LncRNA H19 gene rs2839698 polymorphism is associated with a decreased risk of colorectal cancer in a Chinese Han population: A case-control study

Bingqu Yu1 | Jiayuan Chen1 | Chenfeng Hou1 | Lei Zhang2 | Jie Jia1

1Department of Gastroenterology, Wenzhou Hospital of Integrated Traditional Chinese and Western Medicine, Wenzhou, China
2Department anorectal surgery, The Second Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou, China

Correspondence
Jie Jia, Department of Gastroenterology, Wenzhou Hospital of Integrated Traditional Chinese and Western Medicine, No.75 Jinxiu Road, Lucheng District, Wenzhou 325028, Zhejiang Province, China.
Email: jjwzzxy@126.com

Funding information
This work was supported by grants from Traditional Chinese Medical science and technology plan of Zhejiang Province (2015ZB069).

Abstract
Background: Long non-coding RNA (lncRNA) H19 is involved in the carcinogenesis, progression, and metastasis of colorectal cancer (CRC). Recently, a few studies explored the relationship between lncRNA H19 gene rs2839698 polymorphism and CRC risk, but with conflicting findings.

Materials and methods: A case-control study with 315 CRC cases and 441 controls was designed in a Chinese population. Genotyping was performed using PCR-RFLP.

Results: It was found rs2839698 polymorphism was associated with a decreased risk of CRC (AA vs GG: OR, 0.73; 95% CI, 0.54-0.98; P = .037; A vs G: OR, 0.78; 95% CI, 0.63-0.96; P = .021). Stratified analyses indicated this positive association was also significant in the non-smokers (AA vs GG: OR, 0.49; 95% CI, 0.25-0.93; P = .029), non-drinkers, those aged ≥ 60 years, and overweight individuals (BMI ≥ 24). In addition, rs2839698 polymorphism was also related to the lymph node metastasis (AA vs GG: OR, 0.43; 95% CI, 0.21-0.88; P = .019) and tumor size (AA vs GG: OR, 0.42; 95% CI, 0.20-0.88; P = .020) for patients with CRC.

Conclusion: To sum up, the lncRNA H19 gene rs2839698 polymorphism decreases the risk of CRC in Chinese individuals, especially among the non-smokers, non-drinkers, individuals aged ≥ 60 years, and overweight individuals (BMI ≥ 24). Thus, the lncRNA H19 gene rs2839698 polymorphism might be an important biomarker and diagnostic marker for predicting the susceptibility to CRC in Chinese Han population.

KEYWORDS
case-control study, colorectal cancer, lncRNA H19, rs2839698 polymorphism

1 | INTRODUCTION

Colorectal cancer (CRC) was among the most commonly diagnosed cancers and cancer-related causes of death worldwide. The global number of CRC was supposed to increase by 60% to more than 2.2 million new patients and 1.1 million CRC-related deaths by 2030. CRC was reported to be the world’s 4th most deadly cancer with approximately 900,000 deaths annually. Studies showed that about 140,250 patients with CRC occurred in the United States in 2018. In China, CRC is the fourth and fifth most...
common cancer in women and men, respectively. Treatments for CRC included endoscopic and surgical local excision, chemotherapy and radiotherapy, targeted therapy, and immunotherapy and so on. The pathogenesis of CRC was complex and multifactorial, thus poorly understood. Although risk factors including smoking, excessive alcohol, excessive obesity, lack of physical exercise, and high consumption of red meat contributed to the risk of CRC, there were still CRC patients without exposure to these risk factors, indicating genetic susceptibility might play an important role in the pathogenesis of CRC. As reported, environmental factors, genetic factors, and their interactions contributed to the risk of CRC. Many studies have identified novel risk variants in patients with CRC.

Long non-coding RNAs (lncRNAs), deemed as non-protein-coding transcripts longer than 200 nucleotides, were associated with crucial functions of various biological processes that affected cancer susceptibility. LncRNAs played different roles in multiple physiological and pathological processes, including transcriptional regulation, posttranscriptional process, genome rearrangement, epigenetic control, chromatin modification, metabolic processes, and apoptosis. Increasing evidence identified the key roles of lncRNAs in human diseases, especially in cancer. The aberrant lncRNA expression may result in tumorigenesis. H19 was the first discovered lncRNA and was recognized as an important imprinted gene. LncRNAH19 was related to cancer, and it was regarded as an important cancer biomarker for human cancer diagnosis and detection. Aberrant change in lncRNA H19 expression was shown in various cancers, suggesting a pivotal role of H19 in cancer progression. Cui et al. indicated that H19 was upregulated in CRC. Yokoyama et al. showed that changes in H19 were considered for predicting the susceptibility to 5-FU-based neoadjuvant chemotherapy in rectal cancer. H19 was also reported as a regulator of drug resistance in CRC.

