Association between long noncoding RNA rs944289 and rs7990916 polymorphisms and the risk of colorectal cancer in a Chinese population

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Long non-coding RNAs (lncRNAs) play vital roles in the tumorigenesis of many cancers. Single nucleotide polymorphisms (SNPs) of the lncRNA also play vital roles in tumorigenesis. We explored lncRNA rs944289 and rs7990916 polymorphisms and analyzed the relationship between these lncRNA polymorphisms with the colorectal cancer (CRC) risk in a Chinese population. We recruited 1003 CRC patients from the Affiliated People’s Hospital of Jiangsu University and the Fujian Medical University Union Hospital from October 2014 to August 2017. Genomic DNA was extracted using a DNA Kit from lymphocytes of peripheral blood and the genotyping was performed with a SNPscan method. We found that the rs944289 TT homozygote was associated with the decreased CRC risk in the overall population. LncRNA rs944289 TT decreased the CRC risk in the subgroup of female, male, age ≥ 61, without alcohol intake, smoking and BMI ≥ 24 by logistic regression. The subgroup analysis revealed that lncRNA rs7990916 was not associated with CRC risk except for age < 61. Logistic regression analysis revealed that lncRNA rs944289 TT homozygote was associated with the increased risk of rectum cancer (TT vs. CC + CT: adjusted OR = 1.29, 95% CI 1.10–1.66, P = 0.041) or colon cancer. In summary, we proved that lncRNA rs944289 might be significantly related to the decreased CRC risk in the Chinese Han populations and lncRNA rs7990916 was not associated with the CRC risk except for patients of age < 61. In the future, studies with larger samples should be conducted to validate our results.

Colorectal cancer (CRC) has ranked third in terms of incidence but second in terms of mortality in the world1. In China, CRC has ranked both fifth in terms of incidence and mortality2. The incidence of CRC has been increasing, mostly due to unhealthy lifestyle, aging and environmental factors3, but accumulating evidences have shown that an individual’s inherited factors also contribute to the development of CRC.

Long non-coding RNAs (lncRNAs) are a sort of noncoding RNA molecules with more than 200 nucleotides in length, and are disease- or tissue-specific expression patterns4,5. LncRNAs play crucial roles in chromatin dynamics, genome packaging, gene regulation, cellular pathways and biological processes6. LncRNAs also play vital roles in the oncogenesis and metastasis of CRC7,8. Yu et al. found that linc-UFC1 participated in the progression of CRC, and overexpression of linc-UFC1 in CRC patients was positively associated with tumor grade and stage7. Zhao et al. also reported overexpression of Linc-A was correlated with poor survival in CRC patients8.

Single nucleotide polymorphisms (SNPs) occurring in the functional region of lncRNAs can influence disease risk and can also promote cancer development9. LncRNA rs944289 and rs7990916 polymorphisms increased the risk of different diseases. For example, lncRNAs rs7990916 TT genotype was found to increase...
Alzheimer’s disease (AD) risk. Papillary thyroid carcinoma susceptibility candidate 3 (PTCSC3) rs944289 polymorphism increased the risk of papillary thyroid cancer (PTC). Cao et al. also reported that IncRNA rs944289 may increase the risk of esophageal cancer and breast cancer (BC) in Asian populations. These data indicate SNPs in IncRNAs play important roles in tumorigenesis. Although IncRNA rs944289 and rs7990916 polymorphisms have a risk effect on some diseases, there are no studies concerning the relationship of these two variants with CRC risk. Based on previous studies, we explored IncRNA rs944289 and rs7990916 polymorphisms in CRC patients and analyzed the relationship between these IncRNA polymorphisms and CRC risk.

Materials and methods

Patients and samples. We recruited 1003 CRC patients from the Affiliated People’s Hospital of Jiangsu University and the Fujian Medical University Union Hospital from October 2014 to August 2017. Patients with histologically confirmed CRC were enrolled and the major exclusion criteria were as follows: (1) presence of immunological diseases, (2) with other primary cancers, and (3) with other colonic diseases (e.g., Crohn’s disease), (4) exposure to antitumor treatments before surgery. One thousand three hundred and three healthy subjects were selected as healthy controls from the departments of physical examination in these two hospitals. The healthy controls were Chinese Han populations with the following exclusion criteria: (1) with history of any cancer, (2) with metabolic or autoimmune diseases, and (3) with liver/kidney dysfunction, (4) with any other systemic diseases. The demographic characteristics were recorded, including body mass index (BMI), age, gender, alcohol intake and smoking.

