Genetic variants in DNA repair pathway genes and risk of esophageal squamous cell carcinoma and gastric adenocarcinoma in a Chinese population

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The DNA repair pathways help to maintain genomic integrity and therefore genetic variation in the pathways could affect the propensity to develop cancer. Selected germline single nucleotide polymorphisms (SNPs) in the pathways have been associated with esophageal cancer and gastric cancer (GC) but few studies have comprehensively examined the pathway genes. We aimed to investigate associations between DNA repair pathway genes and risk of esophageal squamous cell carcinoma (ESCC) and GC, using data from a genome-wide association study in a Han Chinese population where ESCC and GC are the predominant cancers. In sum, 1942 ESCC cases, 1758 GC cases and 2111 controls from the Shanxi Upper Gastrointestinal Cancer Genetics Project (discovery set) and the Linxian Nutrition Intervention Trials (replication set) were genotyped for 1675 SNPs in 170 DNA repair-related genes. Logistic regression models were applied to evaluate SNP-level associations. Gene- and pathway-level associations were determined using the resampling-based adaptive rank-truncated product approach. The DNA repair pathways overall were significantly associated with risk of ESCC (\(P = 6.37 \times 10^{-10}\)), but not with GC (\(P = 0.20\)). The most significant gene in ESCC was CHEK2 (\(P = 2.00 \times 10^{-10}\)) and in GC was CLK2 (\(P = 3.02 \times 10^{-10}\)). We observed several other genes significantly associated with either ESCC (SMUG1, TDG, TP53, GTF2H3, FEN1, POLQ, HEL308, RAD54B, MPG, FANCE and BRCA1) or GC risk (MRE11A, RAD54L and POLE) (\(P < 0.05\)). We provide evidence for an association between specific genes in the DNA repair pathways and the risk of ESCC and GC. Further studies are warranted to validate these associations and to investigate underlying mechanisms.

Introduction

Gastric cancer (GC) and esophageal cancer represent the second and sixth most frequent causes of cancer-related deaths worldwide, respectively (1,2). People living around the Taihang Mountains of north central China have a high risk of esophageal squamous cell carcinoma (ESCC) and GC (3,4). Numerous studies have evaluated environmental risk factors for ESCC and GC, but the molecular mechanisms underlying carcinogenesis remain ill defined (5–7). The increased risk of non-cardia GC associated with \textit{Helicobacter pylori} infection has been well described, but only a small proportion of infected subjects develop GC (8). In Western populations, smoking is an established risk factor for ESCC and GC and heavy alcohol intake is a risk factor for ESCC (9). In contrast, smoking and alcohol intake are not major contributing factors for ESCC and GC in high-risk populations (6,7). These findings suggest the likely significance of genetic or other lifestyle contributions.

Genomic instability due to DNA damage by carcinogens has been implicated in the development of cancer (10–12). DNA damage response and repair counteract the threats to genomic integrity, and variations in DNA repair capacity resulting from genetic polymorphisms could therefore correlate with cancer predisposition (10,11,13). Polymorphisms in candidate DNA repair genes from small-scale studies have been associated with risk of ESCC or GC, but the findings have been inconsistent and coverage of genes limited (14–20). One review of candidate gene association studies provided only sparse evidence for an association between DNA repair-related genes and cancer (21). Prior genome-wide association studies (GWAS) have identified a number of genetic loci linked to risk of ESCC or GC, but information on DNA repair genes is limited (5,22–29). Instead of one-by-one single nucleotide polymorphism (SNP) analysis, the analysis of pathways offers the opportunity to combine evidence from multiple potentially related genetic variants and may provide additional insight about the genetic architecture of complex diseases (30,31). We, therefore, sought to comprehensively examine associations between DNA repair pathway genes and the risk of ESCC and GC in ethnic Chinese subjects in a combined analysis of 1942 ESCC cases, 1758 GC cases and 2111 controls drawn from the Shanxi Upper Gastrointestinal (UGI) Cancer Genetics Project and the Linxian Nutrition Intervention Trials (NITs).