The lncRNA H19 gene is located on human chromosome 11p15.5, which contains four small introns and five exons. The single nucleotide polymorphisms (SNPs) in H19 gene may affect its gene expression and function, thereby conferring the susceptibility to CRC. Several studies explored the association between the H19 gene rs2839698 polymorphism and the risk of cancers, but the findings concerning different types of cancers were conflicting. Among these studies, Li et al. found that H19 gene rs2839698 polymorphism increased the risk of CRC. However, no other studies investigated the relationship between this SNP and CRC risk. Thus, we designed this case-control study to assess the effects of H19 gene rs2839698 polymorphism on the risk of CRC.

2. PATIENT AND METHODS

2.1. Subjects

This study enrolled 315 CRC cases and 441 gender- and age-matched controls from the Wenzhou Hospital of Integrated Traditional Chinese and Western Medicine Affiliated to Zhejiang Chinese Medical University and the Second Affiliated Hospital of Zhejiang Chinese Medical University between 2012 and 2018. No patients with CRC received chemotherapy or radiotherapy before surgery. The histology of patients with CRC was histopathologically confirmed by two local pathologists. The family history, the tumor node metastasis (TNM) stage, histological grade, tumor size, location of CRC, lymph node metastasis, and the histology were collected from the medical records. The controls were selected from individuals receiving health examinations at the same period in these hospitals. The individuals with family history of cancer or digestive diseases, metastases from other origins, and history of radiotherapy or chemotherapy were excluded.

The demographic information of all subjects was retrieved through a structured questionnaire, including age, smoking status, gender, alcohol consumption, and family history of cancers. This study was approved by the Ethics Committees of the two hospitals and met the standards of Declaration of Helsinki. Written informed consent was obtained from each subject.

2.2. Blood sampling and genotyping

Peripheral blood (2 mL) was taken from each of the cases and controls. Genomic DNA was extracted from peripheral blood leukocytes by a TIANamp Blood DNA kit (Tiangen Biotech). The quality and concentration of the extracted DNA were measured at optical density (OD) wavelengths 260 and 280 nm using NanoDrop (Thermo Scientific). This SNP was genotyped using a fluorescent-based restriction fragment length polymorphism method. The primers used for the nucleotide extension reaction were CATCGTCCCCAGCTGATGTC (forward) and GGAGTGATGACGGTGGAG (reverse). PCR was performed in 25 μL of reaction mixture including 1.25 μL Genotyping Assays (20×), 20 ng DNA, 12.5 μL Genotyping Master Mix (2×). PCRs were carried out with an initial denaturation at 96°C for 5 minutes, followed by 35 cycles of 96°C for 30 seconds, annealing at 57°C for 40 seconds, and ending with a final elongation step at 72°C for 5 minutes. About 10% of the selected samples were randomly chosen for genotyping twice to ensure the genotyping accuracy, and the results were 100% concordant.

2.3. Statistical analysis

The epidemiological variables of cases and controls were calculated using either Student’s t test (continuous variables) or chi-square (χ²) test (categorical variables). The deviation between the observed and the expected frequencies among controls was evaluated by Hardy-Weinberg equilibrium (HWE) test through a goodness-of-fit chi-square test. The relationship between the lncRNA H19 gene rs2839698 polymorphism and the CRC risk was evaluated by computing the crude and adjusted odds ratios (ORs) and their 95%
Subgroup analyses were conducted according to gender, age, alcohol, BMI, and smoking. In addition, the association between the lncRNA H19 gene rs2839698 polymorphism and clinicopathologic features of patients with CRC was also investigated. All statistical analyses were performed using SPSS 22.0 (SPSS Inc) with the significance level at $P < .05$.