The study was approved by the Ethics Committee of the Affiliated People’s Hospital of Jiangsu University and conducted according to the Declaration of Helsinki. All participants signed an informed consent before enrolled in this research and all methods were performed in accordance with the relevant guidelines and regulations.

SNP genotyping. We collected blood samples from each participant after their admission to the hospital. The blood samples collected in a test tubes containing EDTA were used for genotyping assay. Genomic DNA was extracted using a DNA Kit (Promega, Madison, USA) from lymphocytes of peripheral blood. The DNA was quantified by a measurement of OD260 and then was stored at -80°C. SNPs of IncRNA rs944289 and rs7990916 were analyzed by a SNPscan Kit (Genesky Biotechnologies Inc., Shanghai, China). 4% DNA samples were selected randomly and analyzed by PCR/Sanger sequencing. The rs944289 locus primers were: 5-TGG TTT GAA GATAGTCAATG-3 (forward) and 5-AGATTTGTAATAGCTGGGAA-3 (reverse). The rs7990916 locus primers were: 5-CTTTGTATCTCTTCTTTA-3 (forward) and 5-CAAGTGTACCTGAAATGTTCA-3 (reverse). For quality control, replicate blinded samples were included to check for the reproducibility of the results by another technician and the results were unchanged.

Statistical analysis. All data were analyzed by using SPSS 23.0 (IBM Corporation, Armonk, NY, USA). The chi-square or Fisher’s exact test was applied to compare the categorical variables, whereas the continuous variables were evaluated by the student’s t-test or Wilcoxon signed-rank test. The relationship between the IncRNA rs944289/7990916 polymorphism and CRC risk was assessed by odds ratios (OR) and 95% confidence intervals (CIs). Logistic regression model was conducted to analyze the associations among IncRNA rs944289 and rs7990916 polymorphisms, the clinical characteristics and CRC risk. Hardy–Weinberg equilibrium (HWE) was used to analyze the genotype distributions of IncRNA rs944289/7990916. A P<0.05 (two-tailed) was adopted as the statistically significant level.

Ethics approval and consent to participate. The Ethics Committee of the Affiliated People’s Hospital of Jiangsu University approved the protocol of the study (K-20210105-W), and all participants signed an informed consent before enrolled in this research.

Consent for publication. The authors appreciate all the patients in this work for their cooperation and permission for the publication of the article.

Results

Characteristics of CRC patients. In our study, 1003 CRC cases (431 colon cancer and 572 rectum cancer patients) and 1303 healthy controls were enrolled to investigate the correlation of the two SNPs (rs944289 and rs7990916) with CRC risk. Table 1 listed detailed demographics data. The mean age of CRC patients and controls were 61.10 ± 12.17 years and 61.40 ± 9.61 years, respectively. There were no statistically significant differences in age and gender between CRC patients and controls (both P>0.05). However, smoking, alcohol intake and BMI increased the risk of CRC (both P<0.05), so we adjusted these factors by multiple logistic regression analyses.

Primary information for IncRNA rs944289 and rs7990916. The genotypic frequencies of IncRNA rs944289 and rs7990916 met the HWE (P=0.105 and P=0.359, respectively). Minor allele frequency (MAF) of IncRNA rs944289 polymorphism was 0.28, which was similar to SNP database for Chinese populations (MAF=0.24). MAF of IncRNA rs7990916 polymorphism was 0.23, which was similar to SNP database for Chinese populations. Table 2 summarized the corresponding information of IncRNA rs944289 and rs7990916.

