Significant association between long non-coding RNA HOTAIR polymorphisms and cancer susceptibility: a meta-analysis

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Abstract: HOTAIR, a well-known long non-coding RNA, is involved in carcinogenesis and progression of multiple cancers. Molecular epidemiological studies suggest that HOTAIR polymorphisms may be associated with cancer susceptibility, but the results remain controversial. To derive a more precise evaluation, we performed a meta-analysis focused on the associations between HOTAIR polymorphisms and cancer risk for the first time. PubMed, Embase, China National Knowledge Infrastructure, and Wanfang databases were searched. Odds ratios (ORs) with 95% confidence interval (CI) were applied to assess the association between HOTAIR rs920778 C>T, rs4759314 A>G, rs7958904 G>C, and rs1899663 G>T polymorphisms and cancer susceptibility. Analyses were conducted to detect heterogeneity, sensitivity, and publication bias in order to measure the robustness of our findings. Overall, 13 related studies involving 7,151 patients and 8,740 control samples were analyzed. Significant associations between the HOTAIR rs920778 polymorphism and cancer risk were observed (T vs C: OR = 1.33, 95% CI = 1.17–1.53; TT vs TC + CC: OR = 1.55, 95% CI = 1.21–2.00; TC + TT vs CC: OR = 1.33, 95% CI = 1.11–1.59; TT vs CC: OR = 2.02, 95% CI = 1.31–3.10) in the total population, as well as in subgroup analyses. For rs4759314 A>G polymorphism, a similarly increased risk was found in the gastric cancer group. However, significant decreases in cancer risk were observed both in the overall population and colorectal cancer group for rs7958904 G>C polymorphism. In addition, no significant association was detected between rs1899663 G>T polymorphism and cancer susceptibility. In conclusion, our meta-analyses suggest that HOTAIR polymorphisms may be associated with the risk of cancer development.

Keywords: HOTAIR, polymorphism, cancer susceptibility

Introduction
Cancer has now become one of the main causes of morbidity and mortality worldwide.¹ Overall, approximately 14.1 million new cases and 8.2 million deaths occurred in 2012, and most of them occurred in less developed countries.² Despite recent advances in treatment of surgery, chemotherapy, and radiotherapy, the 5-year survival rate remains low in many types of cancers.³ Therefore, it is vital to identify the factors leading to cancer susceptibility. Nowadays, many molecular epidemiological studies have reported that genetic factors may play an important role in cancer development, and the genetic predisposition is receiving increasing attention.⁴⁵

Long non-coding RNAs (lncRNAs) are defined as a new group of transcribed RNA molecules that are longer than 200 nucleotides and have no obvious protein-coding capacity.⁶⁷ LncRNAs were previously considered as a fake transcriptional noise,⁸ but now accumulating evidence suggests that they are crucial players in a wide range of
biological processes including cell proliferation, survival, metabolism, and differentiation. Moreover, IncRNAs exhibit unique profiles in many types of cancers, contribute to carcinogenesis and progression, and are reasonably regarded as predictors of patient outcomes. HOTAIR, a prominently focused IncRNA, was initially identified to be implicated in breast cancer and promote tumor invasiveness and metastasis in 2007. It has been reported that HOTAIR could interact with PRC2 and induce its relating methylation of H3K27 to reprogram chromatin organization. Recently, the overexpression of HOTAIR and significant association with poor prognosis in a variety of human cancers including liver, breast, colon, lung, stomach, and esophageal cancers has been found. All this convincing proof indicates the oncogenic role of HOTAIR in the course of several human carcinogenesis. Therefore, increasing studies have investigated the single nucleotide polymorphisms (SNPs) in the HOTAIR locus with cancer risk. However, the results were inconsistent and inconclusive. Thus, a comprehensive meta-analysis involving the related studies was performed to assess the possible association between HOTAIR polymorphisms and cancer susceptibility.

**Material and methods**

**Search strategy**

The PubMed, Embase, China National Knowledge Infrastructure, and Wanfang databases were searched to identify studies that examined the association between HOTAIR polymorphisms and cancer susceptibility prior to January 31, 2016. The following medical subject heading terms were used: (HOTAIR OR HOX transcript antisense RNA OR long noncoding RNA OR IncRNA OR lincRNA) AND (cancer OR carcinoma OR tumor OR neoplasia OR neoplasm) AND (polymorphism OR genotype OR allele OR variant OR SNP).