### 3 | RESULT

#### 3.1 | Characteristics of the study population

Demographic information and clinical characteristics of the subjects are summarized in Table 1. The distributions of age, gender, smoking, and body mass index (BMI) did not differ significantly between the cancer cases and controls.

| Characteristics                  | Case (N = 315) | Control (N = 441) | $P$  |
|----------------------------------|---------------|------------------|------|
| Age                              | 63.35 ± 7.33  | 62.50 ± 7.33     | .116 |
| BMI                              | 25.18 ± 1.45  | 25.15 ± 1.51     | .802 |
| Gender                           |               |                  | .816 |
| Male                             | 60 (19.0%)    | 87 (19.7%)       |      |
| Female                           | 255 (81.0%)   | 354 (80.3%)      |      |
| Smoking                          |               |                  | .001 |
| Yes                              | 204 (64.8%)   | 203 (46.0%)      |      |
| No                               | 111 (35.2%)   | 238 (54.0%)      |      |
| Alcohol                          |               |                  | .001 |
| Yes                              | 277 (87.9%)   | 220 (49.9%)      |      |
| No                               | 38 (12.1%)    | 221 (50.1%)      |      |
| Family history                   |               |                  |      |
| Yes                              | 44 (14.0%)    |                  |      |
| No                               | 271 (86.0%)   |                  |      |
| Histological grade               |               |                  |      |
| Well differentiated              | 32 (10.2%)    |                  |      |
| Moderately differentiated        | 248 (78.7%)   |                  |      |
| Poorly differentiated            | 35 (11.1%)    |                  |      |
| TNM stage                        |               |                  |      |
| I                                | 67 (21.3%)    |                  |      |
| II                               | 90 (28.6%)    |                  |      |
| III                              | 93 (29.5%)    |                  |      |
| IV                               | 65 (20.6%)    |                  |      |
| Tumor size                       |               |                  |      |
| >4 cm                            | 165 (52.4%)   |                  |      |
| ≤4 cm                            | 150 (47.6%)   |                  |      |
| Lymph node metastasis            |               |                  |      |
| No                               | 182 (57.8%)   |                  |      |
| Yes                              | 133 (42.2%)   |                  |      |
| Location of colorectal cancer    |               |                  |      |
| Colon cancer                     | 113 (35.9%)   |                  |      |
| Rectal cancer                    | 202 (64.1%)   |                  |      |
| Pathology subtypes               |               |                  |      |
| Adenocarcinoma                   | 300 (95.1%)   |                  |      |
| Squamous cell carcinoma          | 13 (4.1%)     |                  |      |
| Others                           | 2 (0.8%)      |                  |      |

**Note:** Bold values are significant results.

**Abbreviations:** BMI, body mass index; TNM, tumor node metastasis.
cases and the controls. The percentage of drinkers in the patients with CRC was significantly higher than in the controls (P < .001). Location of CRC showed that 113 cases were colon cancer and 202 were rectal cancer. The 315 patients with CRC included 300 cases with adenocarcinoma, 13 cases with squamous cell carcinoma, and 2 cases with other types of CRC. Based on the histological grade of cancer cell differentiation, 32, 248, and 35 CRC cases were well, moderately, and poorly differentiated, respectively. Other clinical characteristics of patients with CRC including lymph node metastasis, family history, TNM stage, tumor stage, and tumor size are shown in Table 1.

3.2 Relationship between IncRNA H19 gene rs2839698 polymorphism and CRC risk

The genotype and allele distributions for the IncRNA H19 gene rs2839698 polymorphism were significantly different between the patients with CRC and the controls (Table 2). The genotype frequencies of H19 gene rs2839698 polymorphism were in accordance with HWE test among the control subjects. The AA genotype or AA + GA genotype carriers showed a significantly decreased risk for CRC (AA vs GG: OR, 0.73; 95% CI, 0.54-0.98; P = .037; AA + GA vs GG: OR, 0.73; 95% CI, 0.54-0.98; P = .037). Similarly, the A allele of the H19 gene rs2839698 polymorphism was also associated with a decreased risk for CRC (A vs G: OR, 0.78; 95% CI, 0.50-0.96; P = .030). However, the results were significant in dominant genetic models after adjusting for gender, age, BMI, alcohol, and smoking (AA + GA vs GG: adjusted OR, 0.69; 95% CI, 0.50-0.96; P = .030).