Association of IncRNA polymorphisms with CRC risk in the overall population. The genotypes and allele distributions of IncRNA rs944289 and rs7990916 in CRC patients and controls were presented in
Table 3. LncRNA rs944289 frequencies were 29.55% (CC), 46.73% (CT) and 23.72% (TT) in CRC patients, whereas in controls, the distributions of those genotypes were 29.69%, 51.62% and 18.69%, respectively. We found that rs944289 TT homozygote was associated with decreased CRC risk when compared with the CC or CC + CT (TT vs. CC: adjusted OR = 0.88, 95% CI 0.78–0.99, \( P = 0.037 \); TT vs. CC + CT: adjusted OR = 0.86, 95% CI 0.78–0.95, \( P = 0.004 \)). LncRNA rs7990916 frequencies were 79.69% (CC), 19.49% (CT) and 0.82% (TT) in CRC patients, and 77.31% (CC), 20.92% (CT) and 1.77% (TT) in controls. There was no significant difference between lncRNA rs7990916 and the risk of CRC (all \( P > 0.05 \)) in the overall population.

Stratified analyses between lncRNA rs944289 polymorphism and CRC risk. Stratified analysis was performed and revealed that rs944289 TT genotype was associated with decreased CRC risk in the subgroup of male (adjusted OR = 0.88, 95% CI 0.77–0.99, \( P = 0.045 \)), female (adjusted OR = 0.81, 95% CI 0.68–0.99, \( P = 0.097 \)), age ≥ 61 (adjusted OR = 0.86, 95% CI 0.74–0.99, \( P = 0.035 \)), smoking (adjusted OR = 0.66, 95% CI 0.53–0.81, \( P < 0.001 \)), never alcohol intake (adjusted OR = 0.88, 95% CI 0.78–0.98, \( P = 0.021 \)) and BMI ≥ 24 (adjusted OR = 0.82, 95% CI 0.69–0.94, \( P = 0.0016 \)) (Table 4).

Stratified analyses between lncRNA rs7990916 polymorphism and CRC risk. We further analyzed stratified effects of LncRNA rs7990916 on CRC risk by logistic regression model. Genotype distributions of rs7990916 were evaluated with age, sex, BMI, drinking and smoking. Results show that there was no significant association between CRC patients and controls except for age < 61 (CT vs. CC: adjusted \( P = 0.18 \), TT vs. CC: adjusted \( P = 0.007 \)) or rectum cancer (TT vs. CC + CT: adjusted OR = 1.44, 95% CI 1.11–1.88, \( P = 0.007 \)) or resect cancer (TT vs. CC + CT: adjusted OR = 1.29, 95% CI 1.10–1.66, \( P = 0.041 \)) when compared with CC + CT (Table 6). We also found LncRNA rs7990916 did not alter the risk of colon cancer (CT vs. CC: adjusted \( P = 0.21 \), TT vs. CC: adjusted \( P = 0.11 \), and TT vs. CC + CT: adjusted \( P = 0.24 \)) or rectal cancer (CT vs. CC: adjusted \( P = 0.58 \), TT vs. CC: adjusted \( P = 0.11 \), CT + TT vs. CC: adjusted \( P = 0.37 \), and TT vs. CC + CT: adjusted \( P = 0.12 \)) (Table 6).
### Table 3. Genotype Frequencies of LncRNA rs944289 C>T and rs7990916 C>T Polymorphisms and the CRC Risk. Bold values are statistically significant ($P < 0.05$). *Adjusted for age, gender, smoking, alcohol use and BMI status.