**Eligibility criteria**

All selected studies had to meet the following criteria: 1) published studies based on case-control design assessing the association between the HOTAIR polymorphisms and cancer susceptibility; 2) the study included sufficient genotype distribution data to calculate odds ratios (ORs) and 95% confidence intervals (CIs). Studies were excluded if they investigated the progression, severity, phenotype modification, response to treatment, survival or family based studies. Moreover, meeting abstracts, case reports, editorials, and review articles were also excluded. For duplicate publications, the one with more complete design or larger sample size was finally selected.

**Data extraction**

Two independent researchers extracted the data from each relevant study including the first author, publication year, study country/region, ethnicity of participants (such as Asian or Caucasian), sources of controls, genotyping method, case-control matched status, type of cancers, Hardy-Weinberg equilibrium (HWE) status of controls, and number of genotypes in cancer cases and controls. Disagreements were reconciled through group discussion. The HWE was calculated based on the genotypes of the controls.

**Statistical analysis**

ORs with 95% CIs were used to assess the strength of the association between the HOTAIR polymorphisms and cancer risk. For the HOTAIR rs920778 C>T polymorphism, the pooled ORs were obtained for allele (T vs C), recessive (TT vs TC + CC), dominant (TC + TT vs CC), and homozygous (co-dominant) model (TT vs CC). Similar genetic models were also assessed for HOTAIR rs4759314 A>G, rs7958904 G>C, and rs1899663 G>T variants. Subgroup analyses were performed based on ethnicity, source of controls, genotyping methods, type of cancers, case-control matched status, and HWE status of controls. ORs were calculated using the random-effect model when the $I^2$ was greater than 50%. Otherwise, a fixed-effect model was adopted. In order to evaluate the stability of the results, sensitivity analysis was used, which meant omitting one study at a time, and then compared to show whether a significant difference existed between the former and the latter results. Publication bias was examined by the visual inspection of funnel plot, and Egger’s regression test. Data were analyzed and processed using Stata 12.0 (StataCorp LP, College Station, TX, USA). $P<0.05$ was considered statistically significant.

**Results**

**Study characteristics**

A systematic search of the literature identified 135 relevant studies. The study selection process is shown in Figure 1. Following the selection criteria, 127 studies were excluded from our research due to various deficiencies. Ultimately, eight eligible articles were selected with adequate data, including eight studies on rs920778 C>T, eight studies on rs4759314 A>G, three publications on rs1899663 G>T, and three studies on rs7958904 G>C, respectively. All studies were published between 2014 and 2016. Only two studies involved Caucasian populations, and other studies involved Asian populations. The genotype distribution was in agreement with HWE in all studies except for one study.
of HOTAIR rs920778 C>T polymorphism. Detailed characteristics of studies included are summarized in Table 1.

**Association between the HOTAIR rs920778 C>T polymorphism and cancer risk**

A total of eight relevant studies, consisting of 3,627 patients and 4,585 controls, were examined for the association between the HOTAIR rs920778 C>T polymorphism and cancer risk. The combined analyses revealed a significantly increased risk of cancer for this polymorphism in all four genetic models (T vs C: OR = 1.33, 95% CI = 1.17–1.53, \( P = 0.01, I^2 = 68.1\% \); TT vs TC + CC: OR = 1.55, 95% CI = 1.21–2.00, \( P = 0.001, I^2 = 59.7\% \); TC + TT vs CC: OR = 1.33, 95% CI = 1.11–1.59, \( P = 0.002, I^2 = 63.6\% \); TT vs CC: OR = 2.01, 95% CI = 1.31–3.10, \( P = 0.001, I^2 = 77.0\% \); Figure 2, Table 2). Subsequent analyses accounting for ethnicity revealed similar results in Asian populations, using all four genotype models. Significant correlations with increased cancer risk were also observed in the population-based control group and studies restricted to HWE. Enhanced cancer risk was also observed in the subgroup analysis with genotyping method of restriction fragment length polymorphism under all four genetic models. Moreover, elevated risks of gastric cancer (T vs C: OR = 1.32, 95% CI = 1.01–1.72, \( P = 0.045, I^2 = 73.8\% \); TC + TT vs CC: OR = 1.36, 95% CI = 1.02–1.83, \( P = 0.039, I^2 = 59.0\% \); TT vs CC: OR = 2.12, 95% CI = 1.00–4.51, \( P = 0.050, I^2 = 78.1\% \)) and esophageal cancer (T vs C: OR = 1.46, 95% CI = 1.32–1.61, \( P < 0.001, I^2 = 0\); TT vs TC + CC: OR = 1.96, 95% CI = 1.48–2.59, \( P < 0.001, I^2 = 59.7\% \); TC + TT vs CC: OR = 1.44, 95% CI = 1.27–1.62, \( P < 0.001, I^2 = 0\); TT vs CC: OR = 2.81, 95% CI = 2.13–3.71, \( P < 0.001, I^2 = 2.2\% \); Table 2) were detected.