Stratified analyses were analyzed according to gender, age, alcohol, smoking, and BMI (Table 3). A significantly decreased risk of CRC was found in non-smokers (AA vs GG: OR, 0.49; 95% CI, 0.25-0.93; P = .029), non-drinkers, the subgroup of older patients with CRC (age ≥ 60 years), and overweight individuals (BMI ≥ 24). However, stratified analysis by gender did not obtain positive findings. After adjusting for gender, age, alcohol, smoking, and BMI, similar results were obtained in Table S1. Those data indicated that H19 gene rs2839698 polymorphism correlated with a decreased risk of CRC among non-smokers, non-drinkers, age ≥ 60 years subjects, and overweight individuals (BMI ≥ 24).

3.3 Correlation between IncRNA H19 gene rs2839698 polymorphism and clinicopathological characteristics of CRC patients

At last, the association between IncRNA H19 gene rs2839698 polymorphism and the clinicopathologic features of patients with CRC was investigated (Table 4). The patients with CRC were not prone to lymph node metastasis (AA vs GG: OR, 0.43; 95% CI, 0.21-0.88; P = .019). In addition, a significantly decreased risk was shown in CRC patients with tumor size < 4 cm (AA vs GG: OR, 0.42; 95% CI, 0.20-0.88; P = .020). No association between this SNP and CRC risk was obtained regarding histological grade, TNM stage, family history, histology, and location of CRC. To sum up, IncRNA H19 gene rs2839698 polymorphism was related with lymph node metastasis and the tumor size of CRC.

4 DISCUSSION

The H19 gene rs2839698 polymorphism was shown to decrease the risk of CRC in a Chinese population. Stratified analyses showed H19 gene rs2839698 polymorphism decreased the risk of CRC among non-smokers, non-drinkers, aged ≥ 60 years, and overweight individuals (BMI ≥ 24). In addition, the rs2839698 polymorphism was significantly correlated with lymph node metastasis and tumor size in patients with CRC.

LncRNAs are transcripts longer than 200 nucleotides, which could not be translated into proteins. LncRNAs were localized in the nucleus or cytoplasm. There were approximately more than 60 000 lncRNAs found in humans. LncRNAs could be further classified into four types: long intergenic ncRNAs (lincRNAs),

### TABLE 2 Association between H19 gene rs2839698 polymorphism and colorectal cancer risk determined by logistic regression analyses

| Models     | Genotype | Case (n, %) | Control (n, %) | OR (95% CI) | P-value | OR (95% CI)* | P-value* |
|------------|----------|------------|---------------|-------------|---------|-------------|---------|
| Co-dominant| GG       | 134 (42.7%)| 154 (35.1%)   | 1.00        | -       | 1.00        | -       |
| Heterozygote| GA      | 140 (44.6%)| 211 (48.1%)   | 0.77 (0.56-1.05) | .098 | 0.72 (0.50-1.02) | .062 |
| Homozygote | AA       | 40 (12.7%) | 74 (16.9%)    | 0.62 (0.40-0.97) | .038 | 0.63 (0.38-1.02) | .062 |
| Dominant   | GG       | 134 (42.7%)| 154 (35.1%)   | 1.00        | -       | 1.00        | -       |
|            | AA + GA  | 180 (57.3%)| 285 (64.9%)   | 0.73 (0.54-0.98) | .037 | 0.69 (0.50-0.96) | .030 |
| Recessive  | AA + GG  | 274 (87.3%)| 365 (83.1%)   | 1.00        | -       | 1.00        | -       |
|            | AA       | 40 (12.7%) | 74 (16.9%)    | 0.72 (0.47-1.09) | .118 | 0.75 (0.48-1.18) | .214 |
| Allele     | G        | 408 (65.0%)| 519 (59.1%)   | 1.00        | -       | -           | -       |
|            | A        | 220 (35.0%)| 359 (40.9%)   | 0.78 (0.63-0.96) | .021 | -           | -       |

Note: The genotyping was successful in 314 cases and 439 controls for rs2839698 polymorphism; Bold values are statistically significant (P < .05).

