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***Case Control Study***

**Association of *XPG*** **rs2094258 polymorphism with** **gastric cancer prognosis**

Wang XQ *et al*. Association of *XPG* polymorphisms with GC prognosis

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**Abstract**

***BACKGROUND***

The xeroderma pigmentosum group G (*XPG*) gene at chromosome 13q33 consists of 15 exons, which may be related to the occurrence and development of gastric cancer (GC).

***AIM***

To examine the association of several common single nucleotide polymorphisms (SNPs) of the *XPG* gene with GC risk and survival.

***METHODS***

Five SNPs of *XPG* (rs2094258, rs751402, rs873601, rs2296147, and rs1047768) were genotyped by PCR restriction fragment length polymorphism in 956 histologically confirmed GC cases and 1012 controls in North China. GC patients were followed for survival status and, if deceased, cause of death. Logistic regression and Cox regression were used for analysing associations of *XPG* SNPs with risk of GC and prognosis, respectively. For rs2094258, heterozygous model (CT *vs* CC), homozygous model (TT *vs* CC), recessive model (TT *vs* CT + CC), and dominant model (TT + CT *vs* CC) were analyzed.

***RESULTS***

None of the examined loci were statistically associated with GC risk, although rs2296147 was marginally associated with GC risk (*P* = 0.050). GC patients with the rs2094258 CT + CC genotype showed worse survival than those with the TT genotype (log-rank test, *P* = 0.028), and patients with the CC genotype had a tendency of unfavourable prognosis compared with those with the TT + CT genotype (log-rank test, *P* = 0.039). The increase in C alleles of rs2094258 [hazard ratio (HR) = 1.19, 95% confidence interval (CI): 1.02-1.45, *P* = 0.037] were associated with the long-term survival of GC cases. Other risk factors for survival included tumor differentiation (HR = 4.51, 95%CI: 1.99-8.23, *P* < 0.001), lymphovascular invasion (HR = 1.97, 95%CI: 1.44-3.01, *P* < 0.001), and use of chemotherapy (HR = 0.81, 95%CI: 0.63-0.98, *P* = 0.041).

***CONCLUSION***

The *XPG* rs2094258 polymorphism may be associated with overall survival in GC patients.

**Key words:** Xeroderma pigmentosum group G; Single nucleotide polymorphisms; rs2094258; Gastric cancer; Prognosis

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**Core tip:** This study investigated the relationships between five functional single nucleotide polymorphisms of the xeroderma pigmentosum group G (*XPG*) (rs2094258, rs751402, rs2296147, rs1047768, and rs873601) and gastric cancer (GC) risk and survival. The results showed an association between the *XPG* rs2094258 polymorphism and overall survival in patients with GC. GC patients with the rs2094258 CT + CC genotype showed a worse survival than those with the TT genotype, and patients with the CC genotype had a tendency of unfavourable prognosis compared with those with the TT + CT genotype. The increase in the number of C alleles of rs2094258 was associated with the long-term survival of GC cases.

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**INTRODUCTION**

Gastric cancer (GC) is one of the global leading causes of cancer-related death[1]. The World Health Organization (WHO) estimates that 1.03 million people are diagnosed and 783000 die of the disease each year[2]. The highest age standard incidence per 100000 population is observed in Eastern Asia[3], especially in China, at 22.7 per 100000[4]. Multiple factors contribute to the development of this disease, including environmental and genetic factors, such as *Helicobacter pylori* (*H. pylori*) infection, drinking, obesity, a high-salt diet, and various genetic factors[5]. Although GC morbidity and mortality have declined in recent years, the social and economic burden of the disease remains high[1,6,7].

DNA repair genes play a key role in maintaining the genomic DNA stability and integrity. Functional genetic variants of DNA repair genes may change the host DNA repair ability and thus affect tumor prognosis[8]. DNA repair genes participate in many crucial pathways including nucleotide excision repair (NER), which is involved in the repair of some types of DNA damage. Recent evidence suggests that NER factors function in processes that facilitate mRNA synthesis or shape three-dimensional chromatin structure[9]. Xeroderma pigmentosum group G (XPG or ERCC5) plays a key role in NER repair, as it can recognize DNA damage and initiate the NER process[10]. XPG has 3’-junction cutting ability on bubble substrates, resulting in 3’-incision in the human double-incision) repair system, and non-catalytically XPG is needed for subsequent 5’-incision by XPF-ERCC1[11].