Sensitivity analysis showed that no single study qualitatively changed the pooled ORs with corresponding 95% CI, indicating that the results of this meta-analysis were highly stable (see Figure 3 for allele contrast model). Visual inspection of funnel plot did not reveal any asymmetrical evidence (see Figure 4 for allele contrast model). The results were further supported by the analysis of the data with Egger’s test (T vs C: \( P = 0.121 \); TT vs TC + CC: \( P = 0.062 \); TC + TT vs CC: \( P = 0.243 \); TT vs CC: \( P = 0.195 \)).

**Association between HOTAIR rs4759314 A>G polymorphism and cancer risk**

Eight studies consisting of 5,526 cases and 6,659 controls were included in the analysis to determine whether the HOTAIR rs4759314 A>G polymorphism was associated with cancer risk. Overall, no significant association was observed in all four models (Table 2). Only two genetic models (for G vs A, OR = 1.29, 95% CI = 1.10–1.51, \( P = 0.002, I^2 = 43.5\% \); for GA + GG vs AA, OR = 1.32, 95% CI = 1.12–1.56, \( P = 0.002, I^2 = 4.2\% \) were detected. (Table 2).
| Reference | Year | Country/region | Ethnicity | Source of controls | Case | Control | Genotype distribution | Genotyping methods | Age- and sex-matched | Type of cancer | P for HWE |
|-----------|------|----------------|-----------|-------------------|------|---------|----------------------|-------------------|---------------------|---------------|----------|
| rs920778 C>T |      |                |           |                   |      |         | TT | TC | CC | TT | TC | CC | RFLP | Matched | Gastric cancer | 0.000 |
| Pan et al25 | 2016 | People’s Republic of China | Asian | Population | 500 | 1,000 | 31 | 194 | 275 | 24 | 368 | 608 | RFLP | Matched | Gastric cancer | 0.230 |
| Yan et al24 | 2015 | Turkey | Caucasian | Hospital | 123 | 122 | 40 | 52 | 31 | 41 | 66 | 15 | Taqman | Matched | Gastric cancer | 0.738 |
| Zhang et al26 | 2014 | People’s Republic of China | Asian | Population | 502 | 504 | 339 | 151 | 12 | 296 | 190 | 18 | RFLP | Matched | Breast cancer | 0.140 |
| Zhang et al26 | 2014 | People’s Republic of China | Asian | Population | 1,000 | 1,000 | 83 | 389 | 528 | 41 | 358 | 601 | RFLP | Matched | Esophageal cancer | 0.173 |
| Zhang et al26 | 2014 | People’s Republic of China | Asian | Population | 510 | 550 | 47 | 207 | 256 | 20 | 186 | 344 | RFLP | Matched | Esophageal cancer | 0.401 |
| Zhang et al26 | 2014 | People’s Republic of China | Asian | Population | 588 | 600 | 51 | 203 | 307 | 17 | 205 | 378 | RFLP | Matched | Esophageal cancer | 0.082 |
| rs4759314 A>G |      |                |           |                   |      |         | GG | GA | AA | GG | GA | AA | RFLP | Matched | Gastric cancer | 0.448 |
| Pan et al25 | 2016 | People’s Republic of China | Asian | Population | 500 | 1,000 | 1 | 48 | 451 | 3 | 83 | 914 | RFLP | Matched | Gastric cancer | 0.699 |