| Genotype     | CRC Cases (n = 1003) | Controls (n = 1303) | Crude OR (95%CI) | $P$ | Adjusted OR* (95%CI) | $P$ |
|--------------|----------------------|---------------------|------------------|-----|----------------------|-----|
| rs944289 C>T |                      |                     |                  |     |                      |     |
| CC          | 289                  | 386                 | 1.00             | 1.00|                      |     |
| CT          | 457                  | 671                 | 0.91 (0.75–1.10) | 0.34| 1.07 (0.88–1.30)     | 0.53|
| TT          | 232                  | 243                 | 1.27 (1.01–1.61) | 0.043| 0.88 (0.78–0.99)     | 0.037|
| CT + TT     | 689                  | 914                 | 1.01 (0.84–1.21)| 0.94| 0.97 (0.81–1.17)     | 0.75|
| CC + CT     | 746                  | 1057                | 1.00             | 1.00|                      |     |
| TT          | 232                  | 243                 | 1.15 (1.10–1.66)| 0.044| 0.86 (0.78–0.95)     | 0.004|
| T allele    | 921                  | 1157                | 1.00             | 1.00|                      |     |
| rs7990916 C>T |                    |                     |                  |     |                      |     |
| CC          | 781                  | 1005                | 1.00             | 1.00|                      |     |
| CT          | 191                  | 272                 | 0.90 (0.73–1.14) | 0.34| 0.89 (0.72–1.10)     | 0.27|
| TT          | 8                    | 23                  | 0.45 (0.20–1.01) | 0.666| 0.45 (0.20–0.93)     | 0.059|
| CT + TT     | 199                  | 295                 | 0.87 (0.71–1.06)| 0.18| 0.85 (0.70–1.05)     | 0.13|
| CC + CT     | 972                  | 1277                | 1.00             | 1.00|                      |     |
| TT          | 8                    | 23                  | 0.46 (0.20–1.03) | 0.067| 0.47 (0.21–1.06)     | 0.067|
| T allele    | 207                  | 318                 | 1.00             | 1.00|                      |     |

### Table 4. Stratified analyses between LncRNA rs944289 C>T polymorphism and CRC risk by gender, age, BMI, smoking and alcohol intake. *For ICAM-1 rs944289 C>T, the genotyping was successful in 980 (97.71%) CRC cases, and 1300 (99.77%) controls; *Adjusted for multiple comparisons [age, gender, BMI, smoking status and alcohol intake (besides stratified factors accordingly)] in a logistic regression model.

| Variable | LncRNA rs944289 C>T (case/control) | Adjusted OR* (95% CI); $P$ |
|----------|-----------------------------------|---------------------------|
|          | CC | CT | TT | CC | CT | TT | CC/TT | TT vs. (CT/CC) |
| Sex      |    |    |    |    |    |    |        |                  |
| Male     | 176/231 | 276/407 | 150/161 | 1.00 | 1.08 (0.84–1.39); P: 0.56 | 0.91 (0.78–1.05); P: 0.20 | 0.99 (0.78–1.26); P: 0.0045 | 0.88 (0.77–0.99); P: 0.019 |
| Female   | 113/155 | 181/264 | 82/82 | 1.00 | 1.04 (0.76–1.43); P: 0.79 | 0.82 (0.67–1.00); P: 0.053 | 0.93 (0.69–1.25); P: 0.62 | 0.81 (0.68–0.97); P: 0.035 |
| Age < 61 | 115/168 | 216/312 | 111/118 | 1.00 | 0.96 (0.71–1.30); P: 0.80 | 0.87 (0.72–1.03); P: 0.13 | 0.89 (0.67–1.19); P: 0.43 | 0.87 (0.75–1.02); P: 0.082 |
| Age ≥ 61 | 174/218 | 241/359 | 121/125 | 1.00 | 1.15 (0.88–1.49); P: 0.30 | 0.90 (0.77–1.06); P: 0.22 | 1.04 (0.81–1.33); P: 0.76 | 0.86 (0.74–0.99); P: 0.035 |
| Smoking  |    |    |    |    |    |    |        |                  |
| Never    | 223/314 | 351/520 | 154/201 | 1.00 | 1.02 (0.82–1.27); P: 0.88 | 0.93 (0.81–1.06); P: 0.28 | 0.91 (0.71–1.78); P: 0.49 | 0.93 (0.83–1.05); P: 0.25 |
| Ever     | 66/72 | 106/151 | 78/42 | 1.00 | 1.26 (0.82–1.93); P: 0.29 | 0.70 (0.54–0.90); P: 0.006 | 0.95 (0.64–1.41); P: 0.79 | 0.66 (0.53–0.81); P: 0.000 |
| Alcohol intake |    |    |    |    |    |    |        |                  |
| Never    | 238/348 | 387/598 | 184/218 | 1.00 | 1.03 (0.83–1.27); P: 0.81 | 0.88 (0.77–1.00); P: 0.056 | 0.94 (0.77–1.15); P: 0.56 | 0.88 (0.78–0.98); P: 0.021 |
| Ever     | 51/38 | 70/73 | 48/25 | 1.00 | 1.33 (0.77–2.30); P: 0.30 | 0.86 (0.61–1.20); P: 0.38 | 1.14 (0.69–0.91); P: 0.61 | 0.77 (0.58–1.03); P: 0.074 |
| BMI (kg/m²) |    |    |    |    |    |    |        |                  |
| < 24     | 202/216 | 303/341 | 150/129 | 1.00 | 1.05 (0.82–1.34); P: 0.71 | 0.90 (0.77–1.05); P: 0.17 | 0.97 (0.77–1.23); P: 0.80 | 0.88 (0.77–1.01); P: 0.064 |
| ≥ 24     | 87/170 | 154/330 | 82/114 | 1.00 | 1.10 (0.80–1.52); P: 0.56 | 0.84 (0.69–1.02); P: 0.085 | 0.97 (0.72–1.32); P: 0.86 | 0.82 (0.69–0.94); P: 0.016 |
Table 5. Stratified analyses between LincRNA rs7990916 C>T Polymorphism and CRC risk by gender, age, BMI, smoking status and alcohol intake. *For LincRNA rs7990916 C>T, the genotyping was successful in 977 (97.41%) CRC cases, and 1298 (99.62%) controls; aAdjusted for multiple comparisons [age, sex, BMI, smoking status and alcohol intake (besides stratified factors accordingly)] in a logistic regression model. Significant values are in [bold].