Some studies have demonstrated that the single nucleotide polymorphisms (SNPs) of *XPG* may affect the development of cancer, such as lung cancer[12,13], colorectal cancer[14,15], breast cancer[16], neuroblastoma[17], Hodgkin’s lymphoma[18], and oral squamous cell carcinoma[19]. However, only a few studies have explored the associations between *XPG* gene SNPs and GC, and those studies show inconsistent results. Some studies reported no associations[20-22], while others demonstrated varying degrees of association[23,24]. Furthermore, few studies have explored the potential prognostic importance of *XPG* SNPs in GC patients[25]. Therefore, we examined GC risk and survival in relation to common functional *XPG* SNPs in a case-control study in North China.

**MATERIALS AND METHODS**

***Study subjects***

From September 2010 to June 2013, pathologically confirmed incident GC cases were selected from the First Affiliated Hospital of Xi’an Jiaotong University. During the same time period, controls were recruited from the Physical Examination Centre of the First Affiliated Hospital of Xi’an Jiaotong University. The cases and controls were matched by sex, age (within 5 years), and residential district. Socio-demographic and clinical data were collected during recruitment, such as alcohol consumption and smoking status. TNM staging of GC tumors was done according to the WHO standard. *H. pylori* infection status was tested by ELISA.The present study protocol was approved by the Institutional Review Board of Health Science Center of Xi’an Jiaotong University. Informed consent was obtained from all study participants.

***Follow-up***

Cases were followed for survival status and chemotherapy data every 3 mo within the first year and then annually afterwards. Causes and dates of death were recorded, and survival time was calculated from the date of recruitment. Survival time was calculated from time of recruitment to date of death, date of last contact (for those lost to follow-up), or to the last contact with living subjects at the end of the study.

***Genotyping***

Peripheral blood samples from all cases and controls were collected by the investigators. The TIANamp Blood DNA Kit (Tiangen, Beijing, China) was used for DNA extraction. XPG rs2094258, rs751402, rs873601, rs2296147, and rs1047768 polymorphism genotyping was performed by PCR restriction fragment length polymorphism (PCR-RFLP). The conditions of PCR amplification were: (1) denaturation at 95 °C for 5 min; (2) 30 cycles of denaturation at 94 °C for 60 s, annealing at 60 °C for 60 s, and extension at 72 °C for 60 s; and (3) extension at 72 °C for 10 min. PCR products were confirmed by agarose gel electrophoresis. Ten percent of the samples were randomly selected for repeated genotyping and the results were 100 percent consistent.

***Statistical analysis***

The socio-demographic data and clinical data between case and control subjects were compared by the chi-square test. A goodness-of-fit chi-squared test was also used to analyze whether the SNP (XPG rs2094258, rs751402, rs2296147, rs1047768 and rs873601) distributions conform to the Hardy-Weinberg equilibrium (HWE) in controls. Odds ratios (ORs) and 95% confidence intervals (CIs) for examined SNPs were analyzed by Logistic regression method and adjusted by age, gender, and *H. pylori* infection status. The heterozygous model, homozygous model, recessive model, and dominant model were all analyzed for five SNPs. For rs2094258, heterozygous model, homozygous model, recessive model, and dominant model were CT *vs* CC, TT *vs* CC, TT *vs* CT + CC, TT + CT *vs* CC, respectively. Kaplan-Meier method and log-rank test were used for plotting cases’ survival curves and for comparisons, respectively.

Multivariate Cox regression was used for exploring possible prognostic factors, which included gender, age, drinking, smoking, *H. pylori*, TNM stage, tumor differentiation, lymphovascular invasion, neural invasion, and chemotherapy. SPSS 24.0 statistical software was used for all statistical analyses (Statistical Package for the Social Sciences, version 24, SSPS Inc, Chicago, IL, United States). All statistical tests were two-sided, with *P* < 0.05 as the boundary value.