*Adjustment for age, sex, BMI, alcohol, and smoking.
pseudogenes, antisense RNAs (asRNAs), and circular RNAs (circRNAs). LncRNAs were the main components of the human transcriptome. LncRNAs were involved in biological processes by interfering with gene expression in some cancer types. Recently, increasing studies revealed the critical roles of lncRNAs in the development of cancers. The dysregulated lncRNAs regulated cell proliferation and apoptosis, invasion, epithelial-to-mesenchymal transition, migration, and drug resistance. In addition, some lncRNAs were biomarkers for the prognosis and diagnosis of some cancers. H19, a 2.3 kb intergenic and maternally expressed lncRNA, is located on chromosome 11p15.5. H19 had a pivotal role in cancer development including lung cancer, pancreatic cancer, ovarian cancer, bladder cancer, neuroblastoma, and CRC. H19 gene rs2839698 polymorphism increased the risk of gastric cancer in a Chinese Han population and the rs2839698 CT and TT genotypes were also associated with higher serum H19 mRNA levels. Li et al observed that the A allele of rs2839698 polymorphism increased the risk of CRC and this SNP may change the crucial folding structures and the target microRNAs of H19. This present study showed H19 gene rs2839698 polymorphism was associated with a deceased risk of CRC, which was different from the study by Li et al We thought the inconsistency may be attributed to four reasons. Firstly, our data indicated H19 gene rs2839698 polymorphism interacted with some exposure factors, which were evidently diverse. Secondly, populations from different areas had different eating habits and living environments. Thirdly, differences in genotyping methods and the inclusion criteria may contribute to the inconsistent results. Fourthly, clinical heterogeneity of CRC may be attributed to the conflicting findings because the malignancy degree and pathological types of CRC differed among different studies.

The stratified analyses uncovered a decreased CRC risk in non-smokers, non-drinkers, aged ≥ 60 years, and overweight individuals (BMI ≥ 24). The above data suggested that the individuals exposed to these risk factors were not prone to CRC. Next, we explored the relationship between this SNP and clinicopathologic features of patients with CRC and uncovered that the CRC patients with rs2839698 polymorphism genotypes were not prone to lymph node metastasis and showed a decreased risk in the subgroup with tumor size < 4 cm. However, we did not obtain positive findings in the analyses of histological grade, TNM stage, family history, histology, or location of CRC. It should be noted that Li et al showed that colon

### TABLE 3 Stratified analyses between H19 gene rs2839698 polymorphism and the risk of colorectal cancer

| Variable | GG | GA | AA | GA vs GG | AA vs GG | AA vs GG + GA | AA + GA vs GG |
|----------|----|----|----|---------|---------|-------------|--------------|
| Sex      |    |    |    |         |         |             |              |
| Male     | 30/33 | 24/44 | 6/10 | 0.60 (0.30-1.21) | 0.153 | 0.66 (0.21-2.04) | 0.470 |
| Female   | 104/121 | 116/167 | 34/64 | 0.81 (0.57-1.16) | 0.251 | 0.62 (0.38-1.01) | 0.055 |
| Smoking  |    |    |    |         |         |             |              |
| Yes      | 80/77 | 101/102 | 23/24 | 0.96 (0.63-1.46) | 0.858 | 0.92 (0.48-1.77) | 0.808 |
| No       | 54/77 | 39/109 | 17/50 | 0.51 (0.31-0.85) | 0.009 | 0.49 (0.25-0.93) | 0.029 |
| Alcohol  |    |    |    |         |         |             |              |
| Yes      | 109/83 | 131/97 | 36/40 | 1.04 (0.71-1.53) | 0.847 | 0.69 (0.40-1.17) | 0.165 |
| No       | 25/71 | 9/114 | 4/34 | 0.22 (0.10-0.51) | 0.001 | 0.33 (0.11-0.14) | 0.058 |
| Age (y)  |    |    |    |         |         |             |              |
| <60      | 28/56 | 36/68 | 14/23 | 1.06 (0.58-1.94) | 0.854 | 1.22 (0.55-2.72) | 0.632 |
| ≥60      | 106/98 | 104/143 | 26/51 | 0.68 (0.47-0.98) | 0.041 | 0.47 (0.27-0.81) | 0.007 |
| BMI      |    |    |    |         |         |             |              |
| <24      | 28/38 | 25/43 | 11/11 | 0.79 (0.39-1.58) | 0.503 | 1.36 (0.52-3.57) | 0.536 |
| ≥24      | 106/116 | 115/168 | 29/63 | 0.75 (0.53-1.07) | 0.110 | 0.50 (0.30-0.84) | 0.008 |

Note: Bold values are statistically significant (P < .05).
The tumor site, the well-differentiated grade, and Duke’s stage of C/D were significantly related to CRC risk. To sum up, our study indicated that lncRNA H19 gene rs2839698 polymorphism was correlated with lymph node metastasis and the tumor size of CRC.