| Du et al28 | 2015 | People’s Republic of China | Asian | Hospital | 753 | 1,057 | 3 | 126 | 624 | 6 | 136 | 915 | Tagman | Matched | Gastric cancer | 0.098 |
| Yan et al24 | 2015 | People’s Republic of China | Asian | Hospital | 522 | 589 | 3 | 60 | 459 | 2 | 36 | 549 | Taqman | Matched | Gastric cancer | 0.785 |
| Guo et al27 | 2015 | People’s Republic of China | Asian | Population | 515 | 654 | 1 | 53 | 461 | 1 | 64 | 589 | RFLP | Matched | Gastric cancer | 0.587 |
| Xue et al29 | 2015 | People’s Republic of China | Asian | Hospital | 1,147 | 1,203 | 1 | 135 | 1,011 | 9 | 157 | 1,037 | Tagman | Matched | Colorectal cancer | 0.260 |
| Xue et al29 | 2015 | People’s Republic of China | Asian | Hospital | 587 | 652 | 4 | 65 | 517 | 2 | 79 | 571 | Tagman | Matched | Colorectal cancer | 0.673 |
| Zhang et al26 | 2014 | People’s Republic of China | Asian | Population | 1,000 | 1,000 | 2 | 81 | 917 | 1 | 89 | 910 | RFLP | Matched | Esophageal cancer | 0.436 |
| rs7958904 G>C |      |                |           |                   |      |         | CC | CG | GG | CC | CG | GG | Taqman | Matched | Gastric cancer | 0.271 |
| Du et al28 | 2015 | People’s Republic of China | Asian | Hospital | 753 | 1,057 | 51 | 276 | 412 | 85 | 404 | 568 | Tagman | Matched | Gastric cancer | 0.147 |
| Xue et al29 | 2015 | People’s Republic of China | Asian | Hospital | 1,147 | 1,203 | 74 | 399 | 672 | 99 | 456 | 646 | Tagman | Matched | Colorectal cancer | 0.192 |
| Xue et al29 | 2015 | People’s Republic of China | Asian | Hospital | 587 | 652 | 33 | 206 | 347 | 57 | 248 | 346 | Tagman | Matched | Colorectal cancer | 0.430 |
| rs1899663 G>T |      |                |           |                   |      |         | TT | TG | GG | TT | TG | GG | RFLP | Matched | Gastric cancer | 0.078 |
| Pan et al25 | 2016 | People’s Republic of China | Asian | Population | 500 | 1,000 | 6 | 118 | 376 | 13 | 255 | 732 | RFLP | Matched | Gastric cancer | 0.876 |
| Yan et al24 | 2015 | People’s Republic of China | Asian | Population | 502 | 504 | 14 | 149 | 339 | 20 | 158 | 326 | RFLP | Matched | Breast cancer | 0.430 |

Note: %HWE in control.
Abbreviations: HWE, Hardy-Weinberg equilibrium; RFLP, restriction fragment length polymorphism.
**Figure 2** Calculated OR and 95% CIs for the associations between HOTAIR rs920778 polymorphism and cancer risk in overall populations.

Notes: (A) The allele contrast model; (B) the recessive model; (C) the dominant model; (D) the homozygous (co-dominant) model. The area of each square indicates the weight of the study in the meta-analysis. Weights are from random effect analysis.

Abbreviations: OR, odds ratio; CIs, confidence intervals.
### Table 2 Summary of ORs and 95% CI of HOTAIR polymorphisms and cancer risk