**RESULTS**

The majority of study participants were male and less than age 60, with no significant differences in these factors between cases and controls (Table 1). All five loci in the control group were consistent with the Hardy-Weinberg equilibrium. The rate of *H. pylori* infection in GC patients was significantly higher than that in the control group (70.6% *vs* 53.6%, *P* < 0.001). None of the associations between studied loci (rs2094258, rs751402, rs2296147, rs1047768, and rs873601) and GC risk was statistically significant (Table 2). However, the rs2296147 CC genotype frequency was higher in the GC case group than that in the control group (5.9% *vs* 3.9%, *P* = 0.050). After adjustment for age, sex, and *H. pylori* status, this genotype was marginally associated with a slightly higher risk of GC (OR = 1.40, 95%CI: 0.97-2.50, *P* = 0.061) than the TT genotype. The CC genotype was found to be marginally associated with a higher risk of GC (OR = 1.36, 95%CI = 0.99-2.49, *P* = 0.053) in the recessive model (CC *vs* CT + TT).

As the number of C alleles of rs2094258 increased, the survival rate of GC cases decreased (log-rank test, *P* = 0.032) (Table 3). Among all the cases, mortality was 45.4% with rs2094258 TT genotype (no C allele), 53.7% with CT genotype (one C allele), and 59.4% with CC genotype (two C alleles). The other four SNP loci (rs751402, Rs2296147, rs1047768, and rs873601) had no significant correlation with overall survival in patients with GC. For rs2094258, survival curves varied significantly with genotype (log-rank test, *P* = 0.032) (Figure 1A). GC patients with the rs2094258 CT + CC genotype showed a lower survival than patients with the TT genotype (log-rank test, *P* = 0.028) (Figure 1B). Cases with the CC genotype had a poorer prognosis than those with the TT + CT genotype (log-rank test, *P* = 0.039) (Figure 1C).

In univariate survival analysis, age (*P* = 0.011), TNM stage (*P* < 0.001), no chemotherapy (*P* < 0.001), poor differentiation (*P* < 0.001), neural invasion (*P* < 0.001), and lymphovascular invasion (*P* < 0.001) were positively associated with the 5-year survival of GC cases (Table 4). Gender and *H. pylori* status were not significantly associated with the 5-year survival of GC cases. In multivariate analysis, the increase in the number of C alleles of rs2094258 (hazard ratio [HR] = 1.19, 95%CI: 1.02-1.45, *P* = 0.037), chemotherapy (HR = 0.81, 95%CI: 0.63-0.98; *P* = 0.041), differentiation (HR = 4.51, 95%CI: 1.99-8.23, *P* < 0.001), and lymphovascular invasion (HR = 1.97, 95%CI: 1.44-3.01, *P* < 0.001) were associated with survival in GC cases (Table 5).

**DISCUSSION**

We genotyped five functional SNPs in the *XPG* gene involved in the NER pathway and assessed their associations with GC risk and survival in China. Although rs2296147 was marginally associated with risk of GC (*P* = 0.05), we found no statistically significant associations. However, as the number of C alleles of rs2094258 increased, the survival of GC cases showed a decreasing trend. Poor differentiation, lymphovascular invasion, no chemotherapy, and increase in the number of C alleles of rs2094258 were associated with decreased survival among cases.

Few studies have explored the association of *XPG* SNPs with survival in GC patients. Our results are similar to those of Liu *et al*[25], who analysed the association between *XPG* SNPs and survival among 373 GC patients in China. That study found that in univariate model, the survival rate of those with the *XPG* rs2094258 AG genotype was higher than that of wild-type GG carriers (HR = 0.59, 95%CI: 0.39-0.90, *P* = 0.014), and that in multivariate analysis, the AA + AG genotype presented a significant survival advantage over the GG genotype (adjusted HR = 0.65, 95%CI: 0.44-0.97)[25]. Liu *et al*[25] also found that the AA + AG genotype of the *XPG* rs2094258 polymorphism improved survival in those with the following characteristics: Age more than 60, lymphatic metastasis, TNM stage III-IV, Borrmann III–IV, and diffuse-type gastric tumors[25].