The advantages of this study included the following aspects: One, this is the first study to uncover the protective role of H19 gene rs2839698 polymorphism in CRC development; two, we observed that H19 gene rs2839698 polymorphism was related to a decreased risk for CRC in non-smokers, non-drinkers, and those aged ≥ 60 years; and three, the rs2839698 polymorphism was significantly correlated with lymph node metastasis and tumor size in patients with CRC. We think these abovementioned points were the innovations of this study, which were not found in other studies.

However, this present study had several limitations. First, the sample size was not large, which may yield false-positive results. Second, this case-control study may have some weakness in identifying the cause-effect relationship. Third, the lack of follow-up data on patients with CRC limited further analysis. Fourth, the controls from the two hospitals may not fully represent the general population. Last, we only investigated one SNP of H19 gene.

### CONCLUSION

The lncRNA H19 gene rs2839698 polymorphism is associated with deceased risk for CRC. Further studies with larger sample sizes are warranted to further verify this finding.

### CONFLICT OF INTEREST

The authors declare no competing interests.

### AUTHOR CONTRIBUTIONS

Bingqu Yu, Jiayuan Chen, Chenfeng Hou, Lei Zhang, and Jie Jia conceived of the study and participated in its design. Bingqu Yu, Jiayuan Chen, Chenfeng Hou, Lei Zhang, and Jie Jia conducted the systematic literature review. Jie Jia performed data analyses. Bingqu Yu, Jiayuan Chen, Chenfeng Hou, Lei Zhang, and Jie Jia drafted the study. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

### ORCID

Jie Jia [https://orcid.org/0000-0001-8504-742X](https://orcid.org/0000-0001-8504-742X)
1. Dekker E, Rex DK. Advances in CRC prevention: screening and surveillance. Gastroenterology. 2018;154(7):1970-1984.

2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424.

3. Dekker E, Tanis PJ, Vleugels JLA, Kasi PM, Wallace MB. Colorectal cancer. Lancet. 2019;394(10207):1467-1480.

4. Yarla NS, Gali H, Pathuri G, et al. Targeting the paracrine hormone-dependent guanylate cyclase/cGMP/phosphodiesterases signaling pathway for colorectal cancer prevention. Semin Cancer Biol. 2019;56:168-174.

5. Chen W, Zheng R, Baade PD, et al. Cancer statistics in China, 2015. CA Cancer J Clin. 2016;66(2):115-132.

6. Keum N, Giovannucci E. Global burden of colorectal cancer: emerging trends, risk factors and prevention strategies. Nat Rev Gastroenterol Hepatol. 2019;16(12):713-732.

7. Liang PS, Chen TY, Giovannucci E. Cigarette smoking and colorectal cancer incidence and mortality: systematic review and meta-analysis. Int J Cancer. 2009;124(10):2406-2415.

8. Lichtenstein P, Holm NV, Verkasalo PK, et al. Tablet factors in the causation of cancer–analyses of cohorts of twins from Sweden, Denmark, and Finland. N Engl J Med. 2000;343(2):78-85.

9. Huyghe JR, Bien SA, Harrison TA, et al. Discovery of common and rare genetic risk variants for colorectal cancer. Nat Genet. 2019;51(1):76-87.

10. Zhang B, Jia W-H, Matsuda K, et al. Large-scale genetic study in East Asians identifies six new loci associated with colorectal cancer risk. Nat Genet. 2014;46(6):533-542.

11. Jia W-H, Zhang B, Matsuo K, et al. Genome-wide association analyses in East Asians identify new susceptibility loci for colorectal cancer. Nat Genet. 2013;45(2):191-196.

12. Al-Tassan NA, Whiffin N, Hosking FJ, et al. A new GWAS and meta-analysis with 1000Genomes imputation identifies novel risk variants for colorectal cancer. Sci Rep. 2015;5:10442.

13. Hua RX, Zhuo ZJ, Zhu J, et al. XPG gene polymorphisms contribute to colorectal cancer susceptibility: a two-stage case-control study. J Cancer. 2016;7(12):1701-1709.

14. Hua RX, Zhu J, Jiang D-H, et al. Association of XPC gene polymorphisms with colorectal cancer risk in a Southern Chinese population: a case-control study and meta-analysis. Genes (Basel). 2016;7(10):73.

15. Gupta RA, Shah N, Wang KC, et al. Long non-coding RNA HOTAIR reprograms chromatin state to promote cancer metastasis. Nature. 2010;464(7291):1071-1076.