Materials and methods

\textbf{Study populations}

Our study contained two sets of populations: a discovery set, with participants drawn from the Shanxi UGI Cancer Genetics Project in the western part of the Taihang Mountain area and a replication set, with participants drawn from the NITs in the southern part of the Taihang Mountain area. The Shanxi study was conducted between 1997 and 2007, which had a case–control portion and a case only portion. We identified newly diagnosed, histologically confirmed ESCC and GC cases (7). Controls were matched on age (±5 years), sex and neighborhood for the case–control portion (7). Blood samples were collected at enrollment for all cases and controls. The NITs were initiated in Linxian in 1985 and tested the effect of multiple vitamin and mineral combinations taken for up to 6 years on the incidence and mortality of esophageal cancer and gastric cancer (4). Following a blood survey conducted in 1999 and 2000, all newly diagnosed, histologically confirmed ESCC and GC cases documented during the follow-up through 31 December 2007, along with controls from an age- and gender-stratified randomly sampled subcohort, were included in the current analysis. All examined esophageal cancers were identified as ESCC, and all GCs were adenocarcinomas. Cardia cancers were defined as those located in the proximal 3 cm of the stomach, whereas non-cardia cancers were those in the remainder of the stomach.

Both the Shanxi and NIT studies obtained informed consent from subjects and were approved by their Institutional Review Boards. The NCI Special Studies Institutional Review Board approved both the Shanxi and NIT studies and the overall GWAS.

\textbf{Gene and SNP selection}

A complete list of the 173 genes included can be found on the website of MD Anderson Cancer Center (http://sciencepark.mdanderson.org/labs/wood/).
DNA repair genetic variants and ESCC and GC

Table II

Supplementary Table S1

531 − 4
990 (71.0)
Non-cardia
Linxian NITs (NIT)
43 (42.6)
32
152 (41.9)
ESCC cases
)
57.8 (9.2)
990 (71.0)
Non-cardia
Linxian NITs (NIT)
43 (42.6)
32
152 (41.9)
ESCC cases

Statistical analyses were performed using the SAS (V9.2; SAS Institute, Cary, NC) and R language. We evaluated the LD between SNPs across specific gene regions with Haploview version 4.1.

Results

Characteristics of this study
A total of 1942 ESCCs, 1758 GCs and 2111 controls were drawn from the Shanxi (1421 ESCCs, 1395 GCs and 1660 controls) and NIT studies (521 ESCCs, 363 GCs and 451 controls). Characteristics of participants are shown in Table I. Shanxi participants were older and less likely to be female or have a family history of UGI cancer than NIT participants. In both studies, there were more cases with cardia than non-cardia cancer.

Association of ESCC and GC with individual genes
Among Shanxi participants, we identified 20 genes that were significantly associated with ESCC risk (P < 0.05) (Table II and Supplementary Table S1, available at Carcinogenesis Online). CHEK2 showed the strongest association with ESCC in the combined data (P = 2.00 × 1010), with a significance level that exceeded the Bonferroni-corrected threshold. Another 11 genes, including SMUG1, DLD, TP53, GTF2H3, FEN1, POLQ, HES3, RAD54B, MPG, FANCE and BRCA1, were significant in the combined data (P < 0.05) and had ORs of the most significant SNPs in the same direction in both the Shanxi and NIT data. SMUG1 was the only gene that replicated in NIT. In addition, the most significant SNP (rs4135054) in TDG was replicated in NIT (Table II and Supplementary Table S1, available at Carcinogenesis Online). Additionally adjusting for smoking (Supplementary Table S1, available at Carcinogenesis Online) and other variables for SNP-level analysis (data not shown) did not appreciably change the gene-level P-values from the primary model that adjusted for only age, gender and study.

