.84) 0.591</td>
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<td>1.95 (1.02-3.74) 0.045</td>
<td></td>
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</tbody>
</table>

NOTE: Variant alleles are underlined.

*Alleles in each haplotype are listed from 5′ to 3′ (TNFA, rs1799964 and rs1800629; PTGS2, rs5277, rs5278, rs5279, and rs689470; ERCC5, rs1047768, rs2227869, and rs17685; RAD51, rs209298 and rs2993339; RAD52, rs2887532 and rs10849994). Variant alleles are underlined.

†ORs are adjusted for sex, age, body mass index, education, cigarette smoking, alcohol drinking, very hot foods eating habits, H. pylori CagA status, and green tea drinking.
region SNP significantly impaired DNA repair, and this SNP was also found to be significantly associated with stomach cancer risk (36). This SNP was not included in our study, nor was it in linkage disequilibrium with either of the two SNPs that were genotyped in our study according to the HapMap project. That report, however, supports our finding that genetic variation in RAD51 can influence stomach cancer risk.

Strengths of this study include the population-based recruitment of cases and controls and the use of single- and multi-locus analytic methods. Additionally, study participants were well defined in terms of important stomach cancer risk factors, such as *H. pylori* infection, cigarette smoking, and alcohol habits. One limitation is the relatively small sample size. This study had limited statistical power to detect weak, but potentially important, associations with common SNPs. In addition, the statistical power to detect weak, but potentially important, associations with common SNPs. In addition, the statistical power to detect weak, but potentially important, associations with common SNPs. In addition, the statistical power to detect weak, but potentially important, associations with common SNPs. In addition, the statistical power to detect weak, but potentially important, associations with common SNPs. In addition, the statistical power to detect weak, but potentially

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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