16. Wang KC, Chang HY. Molecular mechanisms of long noncoding RNAs. Mol Cell. 2011;43(6):904-914.

17. Chen X, Yan CC, Zhang X, You ZH. Long non-coding RNAs and complex diseases: from experimental results to computational models. Brief Bioinform. 2017;18(4):558-576.

18. Li Y, Zhuo ZJ, Zhou H, et al. H19 gene polymorphisms and neuroblastoma susceptibility in Chinese children: a six-center case-control study. J Cancer. 2019;10(25):6358-6363.

19. Shi X, Sun M, Liu H, Yao Y, Song Y. Long non-coding RNAs: a new frontier in the study of human diseases. Cancer Lett. 2013;339(2):159-166.

20. Liz J, Esteller M. IncRNAs and microRNAs with a role in cancer development. Biochim Biophys Acta. 2016;1859(1):169-176.

21. Huarte M, Rinn JL. Large non-coding RNAs: missing links in cancer? Hum Mol Genet. 2010;19(2):R152-161.

22. Liu Y, He A, Liu B, Huang Z, Mei H. Potential role of IncRNA H19 as a cancer biomarker in human cancers detection and diagnosis: a pooled analysis based on 1585 subjects. Biomed Res Int. 2019;2019:9056458.

23. Zhang L, Zhou Y, Huang T, et al. The interplay of LncRNA-H19 and its binding partners in physiological process and gastric carcinogenesis. Int J Mol Sci. 2017;18(2):450.

24. Cui H, Onyango P, Brandenburg S, Wu Y, Hsieh CL, Feinberg AP. Loss of imprinting in colorectal cancer linked to hypomethylation of H19 and IGF2. Cancer Res. 2002;62(22):6442-6446.

25. Bermúdez M, Aguilar-Medina M, Lizárraga-Verdugo E, et al. LncRNAs as regulators of autophagy and drug resistance in colorectal cancer. Front Oncol. 2019;9:1008.

26. Sun F, Liang W, Qian J. The identification of CRNDE, H19, UCA1 and HOTAIR as the key IncRNAs involved in oxaliplatin or irinotecan resistance in the chemotherapy of colorectal cancer based on integrative bioinformatics analysis. Mol Med Rep. 2019;20(4):3583-3596.

27. Lu L, Hou Z, Li L, et al. Methylation pattern of H19 exon 1 is closely related to preeclampsia and trophoblast abnormalities. Int J Mol Med. 2014;34(3):765-771.

28. Verhaegh GW, Verkleij L, Vermeulen SH, den Heijer M, Witjes JA, Kiemeney LA. Polymorphisms in the H19 gene and the risk of bladder cancer. Eur Urol. 2008;54(5):1118-1126.

29. Yang C, Tang R, Ma X, et al. Tag SNPs in long non-coding RNA H19 contribute to susceptibility to gastric cancer in the Chinese Han population. Oncotarget. 2015;6(17):15311-15320.

30. Gong W-J, Yin J-Y, Li X-P, et al. Association of well-characterized lung cancer IncRNA polymorphisms with lung cancer susceptibility and platinum-based chemotherapy response. Tumour Biol. 2016;37(6):8349-8358.

31. Li S, Hua Y, Jin J, et al. Association of genetic variants in IncRNA H19 with risk of colorectal cancer in a Chinese population. Oncotarget. 2016;7(18):25470-25477.

32. Hua Q, Lv X, Gu X, et al. Genetic variants in IncRNA H19 are associated with the risk of bladder cancer in a Chinese population. Mutagenesis. 2016;31(5):531-538.

33. Hu C, Yang T, Pan J, et al. Associations between H19 polymorphisms and neuroblastoma risk in Chinese children. Biosci Rep. 2019;39(4):1-7.

34. Wang J, Zhuo Z, Chen M, et al. RAN/RANBP2 polymorphisms and neuroblastoma risk in Chinese children: a three-center case-control study. Aging (Albany NY). 2018;10(4):808-818.

35. Li Y, Zhuo ZJ, Zhou H, et al. Additional data support the role of LINC00673 rs11655237 C>T in the development of neuroblastoma. Aging (Albany NY). 2019;11(8):2369-2377.

36. Cheng J, Zhou Z, Xin Y, et al. Relevance of XPD polymorphisms to neuroblastoma risk in Chinese children: a four-center case-control study. Aging (Albany NY). 2018;10(8):1989-2000.