For the 11 genes associated with risk of GC in Shanxi, 4 remained significant after combination with NIT, including CLK2, MRE11A, RAD54L and POLE (Table III and Supplementary Table S1, available at Carcinogenesis Online). CLK2 showed significance (P = 3.02 ×
The overall DNA repair pathways were associated with ESCC risk in the Shanxi, NIT and combined populations

Association of ESCC and GC with individual SNPs

We found three SNPs in CHEK2 (rs738722, rs1547014 and rs6005863) significantly associated with ESCC risk, exceeding Bonferroni-corrected threshold, and one SNP each in CHEK2 (rs2073327), SMUG1 (rs209166), TDP (rs4135054) and POLM (rs4236374) with P < 0.001 (Supplementary Table S3, available at Carcinogenesis Online), rs41052176 (CLK2) and rs13447720 (MRE11A) were associated with risk of GC (both P < 0.001). Other analyses indicated associations of rs9590896 (BRCA2) and rs7135624 (GTF2H3) with cancer risk (Supplementary Table S4, available at Carcinogenesis Online). rs738722, rs2092166 and rs1052176 were further plotted along with their proxies (based on Hapmap CHB-JPT) as a function of genomic location. The regional LD plots showed associations of rs738722 only in CHEK2 and rs2092166 only in SMUG1, whereas the most significant SNP in CLK2 (rs1052176) was also in LD with portions of HCN3, PKLR and FDPS, and several other genes (Supplementary Figure S1, available at Carcinogenesis Online).

Association of ESCC and GC with the overall pathways and subpathways

The overall DNA repair pathways were associated with ESCC risk (P = 6.37 × 10⁻⁴), but not GC (P = 0.20). We evaluated subpathways and observed significant associations only with homologous recombination (P = 1.27 × 10⁻⁴), which harbors CHEK2, and base excision repair (P = 0.012) (Supplementary Table S2, available at Carcinogenesis Online). For GC, we did not observe significant subpathways (data not shown).

Stratified analysis and interaction analysis

We observed an interaction between rs9590896 (BRCA2) and sex on ESCC (P \textit{OR} = 4.96 × 10⁻⁴) such that the SNP was significantly associated with risk only in men (OR = 1.33, 95% CI = 1.15–1.54), but not in women (OR = 0.87, 95% CI = 0.72–1.06). We did not observe significant interactions between SNPs and smoking or other covariates with P \textit{OR} < 0.001. However, at the threshold of 0.01, we observed an interaction between smoking and rs2092166 (SMUG1) on both ESCC and GC risk, with a significant association with ESCC and GC risk only observed among non-smokers; the P \textit{OR} for association with ESCC risk exceeded the Bonferroni-corrected threshold (P = 1.43 × 10⁻³). Finally, an interaction was found between smoking and rs11614717 (POLE) on GC risk, with the significant association of the SNP only among smokers (Supplementary Table S5, available at Carcinogenesis Online).

Discussion

There have been a number of previous reports relating genetic variants in DNA repair genes and risk of UGI cancer, but results have been inconsistent (14–21). Prior studies have had very limited coverage of DNA repair-related genes, typically evaluating only a handful of genes (e.g. XRCC1, OGG1 and APE1) (14–21). As a complex network, the significance of the DNA repair pathways in UGI cancer is not yet well understood. In our study, we observed that the DNA repair pathways overall, as well as numerous DNA repair-related genes, were associated with risk of ESCC. We also found evidence for associations between several DNA repair-related genes and GC risk, although the overall pathway itself was not significantly associated with GC. To our knowledge, this is the first study to comprehensively evaluate the association between the variants in DNA repair pathway genes and risk of UGI cancer.

The DNA repair pathways can be divided into functionally interwoven subpathways that are distinguished by the type of DNA lesion...
## Table III. The association between DNA repair pathway genes and risk of gastric adenocarcinoma in the Shanxi, NIT and combined populations\textsuperscript{a}