Consistent with our study, a recent meta-analysis did not observe an overall association between the *XPG* rs2094258 SNPs and GC risk[26]. Some studies have found associations between the rs2094258 polymorphism and GC risk[22,26-28]. For example, Yang *et al*[23] assessed three *XPG* SNPs (rs2296147T>C, rs2094258C>T, and rs873601G>A) and found that the rs2094258 C>T polymorphism was associated with an increased GC risk. Meanwhile, *H. pylori*-infected individuals with the rs2094258 TT genotype had a much higher GC risk (OR = 2.13, 95%CI: 1.22-3.35, *P* for interaction = 0.030)[23]. However, *H. pylori* status did not modify associations with this SNP in our data. Varying cofactors among study populations, small sample size, the use of different PCR methods, or the low penetrance of this SNP may account for the inconsistent findings[15].

*XPG* rs2296147 was not associated with GC in the present study, a finding consistent with those of other studies[24,25]. However, significant associations between rs2296147 polymorphisms and GC risk were observed in Asian populations in numerous studies in one meta-analysis (CT *vs* TT: OR = 0.93, 95%CI: 0.87-0.99, *P* = 0.036)[29]. Further, the rs2296147 CC genotype was associated with a reduced risk of GC in a Chinese population (OR = 0.52, 95%CI: 0.27-0.97)[23]. These differences may be due to regional differences, small sample size, or heterogeneity of clinical feature[26].

The NER pathway belongs to the DNA repair pathways, and its functions include removing exogenous or endogenous DNA damage or adduct between chains and recruiting proliferating-cell nuclear antigen to the damage site for the subsequent gap-filling DNA synthesis[30]. DNA repair usually includes two stages of excision and repair synthesis[31]. The *XPG* gene locating at chromosome 13q33 consists of 15 exons[10], which is considered to cut the DNA at the 3’ terminus, initiate transcription-coupled DNA repair, and participate in RNA polymerase II transcription[32]. In the process of DNA repair, XPG binds to XPB as part of the transcription factor IIH (TFIIH) complex and strongly interacts with the TFIIH complex, a multi-subunit complex located at the intersection of transcription and DNA repair[33], which is involved in the DNA demethylation induced by overexpression of Gadd45a[10]. Meanwhile, XPG-related nucleases are used hierarchically for the excision of double-stranded rDNA break resection[34]. Recent report suggests that XPG incises the R-loop structure and participates in the RAD52-dependent resolution of DNA-RNA hybrids[35]. The rs1047768, rs751402, and rs2296147 are located in the exon 2, proximal promoter, and 5' untranslated region of the gene, respectively[36,37]. Based on the dbSNP database, the rs2094258 located at the *XPG* gene intron region participates in the initiation of the transcription-coupled DNA repair.

The limitations of this study are as follows. First, we could not explore and determine the exact mechanism by which *XPG* SNPs influence GC survival. Second, this study only examined five functional SNPs and did not include all the SNPs in the *XPG* gene that might play a key role in GC development. Third, selection bias and information bias are inherent threats to case-control studies, and cannot be ruled out in our study. Genetic factors have been shown to play key roles in the development, progression, and prognosis of GC. If confirmed by other studies, the results of our study suggest that *XPG* rs2094258 polymorphisms may serve as genetic biomarkers for GC prognosis, and may provide clues to biological underpinnings of GC progression.

**ARTICLE HIGHLIGHTS**

***Research background***

Gastric cancer (GC) is one of the leading causes of cancer-related death worldwide, which causes a high social and economic burden. Xeroderma pigmentosum group G (XPG) or ERCC5 may play a key role in DNA repair, thus affecting cancer prognosis. Studies have shown that *XPG* SNPs may affect the development of cancer such as lung cancer, colorectal cancer, and breast cancer.

***Research motivation***

Only a few studies have explored the relationships between *XPG* gene SNPs and GC, and the results are inconsistent.

***Research objectives***

To examine GC risk and survival in relation to common functional *XPG* SNPs through a case-control study, which might improve our understanding of GC and provide new therapeutic targets for this malignancy.