| Genotype | Controls (n = 1303) | Colon cancer cases (n = 431) | Crude OR (95%CI) | P value | Adjusted OR a (95%CI) | P value | Rectum cancer cases (n = 572) | Crude OR (95%CI) | Adjusted OR a (95%CI) | P value |
|----------|---------------------|-----------------------------|-----------------|---------|-----------------------|---------|----------------------------|-----------------|------------------------|---------|
| rs944289 C>T |                     |                             |                 |         |                       |         |                            |                 |                        |         |
| CC       | 386                 | 29.69                       | 130             | 30.73   | 1.00                  |         | 159                       | 28.65           | 1.00                   |         |
| CT       | 671                 | 51.62                       | 189             | 44.68   | 0.84 (0.65–1.08)      | 0.19    | 268                       | 48.29           | 1.04 (0.82–1.30)       | 0.81    |
| TT       | 243                 | 18.69                       | 104             | 24.59   | 1.27 (0.94–1.72)      | 0.14    | 128                       | 23.06           | 1.28 (0.96–1.70)       | 0.10    |
| CT + TT  | 914                 | 70.31                       | 293             | 69.27   | 0.95 (0.75–1.21)      | 0.71    | 396                       | 71.35           | 1.05 (0.85–1.31)       | 0.70    |
| CC + CT  | 1057                | 81.31                       | 319             | 75.41   | 1.00                  |         | 427                       | 76.94           | 1.00                   |         |
| TT       | 243                 | 18.69                       | 104             | 24.59   | 1.42 (0.41–1.24)      | 0.010   | 128                       | 23.06           | 1.35 (1.06–1.73)       | 0.007   |
| T allele | 1157                | 84.50                       | 397             | 46.93   | 1.00                  |         | 524                       | 47.21           | 1.00                   |         |

Table 6. Stratified analyses between LncRNAs rs944289 C>T and rs7990916 C>T polymorphisms and CRC risk by site of tumor. *Adjusted for age, sex, smoking status, alcohol use and BMI status. Significant values are in [bold].
Discussion

LncRNAs play an essential role in various biological processes, including cell proliferation, apoptosis, genomic imprinting, transcriptional interference and other critical processes. Furthermore, lncRNAs have been reported to participate in the process of tumorigenesis in CRC. For instance, lncRNA CCAL could activate Wnt/β-catenin signaling pathway and induce multidrug resistance in CRC. LncRNA SPRY4-IT1 could promote invasion and proliferation as a ceRNA of miRNA-101-3p in CRC. Recently, numerous investigations have suggested lncRNA polymorphisms as one of the contributors to CRC risk. For example, Yang et al. reported lncRNA PCAT1 rs2632159 polymorphism increased CRC risk in a Chinese population. Wang et al. also reported rs2839698 polymorphism was associated with increased CRC risk. On the other hand, lncRNA PRNCR1 rs13252298/rs1456315 and MALAT1 rs1194338 polymorphisms decreased the CRC risk.