<table>
<thead>
<tr>
<th>Gene</th>
<th>Location</th>
<th>Gene-level analysis</th>
<th>No. of SNP</th>
<th>Most significant SNP analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Shangi, NIT, Combined</td>
<td>P  P  P</td>
<td>OR  P  OR  P  OR  P</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CLK2</td>
<td>1p21</td>
<td>3.83×10\textsuperscript{-3}</td>
<td>0.41</td>
<td>3.02×10\textsuperscript{-3}</td>
</tr>
<tr>
<td>MRE1A</td>
<td>1p21</td>
<td>0.049</td>
<td>0.10</td>
<td>6.06×10\textsuperscript{-3}</td>
</tr>
<tr>
<td>RAD54L</td>
<td>1p34</td>
<td>0.021</td>
<td>0.29</td>
<td>0.010</td>
</tr>
<tr>
<td>POLE</td>
<td>12q24</td>
<td>0.014</td>
<td>0.15</td>
<td>0.033</td>
</tr>
<tr>
<td>RECQL5</td>
<td>17q25</td>
<td>5.61×10\textsuperscript{-3}</td>
<td>0.14</td>
<td>0.050</td>
</tr>
<tr>
<td>POLB</td>
<td>8p11</td>
<td>0.022</td>
<td>0.77</td>
<td>0.054</td>
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<tr>
<td>MSH2</td>
<td>2p21</td>
<td>0.013</td>
<td>0.66</td>
<td>0.087</td>
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<tr>
<td>HEL308</td>
<td>4q21</td>
<td>0.028</td>
<td>0.80</td>
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<tr>
<td>SPO11</td>
<td>20q13</td>
<td>0.041</td>
<td>1.00</td>
<td>0.094</td>
</tr>
<tr>
<td>MAD2L2</td>
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<td>0.039</td>
<td>0.62</td>
<td>0.24</td>
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<tr>
<td>REVI</td>
<td>2q11</td>
<td>0.023</td>
<td>0.74</td>
<td>0.44</td>
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<tr>
<td><strong>Cardia cancer</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CLK2</td>
<td>1q21</td>
<td>2.87×10\textsuperscript{-3}</td>
<td>0.30</td>
<td>1.57×10\textsuperscript{-3}</td>
</tr>
<tr>
<td>MRE1A</td>
<td>1q21</td>
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<td>0.043</td>
<td>7.63×10\textsuperscript{-3}</td>
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<tr>
<td>RAD54L</td>
<td>1p34</td>
<td>0.063</td>
<td>0.31</td>
<td>0.021</td>
</tr>
<tr>
<td>POLE</td>
<td>12q24</td>
<td>0.11</td>
<td>0.089</td>
<td>0.25</td>
</tr>
<tr>
<td><strong>Other significant genes for cardia cancer, but not significant for the GC overall</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>BRCA2</td>
<td>13q13</td>
<td>0.013</td>
<td>0.79</td>
<td>7.12×10\textsuperscript{-3}</td>
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<tr>
<td><strong>Non-cardia cancer</strong></td>
<td></td>
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<td></td>
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<tr>
<td>CLK2</td>
<td>1q21</td>
<td>6.84×10\textsuperscript{-3}</td>
<td>0.87</td>
<td>0.010</td>
</tr>
<tr>
<td>MRE1A</td>
<td>1q21</td>
<td>0.16</td>
<td>0.75</td>
<td>0.11</td>
</tr>
<tr>
<td>RAD54L</td>
<td>1p34</td>
<td>0.20</td>
<td>0.71</td>
<td>0.25</td>
</tr>
<tr>
<td>POLE</td>
<td>12q24</td>
<td>0.038</td>
<td>0.46</td>
<td>0.023</td>
</tr>
<tr>
<td><strong>Other significant genes for gastric cancer, but not significant for the GC overall</strong></td>
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<td></td>
<td></td>
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<tr>
<td>ERCC2</td>
<td>19q13</td>
<td>0.020</td>
<td>0.14</td>
<td>0.012</td>
</tr>
<tr>
<td>XPA</td>
<td>9q22</td>
<td>0.022</td>
<td>0.83</td>
<td>0.047</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Genes were ranked by the gene-level P-value for GC overall. Four significant SNPs for GC overall were evaluated by subsite with the same order as in GC overall. Gene-level P-values were calculated using ARTP approach. The P-values and ORs for the SNPs were calculated from unconditional logistic regression models using genotype-trend tests adjusted for age (10 year categories), sex and study (for the combined population).
they process (10). Base excision repair plays a key role in repairing subtle DNA damage due to cellular metabolisms (32). Nucleotide excision repair mainly removes bulky single-strand adducts (32). Homologous recombination and non-homologous end-joining cope with double-strand breaks, where the former only acts in the S and G2 phases of the cell cycle (34). Mismatch excision repair is crucial to DNA repair during replication (10). Although previous studies have provided some insight into possible effects of DNA repair genes in cancer risk, consistent evidence has been sparse (14,21). A systematic review of meta-analyses relating variants in candidate genes to esophageal and GCs identified few robust relations with DNA repair genes (21). GWAS have advanced our understanding regarding the contribution of genetic susceptibility in UGI cancers (5,22–29); however, only CHEK2 among the DNA repair-related genes has been identified in GWAS to date (5,29). Further review of a continually updated Cancer Genome-wide Association and Meta Analyses database (http://www.hugenavigator.net/CancerGEMKB/calIntegratorStartPage.do, updated on 3 May 2012, retrieved 2 September 2012) did not find other noteworthy associations for DNA repair genes and UGI cancer risk (35).