| Locus        | N* | Number of case/control | Allele | P-value | Recessive | Dominate | Homozygote |
|--------------|----|------------------------|--------|---------|-----------|----------|------------|
| rs920778     | 8  | 3,627/4,585            | 1.33   | 0.001   | 0.81      | 0.001    | 0.21       |
| Ethnicity    | 6  | 3,400/4,254            | 1.44   | 0.001   | 0.29      | 0.001    | 2.77       |
| Source of controls | 2 | 227/331                | 0.86   | 0.218   | 0.001     | 0.257    | 0.19       |
| Method       | 2  | 227/331                | 0.86   | 0.218   | 0.001     | 0.257    | 0.19       |
| Type of cancer | 2 | 3,400/4,254            | 1.44   | 0.218   | 0.001     | 0.257    | 0.19       |
| Controls in HWE | 7 | 3,127/3,585           | 1.14   | 0.001   | 0.29      | 0.001    | 2.77       |
| rs4759314    | 8  | 5,526/6,659            | 1.07   | 0.233   | 0.001     | 0.257    | 0.19       |
| Source of controls | 4 | 2,517/3,158           | 1.00   | 0.233   | 0.001     | 0.257    | 0.19       |
| Method       | 4  | 3,400/3,501            | 1.15   | 0.233   | 0.001     | 0.257    | 0.19       |
| Type of cancer | 4 | 2,517/3,158            | 1.15   | 0.233   | 0.001     | 0.257    | 0.19       |
| Age- and sex-matched | 7 | 5,011/6,005          | 1.07   | 0.233   | 0.001     | 0.257    | 0.19       |
| rs7958904    | 3  | 2,487/2,912            | 0.85   | 0.233   | 0.001     | 0.257    | 0.19       |
| Type of cancer | 3 | 2,487/2,912            | 0.85   | 0.233   | 0.001     | 0.257    | 0.19       |
| Dominant     | 0.90–1.30 | 0.001 | 0.257 | 0.19 |
| ORs          | 95% CI | P-value | | | | |
| rs7958904    | 3  | 2,487/2,912            | 0.85   | 0.233   | 0.001     | 0.257    | 0.19       |
| Type of cancer | 3 | 2,487/2,912            | 0.85   | 0.233   | 0.001     | 0.257    | 0.19       |

**Notes:** *Numbers of comparisons. *Test for heterogeneity. -values were obtained from Z-test.

**Abbreviations:** RFLP, restriction fragment length polymorphism; HWE, Hardy-Weinberg equilibrium; NA, not available; ORs, odds ratios; CI, confidence interval; PCR, polymerase chain reaction.
P = 0.001, I^2 = 44.0\%) revealed increased risk in the gastric cancer group. Further subgroup analyses of genotyping method, source of controls, and case-control matched status were conducted, and no significant association was identified (Table 2). The pooled ORs did not exhibit any change with sensitivity analysis, and no publication bias was observed (G vs A: P = 0.350; GG vs GA + AA: P = 0.902; GA + GG vs AA: P = 0.408; GG vs AA: P = 0.823).

Association between HOTAIR rs7958904 G>C polymorphism and cancer risk

Three eligible studies including 2,487 cases and 2,912 controls focused on the association of HOTAIR rs7958904 G>C polymorphism with cancer. The heterogeneity among studies, measured by F statistic, was not significant in all genetic models (F < 0.5). Therefore, the fixed effect model was used in all genetic models. A significant decrease in cancer risk was observed in the overall population (C vs G: OR = 0.85, 95% CI = 0.78–0.93, P < 0.001, F = 0%; CC + GA vs GG: OR = 0.84, 95% CI = 0.76–0.94, P = 0.002, F = 0%; CC vs GG: OR = 0.72, 95% CI = 0.58–0.89, P = 0.002, F = 0%; Table 2). Moreover, these results were consistent with subgroup analysis of the colorectal cancer group (Table 2). Sensitivity analysis was conducted, and no conspicuous change of the pooled ORs was detected. No publication bias was observed, indicating that the results are statistically robust (C vs G: P = 0.757; CC vs CG + GG: P = 0.354; CC + GA vs GG: P = 0.870; CC vs GG: P = 0.587).

Association between the HOTAIR rs1899663 G>T polymorphism and cancer risk

Three studies with 2,002 cases and 2,504 controls were included in the HOTAIR rs1899663 G>T polymorphism and cancer risk research. No significant associations were found in all four models for this SNP locus (Table 2).