***Research methods***

A total of 956 histologically confirmed GC cases and 1012 controls were matched by sex, age (within 5 years), and residential district. Cases were followed and the survival time was recorded. DNA was extracted from peripheral blood samples of all cases and controls. *XPG* rs2094258, rs751402, rs2296147, rs1047768, and rs873601 polymorphisms were genotyped using PCR-RFLP. Logistic regression and Cox regression were used for analyzing associations of *XPG* SNPs with risk of GC and prognosis, respectively.

***Research results***

We found that GC patients with the rs2094258 CT + CC genotype showed a worse survival than those with the TT genotype, and patients with the CC genotype had a tendency of unfavorable prognosis compared with those with the TT + CT genotype. The increase in the number of C alleles of rs2094258 was associated with the long-term survival of GC cases. Other risk factors for survival included tumor differentiation, lymphovascular invasion, and use of chemotherapy. However, the exact mechanisms by which *XPG* SNPs influence GC survival remain to be solved.

***Research conclusions***

The *XPG* rs2094258 polymorphism may be associated with overall survival in patients with GC.

***Research perspectives***

If confirmed by other studies, the results of our study suggest that *XPG* rs2094258 polymorphisms may serve as genetic biomarkers for GC prognosis, and may provide clues to biological underpinnings of GC progression.

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**Country of origin:** China   
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**Grade A (Excellent):** A  
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**Table 1 Demographic characteristics of the participants**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | | **Case** | **Control** | ***X*2** | ***P-*value** |
| ***n* = 956** | ***n* = 1012** |
| Age (yr) |  |  |  |  |  |
|  | ≤60 | 569 (59.5) | 637 (62.9) | 2.289 | 0.130 |
|  | >60 | 387 (40.5) | 375 (37.1) |  |  |
| Gender |  |  |  |  |  |
|  | Male | 667 (69.8) | 724 (71.5) | 0.662 | 0.416 |
|  | Female | 289 (30.2) | 288 (28.5) |  |  |
| *H. pylori* infection |  |  |  |  |  |
|  | Positive | 675 (70.6) | 542 (53.6) | 59.835 | <0.001 |
|  | Negative | 281 (29.4) | 470 (46.4) |  |  |
| Drinking |  |  |  |  |  |
|  | No | 758 (79.3) | 497 (49.1) | 2.787 | 0.095 |
|  | Yes | 198 (20.7) | 515 (50.9) |  |  |
| Smoking |  |  |  |  |  |
|  | No | 560 (58.6) | 517 (51.1) | 1.382 | 0.240 |
|  | Yes | 396 (41.4) | 495 (48.9) |  |  |

*H. pylori*: *Helicobacter pylori*.