Realizing the limitations of conventional single marker association analyses in identifying true gene associations, pathway analyses have been developed to complement GWAS (30). We, therefore, sought to establish an overall understanding of possible relationships between DNA repair pathway genes and the risk of UGI cancer.

In our study, we observed a significant association for the overall DNA repair pathways with ESCC. Among the 12 individual genes associated with risk of ESCC in the combined data, CHEK2 on 22q12, which encodes the checkpoint kinase CHK2, was the most significant. Central to transduction of the DNA damage signal, CHEK2 has been proposed to act as a cancer susceptibility gene (36,37). In our previous GWAS, CHEK2 was the only DNA repair-related gene that had SNPs significantly associated with risk of ESCC (5), a result confirmed recently by another GWAS (29). The present study extends the SNP-based GWAS results and provides evidence for the role of CHEK2 from gene-based analyses. SMUG1 on 12q13 showed significance in both the discovery and replication study sets. The uracil-DNA glycosylase SMUG1 coordinates the initial steps of base excision repair (BER) and is involved in the removal of 5-fluorouracil incorporated into DNA (38,39). Downregulation of SMUG1 was indicated as a typical feature of GC with microsatellite instability (40). The most significant SNP in SMUG1 in our study (rs2029166) was correlated previously with breast cancer risk (41). It remains to be seen whether this association is due to the function of SMUG1 or other yet unannotated genes, although a regional LD plot did indicate that the LD block centered on SMUG1. TDG located on 12q23 is another gene associated with ESCC risk in Shanxi for which the most significant SNP (rs4135054) was replicated in NIT. TDG encodes the thymine-DNA glycosylase and is located in a region of high loss of heterozygosity in GC (42). Previous GWAS have correlated SNPs in ACAD10 (rs11066015), RPL6 (rs11066280), C1orf51 (rs2074356), BRAP (rs3782886) and FZD10 (rs12580487) in this region with risk of ESCC (22,24,26). Our online pairwise LD search did not find close linkage between these previously reported SNPs and rs4135054 (TDG) (33).

Our analysis highlighted several other ESCC susceptibility genes. A prior study from our group revealed frequent somatic inactivation of TP53 in ESCC tissues in this population (43), and our observation of associations between SNPs in TP53 and ESCC provide additional evidence for this gene. We also showed associations for several other genes, including GTF2H3, FEN1, POLQ, HEL308, RAD54B, MFG, FANCI and BRCA1, with risk of ESCC. Further studies are warranted to validate these results.

We observed four significant genes for GC. CLK2 located at 1q21 was significantly associated with risk of GC overall as well as in both cardia and non-cardia subsites. CLK2 protein has been identified as a component of hepatic insulin signaling and glucose metabolism (44). The most significant SNP rs1052176 of CLK2 is also in LD with regions of HCN3, PKLR, FDP5 and several other genes (33); a deeper investigation into this region appears warranted. MRE11A was significantly associated with risk of GC, and the most significant SNP (rs13447720) replicated in the NIT. MRE11A at 11q21 encodes a nuclease involved in homologous recombination and telomere length maintenance, and it is reported that MRE11A expression is impaired in GC with microsatellite instability (45). We observed significant associations for MRE11A and risk of GC overall as well as for cardia cancers, but not for non-cardia cancers. It is worth noting that MRE11A was the only gene significantly associated with GC in both discovery and replication data sets, a finding limited to cardia cancer. Two other genes, RAD54L (1p34) and POLE (12q24), were also associated with GC in the combined data sets. However, RAD54L was only associated with cardia cancer, and POLE was only with non-cardia cancer.