Discussion

Genetic variants, mainly composed of SNPs, have been shown to influence the susceptibility of patients to cancer and have attracted increasing attention. LncRNAs play crucial roles in a wide range of biological processes and are involved in the development and progression of multiple cancers. SNPs in several lncRNAs previously identified to be involved in carcinogenesis have been reported to be associated with cancer risk.\(^{30,31}\)

Recently, several molecular epidemiological studies have been conducted to evaluate the association between polymorphisms of HOTAIR and the risk of cancer development, but results have remained conflicting. Regarding the HOTAIR rs920778 C>T polymorphism, Pan et al reported that the TT carriers had a 1.66- and 1.87-fold increased gastric cancer risk in Jinan and Huaian populations of People’s Republic of China compared with the CC carriers.\(^{25}\) A similar increase in esophageal cancer risk was also observed in three independent case-control sets consisting of 4,248 Chinese subjects.\(^{26}\) However, CC genotype of HOTAIR rs920778 polymorphism was found to significantly increase the risk of breast cancer in a Turkish population, whereas another study demonstrated that the HOTAIR rs920778 polymorphism had not played any major role in genetic susceptibility to gastric carcinogenesis.\(^{22,23}\)

To our knowledge, this is the first meta-analysis to date focused on the association between polymorphisms in
Intronic long non-coding RNA (lncRNA) HOTAIR and cancer susceptibility specially. All the relative studies about cancer risk and four polymorphisms of HOTAIR were collected to make a precise conclusion. Overall, significant increased risk of cancer was observed for the HOTAIR rs920778 C>T polymorphism. In subgroup analyses by ethnicity, we found that individuals with the T allele and mutated genotypes had a significant increased cancer risk in Asian populations, suggesting that the increased cancer risk may be ethn-specific. Furthermore, it is worth noting that some significantly increased risks were observed in gastric and esophageal cancer, but not the breast cancer group. Similarly, the result that rs4759314 A>G polymorphism just increased the risk of gastric cancer rather than other types of cancers was revealed in our meta-analysis. While significant decreases in cancer risk were observed both in overall population and colorectal cancer group, indicating that rs7958904 G>C polymorphism might be a protective factor especially for colorectal cancer. In addition, a negative correlation was observed in the rs1899663 G>T polymorphism analysis.

Although the number of the included studies was relatively small, we believe that the findings can help to explain the association. First, in the sensitivity analysis, no significant changes were found after omitting each study at a time, indicating the relative stability and credibility of the results. Second, the genotype distributions in the controls of four selected SNP loci were all mostly consistent with HWE except for one study in rs920778 polymorphism analysis. Third, the visual inspection of funnel plot and Egger’s test proved that almost no apparent publication bias existed in our meta-analysis. All these would guarantee the reliability of results.

However, it is important to note the limitations of our meta-analysis. First, heterogeneity across studies existed for rs920778 and rs4759314 polymorphisms. Unfortunately, we did not perform meta-regression analysis which is not suitable for assessing heterogeneity with a sample size less than ten. Considering that ethnic diversity, study design difference, and measurement error may contribute to common sources of heterogeneity, we performed subgroup analyses to explore the source of heterogeneity. For rs920778, the results of subgroup analyses did not effectively eliminate the heterogeneity, indicating that all above factors should be taken into consideration. Nevertheless, subgroup analyses were successfully used to relieve moderate heterogeneity bias in the rs4759314 polymorphism analysis within the population-based control group and the genotyping method of restriction fragment length polymorphism group, suggesting that control sources and genotyping method may influence heterogeneity. The second limitation lies in the ethnicity of the subjects. Most of the patients were Asians in the present study and this limited the general application of the results to other populations. Third, all of our results may be influenced by casualness due to the small number of studies included and the limited sample size of each study. Finally, cancer is a multi-factorial malignant disease that likely arises from complex interactions between genetic mutations, environmental changes, lifestyle, diet, age, and sex. In our meta-analysis, we only focused on the HOTAIR polymorphisms, while the fundamental underlying mechanisms cannot be explained clearly due to unadjusted databases.

**Conclusion**

In conclusion, the current meta-analysis indicated that three functional polymorphisms of HOTAIR rs920778 C>T, rs4759314 A>G, and rs7958904 G>C may play an important role in the development of cancer. Given the limitations in the present meta-analysis, the results need to be interpreted with caution. Large-scale, case-control studies with rigorous designs should be conducted to confirm the association of above functional polymorphisms in lncRNA HOTAIR and cancer risk in the future.

**Acknowledgments**

This work was supported by the National Natural Science Foundation of China (grant number 81302127, 81400950) and the Joint Specialized Research Fund for the Doctoral Program of Higher Education in China (grant number 20132104120018).

**Disclosure**

The authors report no conflicts of interest in this work.

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