In this study, we found that lncRNA rs944289 TT homozygote could decrease CRC risk. After adjustment by multiple logistic regression, the TT genotype of lncRNA rs944289 was associated with the decreased CRC risk in the subgroups of female, male, age ≥ 61, BMI ≥ 24, smoking and never alcohol intake populations. LncRNA rs944289 have been confirmed to increase the risk of PTC and rs944289 predisposes to PTC by inhibiting the expression of PTSC3. PTSC3 is a large intergenic noncoding RNA gene that is involved in the regulation of tumorigenesis. The SNP rs944289 is located 3.2 kb upstream of PTSC3 and suppresses PTSC3 by destroying a transcription factor-binding site in the promoter of PTSC3. Cao et al. also found that lncRNA rs944289 may increase the risk of EGJA in the smoking and age < 60 years populations. However, in a Chinese population, Xu et al. confirmed that lncRNA rs944289 have no significant effect on the risk of BC, which might be due to the specific tumorigenesis of BC. However, up to now, no study has reported the association between lncRNA rs944289 polymorphism and CRC risk, and in this study, we observed significant relationships between the lncRNA rs944289 polymorphism and CRC risk.

Our results also revealed that there was no significant difference between lncRNA rs7990916 polymorphism and the CRC risk in an overall comparison. But when stratified by age < 61 years, lncRNA rs7990916 polymorphism decreased the risk of CRC. Similar to our results, Cao et al. observed no close relationship between lncRNA rs7990916 polymorphism and EGJA patients. In contrast, Jendrzejewski et al. found significant relationship between lncRNA rs7990916 and the risk of AD in the Europe populations. But the etiology of CRC is primarily different from that of AD. Thus, these distinct conclusions on the lncRNA rs7990916 polymorphism may be mainly attributed to the heterogeneity of ethnic groups and disease types.

Nevertheless, the mechanism of lncRNA polymorphisms on the tumorigenesis of CRC is unclear. Previous studies reported that lncRNA GAS5 rs55829688 polymorphism increased CRC risk by modulating the binding affinity of the transcription factors YY1 to GAS5 promoter. Moreover, MALAT1 rs664589 polymorphism increased CRC risk by binding to miRNA-194-5p, which resulted in an overexpression of MALAT1. Taken together, lncRNA polymorphisms could induce the occurrence of tumor by binding to transcription factors, binding to miRNA and so on.

To the best of our knowledge, our research focused on the possible association of lncRNA rs944289 and rs7990916 polymorphisms with CRC risk for the first time. There still existed several limitations in the study. Firstly, this case-control study only focused on Chinese Han populations. Secondly, the two lncRNAs selected in our study may not be comprehensive because there may be other genetic polymorphisms that affected the risk of CRC. Thirdly, we did not perform the association of lncRNA rs944289 and rs7990916 polymorphisms with tumor stages, patients’ prognosis, or other associated risk factors, which might affect the precision of estimating the effect of these two polymorphisms on the CRC risk. Finally, we did not investigate the mechanism of the two polymorphisms during the tumorigenesis of CRC. Nevertheless, our study provides clues for a further mechanism study and provides possible biomarkers for CRC diagnosis.

Conclusions

In summary, we proved that the lncRNA rs944289 might be significantly related to the decreased risk of CRC in the Chinese Han populations. However, there was no significant difference between lncRNA rs7990916 polymorphism and CRC risk except for the subgroup of age < 61. In the future studies, larger samples including detailed clinical information and different ethnic populations should be conducted to validate our findings.

Data availability

All data analyzed or generated during this study are included in the article.

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**Author contributions**

All authors contributed to the study conception and design. Clinical data collection, genetic counseling and follow-up were performed by Y.W., Z.Q. and G.T. The experiment was performed by R.Q. and Y.P. SNP analysis was performed by Q.Z. and Z.Z. Formal analysis was performed by W.T. The manuscript was written by S.Z. and Y.X., and all authors read and approved the final manuscript.

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**Competing interests**

The authors declare no competing interests.

**Additional information**

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