**Table 2 Single nucleotide polymorphism and genotype distribution between gastric cancer cases and controls**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **SNP** | **Genotype** | **Case**  ***n* = 956** | **Control**  ***n* = 1012** | **HWE** | ***P*-value** | **OR** | **95%CI** | ***P*-value** | **OR1** | **95%CI** | ***P*-value** |
| Rs2094258 | CC | 390 (40.8) | 437 (43.2) | 0.318 | 0.853 | 1.00 |  |  |  |  |  |
|  | CT | 441 (46.1) | 464 (45.8) |  |  | 1.07 | 0.88-1.29 | 0.545 | 1.05 | 0.86-1.31 | 0.626 |
|  | TT | 125 (13.1) | 111 (11.0) |  |  | 1.26 | 0.94-1.69 | 0.133 | 1.19 | 0.90-1.20 | 0.249 |
|  | Dominant | 566 (59.2) | 575 (56.8) |  |  | 1.10 | 0.92-1.32 | 0.284 | 1.06 | 0.87-1.37 | 0.388 |
|  | Recessive | 831 (86.9) | 901 (89.0) |  |  | 1.22 | 0.93-1.60 | 0.150 | 1.19 | 0.91-1.72 | 0.303 |
| Rs751402 | CC | 366 (38.3) | 371 (36.7) | 0.183 | 0.913 | 1.00 |  |  |  |  |  |
|  | CT | 467 (48.8) | 476 (47.0) |  |  | 0.95 | 0.78-1.16 | 0.618 | 0.98 | 0.77-1.33 | 0.774 |
|  | TT | 123 (12.9) | 165 (16.3) |  |  | 0.88 | 0.67-1.15 | 0.341 | 0.90 | 0.61-1.28 | 0.491 |
|  | Dominant | 590 (61.7) | 632 (62.5) |  |  | 0.95 | 0.79-1.14 | 0.554 | 0.95 | 0.78-1.22 | 0.711 |
|  | Recessive | 833 (87.1) | 847 (83.7) |  |  | 0.90 | 0.71-1.15 | 0.411 | 0.93 | 0.69-1.18 | 0.487 |
| Rs2296147 | TT | 599 (62.7) | 640 (63.2) | 0.076 | 0.963 | 1.00 |  |  |  |  |  |
|  | CT | 301 (31.5) | 332 (32.9) |  |  | 0.97 | 0.80-1.17 | 0.745 | 0.97 | 0.80-1.19 | 0.674 |
|  | CC | 56 (5.9) | 40 (3.9) |  |  | 1.50 | 0.98-2.28 | 0.059 | 1.40 | 0.97-2.50 | 0.061 |
|  | Dominant | 357 (37.3) | 372 (36.8) |  |  | 1.03 | 0.85-1.23 | 0.789 | 1.01 | 0.80-1.38 | 0.865 |
|  | Recessive | 900 (94.1) | 973 (96.1) |  |  | 1.51 | 1.00-2.29 | 0.050 | 1.36 | 0.99-2.49 | 0.053 |
| Rs1047768 | TT | 505 (52.8) | 540 (53.4) | 0.367 | 0.832 | 1.00 |  |  |  |  |  |
|  | CT | 379 (39.6) | 406 (40.1) |  |  | 1.00 | 0.83-1.20 | 0.985 | 1.00 | 0.80-1.28 | 0.989 |
|  | CC | 72 (7.6) | 66 (6.5) |  |  | 1.17 | 0.82-1.66 | 0.395 | 1.11 | 0.79-1.92 | 0.505 |
|  | Dominant | 451 (47.2) | 472 (46.6) |  |  | 1.02 | 0.86-1.22 | 0.812 | 1.01 | 0.81-1.45 | 0.897 |
|  | Recessive | 884 (92.5) | 946 (93.5) |  |  | 1.17 | 0.83-1.65 | 0.381 | 1.12 | 0.74-1.84 | 0.561 |
| Rs873601 | GG | 271 (28.3) | 288 (28.5) | 0.247 | 0.884 | 1.00 |  |  |  |  |  |
|  | AG | 475 (49.7) | 514 (50.8) |  |  | 0.98 | 0.80-1.21 | 0.865 | 0.99 | 0.63-1.88 | 0.931 |
|  | AA | 210 (22.0) | 210 (20.7) |  |  | 1.06 | 0.83-1.37 | 0.638 | 1.03 | 0.71-2.01 | 0.807 |
|  | Dominant | 685 (71.7) | 724 (71.5) |  |  | 1.12 | 0.92-1.37 | 0.245 | 1.07 | 0.82-1.94 | 0.466 |
|  | Recessive | 746 (78.0) | 802 (79.2) |  |  | 1.08 | 0.87-1.33 | 0.511 | 0.98 | 0.88-1.37 | 0.685 |

1ORwas calculated by Logistic regression method after adjusting for age and gender. *H. pylori*: *Helicobacter pylori* infection status; SNP: Single nucleotide polymorphism; HWE: Hardy-Weinberg equilibrium; OR: Odds ratio.