37. Zhuo ZJ, Zhang R, Zhang J, et al. Associations between IncRNA MEG3 polymorphisms and neuroblastoma risk in Chinese children. Aging (Albany NY). 2018;10(3):481-491.

38. Wan Q, Zhang D, Zhou Q, et al. Association of CD44 gene rs187115 polymorphism with colorectal cancer risk and prognosis in Chinese Han population: a case-control study. Aging (Albany NY). 2019;11(21):9616-9625.

39. Qian H, Zhang D, Bao C. Two variants of Interleukin-1B gene are associated with the decreased risk, clinical features, and better overall survival of colorectal cancer: a two-center case-control study. Aging (Albany NY). 2018;10(12):4084-4092.

40. Chan JJ, Tay Y. Noncoding RNA:RNA regulatory networks in cancer. Int J Mol Sci. 2018;19(5):1310.

41. Derrien T, Johnson R, Bussotti G, et al. The GENCODE v7 catalog of human long noncoding RNAs: analysis of their gene structure, evolution, and expression. Genome Res. 2012;22(9):1775-1789.

42. Cabill MN, Dunagin MC, McClanahan PD, et al. Localization and abundance analysis of human IncRNAs at single-cell and single-molecule resolution. Genome Biol. 2015;16:20.

43. Patrushev LJ, Kovalenko TF. Functions of noncoding sequences in mammalian genomes. Biochemistry (Mosc). 2014;79(13):1442-1469.
44. Lanzafame M, Bianco G, Terracciano LM, Ng CKY, Piscuoglio S. The role of long non-coding RNAs in hepatocarcinogenesis. *Int J Mol Sci*. 2018;19(3):682.
45. Klinge CM. Non-coding RNAs: long non-coding RNAs and microRNAs in endocrine-related cancers. *Endocr Relat Cancer*. 2018;25(4):R259-R282.
46. Chi Y, Wang D, Wang J, Yu W, Yang J. Long non-coding RNA in the pathogenesis of cancers. *Cels*. 2019;8(9):1015.
47. Bhan A, Soleimani M, Mandal SS. Long noncoding RNA and cancer: a new paradigm. *Cancer Res*. 2017;77(15):3965-3981.
48. Liao S, Yu C, Liu H, Zhang C, Li Y, Zhong X. Long non-coding RNA H19 promotes the proliferation and invasion of lung cancer cells and regulates the expression of E-cadherin, N-cadherin, and vimentin. *Onco Targets Ther*. 2019;12:4099-4107.
49. Wang L, Sun Y, Yi J, et al. Targeting H19 by lentivirus-mediated RNA interference increases A549 cell migration and invasion. *Exp Lung Res*. 2016;42(7):346-353.
50. Yang W, Ning N, Jin X. The IncRNA H19 promotes cell proliferation by competitively binding to miR-200a and derepressing beta-catenin expression in colorectal cancer. *Biomed Res Int*. 2017;2017:2767484.
51. Tsang WP, Ng EKO, Ng SSM, et al. Oncofetal H19-derived miR-675 regulates tumor suppressor RB in human colorectal cancer. *Carcinogenesis*. 2010;31(3):350-358.
52. Ohtsuka M, Ling H, Ivan C, et al. H19 noncoding RNA, an independent prognostic factor, regulates essential Rb-E2F and CDK8-beta-catenin signaling in colorectal cancer. *EBioMedicine*. 2016;13:113-124.
53. Qin W, Wang X, Wang Y, et al. Functional polymorphisms of the IncRNA H19 promoter region contribute to the cancer risk and clinical outcomes in advanced colorectal cancer. *Cancer Cell Int*. 2019;19:215.
54. Yokoyama Y, Sakatani T, Wada R, et al. In vitro and in vivo studies on the association of long noncoding RNAs H19 and urothelial cancer associated 1 with the susceptibility to 5fluorouracil in rectal cancer. *Int J Onkol*. 2019;56(6):1361-1371.

SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.

**How to cite this article:** Yu B, Chen J, Hou C, Zhang L, Jia J. LncRNA H19 gene rs2839698 polymorphism is associated with a decreased risk of colorectal cancer in a Chinese Han population: A case-control study. *J Clin Lab Anal*. 2020;34:e23311. [https://doi.org/10.1002/jcla.23311](https://doi.org/10.1002/jcla.23311)