Three other DNA repair genes that were not associated with GC risk overall were significantly related to risk in subtype analyses, suggesting possible different genetic susceptibility genes for cardia cancer and non-cardia cancer. BRCA2, a key breast cancer susceptibility gene that cooperates with RAD51 in homologous recombination (32), was associated only with risk of cardia cancer, whereas ERCC2 and XPA, which both act in nucleotide excision repair (32), were associated only with risk of non-cardia cancer.

The causes of the geographic correlation of UGI tumors, particularly ESCC and gastric cardia cancer, in the Taihang Mountain area have not been determined. In our study, we did not identify additional shared genes beyond PLC1E1, which was reported previously as associated with both ESCC and gastric cardia cancer (5). BRCA2 showed some common associations. It was significantly associated with both ESCC and cardia cancer in Shanxi data. Stratified analysis observed a significant interaction between rs9590896 in BRCA2 and gender on ESCC risk, where the significant association only existed in men. This might contribute to the observed difference in effect of this gene between Shanxi and NIT because the Shanxi study has a higher proportion of men. A previous study from our group found more frequent BRCA2 germline mutations in ESCC cases with a family history of UGI cancer, suggesting a possible role for BRCA2 in genetic susceptibility to familial ESCC (46). However, the present study failed to observe an interaction between rs9590896 and family history of UGI cancer for either ESCC or GC. Although risk factors for ESCC remain poorly understood in very high-risk regions such as northern China, nutritional inadequacies and thermal damage have been associated with risk of ESCC (6,7). The roles of predominantly H. pylori infection are well established in the development of GC (6–8). In esophageal and gastric carcinogenesis, exposure to carcinogens with consequent accumulation of DNA damage accompanied by deficits in DNA repair capacity from genetic polymorphisms presumably leads to genetic instability and carcinogenesis (10–13,47,48). In contrast to the findings in Western populations, smoking was only moderately associated with ESCC and GC risk in the Taihang Mountain area (6,7). To further evaluate smoking, we examined the possible interactions between smoking and selected SNPs. The results indicated a possible interaction between smoking and rs2029166 (SMUG1) on risk of ESCC and GC where the significant association with this SNP was only observed among non-smokers. The other possible effect modification by smoking was observed for rs11614717 (POLE) on GC risk. As this study was an association study, further functional studies are warranted to elucidate the mechanisms underlying the observed associations between the genetic variants in DNA repair pathways and risk of ESCC and GC and possible effect modifications by smoking.

Using a pathway-based approach, we comprehensively investigated associations between DNA repair genes and the risk of ESCC and GC in a high-risk population in north central China. We sought to replicate significant associations observed in the discovery population (Shanxi) in a second replication population (NIT). For the gene- and pathway-level analyses, we applied the resampling-based ARTP method to reduce the false positive rate from multiple comparisons. We also acknowledge limitations. Sample size in the NIT was only modest, which limited power in the replication analyses. Generalizability to other populations requires caution since our study was conducted among high-risk Han Chinese.

In conclusion, by taking into account prior biological knowledge, our pathway-based analysis identified significant associations between several DNA repair pathway genes and the risk of ESCC and...
GC, providing further evidence for the role of genetics in the etiology of UGI cancer. Confirmation of these findings in other populations, combined with advances in our understanding of the molecular mechanisms underlying these associations, is needed to solidify our understanding of the role of DNA repair genes in UGI carcinogenesis.

Supplementary material

Supplementary Tables S1–S5 and Figure S1 can be found at http://cacin.oxfordjournals.org/

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