**Table 3 Genotypes of single nucleotide polymorphism and 5-year survival status of gastric cancer cases**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **SNP** | **Genotype** | **Case** | **Death (%)** | **5-yr survival rate (%)** | ***P*-value1** |
| Rs2094258 | CC | 388 | 157 (40.5) | 59.4 | 0.032 |
|  | CT | 440 | 203 (46.1) | 53.7 |  |
|  | TT | 123 | 68 (55.3) | 45.4 |  |
| Rs751402 | CC | 363 | 162 (44.6) | 55.3 | 0.523 |
|  | CT | 465 | 216 (46.5) | 53.3 |  |
|  | TT | 121 | 50 (41.3) | 58.9 |  |
| Rs2296147 | TT | 589 | 281 (47.7) | 52.0 | 0.217 |
|  | CT | 297 | 124 (41.8) | 57.6 |  |
|  | CC | 50 | 23 (46.0) | 57.7 |  |
| Rs1047768 | TT | 501 | 243 (48.5) | 51.2 | 0.102 |
|  | CT | 375 | 152 (40.5) | 59.1 |  |
|  | CC | 67 | 33 (49.3) | 53.4 |  |
| Rs873601 | GG | 268 | 131 (48.9) | 51.2 | 0.362 |
|  | AG | 472 | 203 (43.0) | 56.8 |  |
|  | AA | 207 | 94 (45.4) | 54.7 |  |

1*P* was calculated by log-rank test. SNP: Single nucleotide polymorphism.

**Table 4 Univariate analysis of associations between influencing factors and 5-year survival of gastric cancer cases**

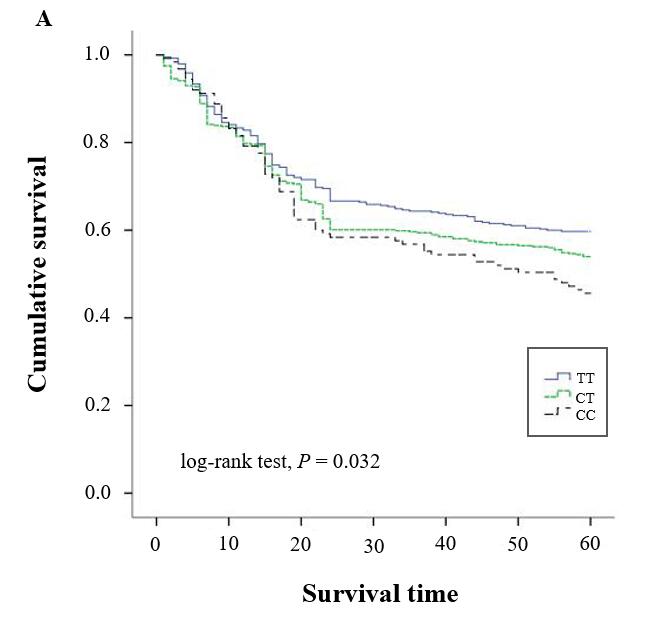
|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Variable** | **Classification** | ***n*** | **Death (%)** | **5-yr survival rate (%)** | ***P*-value1** |
| Gender | Male | 667 | 303 (45.4) | 54.2 | 0.399 |
|  | Female | 289 | 125 (43.3) | 56.1 |  |
| Age (yr) | ≤60 | 569 | 235 (41.3) | 58.5 | 0.011 |
|  | >60 | 387 | 193 (49.9) | 49.7 |  |
| Drinking | No | 758 | 335 (44.2) | 55.6 | 0.259 |
|  | Yes | 198 | 93 (47.0) | 52.9 |  |
| Smoking | No | 560 | 244 (43.6) | 55.9 | 0.417 |
|  | Yes | 396 | 184 (46.5) | 53.3 |  |
| *H. pylori* infection | Negative | 281 | 118 (42.0) | 58.1 | 0.284 |
|  | Positive | 675 | 310 (45.9) | 51.4 |  |
| TNM stage | I | 178 | 18 (10.1) | 87.7 | <0.001 |
|  | II | 366 | 129 (35.2) | 66.9 |  |
|  | III | 404 | 281 (69.6) | 29.8 |  |
| Differentiation | Poor | 661 | 329 (49.8) | 50.0 | <0.001 |
|  | Moderate or high | 280 | 99 (35.4) | 66.7 |  |
| Lymphovascular invasion | Negative | 269 | 57 (21.2) | 79.6 | <0.001 |
|  | Positive | 675 | 371 (55.0) | 44.8 |  |
| Neural invasion | Negative | 396 | 132 (33.3) | 67.4 | <0.001 |
|  | Positive | 548 | 296 (54.0) | 45.7 |  |
| Chemotherapy | No | 361 | 281 (77.8) | 22.9 | <0.001 |
|  | Yes | 592 | 147 (24.8) | 75.1 |  |

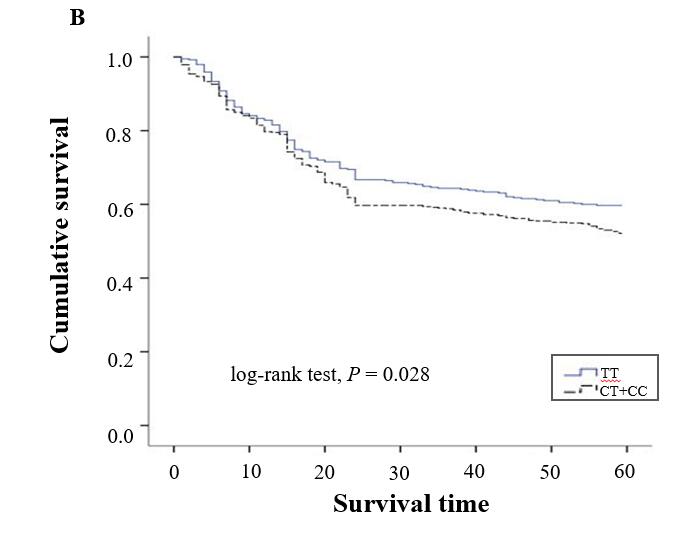
Missing values: 8 for tumor–node–metastasis stage, 15 for differentiation, 12 for lymphovascular invasion and neural invasion, and 3 for chemotherapy. 1*P* was calculated by log-rank test. *H. pylori*: *Helicobacter pylori*; TNM: Tumor–node–metastasis.

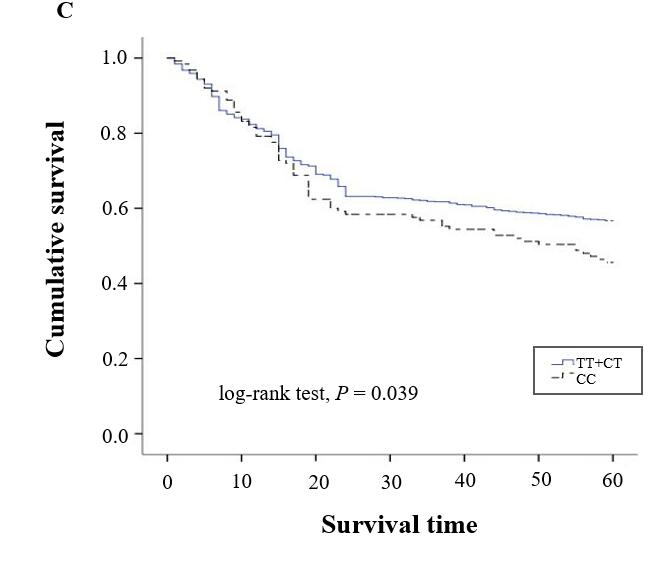
**Table 5 Multivariate analysis of gastric cancer survival**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Variable** | **Comparison** | **HR1** | **95%CI** | ***P*-value** |
| Differentiation | Poor *vs* Moderate or high | 4.51 | 1.99-8.23 | <0.001 |
| Lymphovascular invasion | Positive *vs* Negative | 1.97 | 1.44-3.01 | <0.001 |
| Chemotherapy | Yes *vs* No | 0.81 | 0.63-0.98 | 0.041 |
| Rs2094258 | Increase in C allele | 1.19 | 1.02-1.45 | 0.037 |

1HR was calculated by Cox regression model. HR: Hazard ratio.



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**Figure 1 Survival plots of gastric cancer cases stratified by rs2094258 genotype.** A:Compared with the survival of cases with no C allele (genotype TT, blue line), cases with one C allele (genotype CT, green line) demonstrated a decreased survival rate and cases with two C alleles (genotype CC, dotted line) exhibited the lowest survival rate; B:Compared with the survival of cases with no C allele (genotype TT, blue line), cases with recessive allele (genotype CT + CC, dotted line) demonstrated a decreased survival rate; C:In the dominant model, case with CC allele showed a lower survival rate compared with cases with dominant allele.