Association between IncRNA H19 rs2177727 polymorphism and the risk of cancer: an updated meta-analysis

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Abstract

Background: We have performed this study to evaluate the association between H19 rs2177727 polymorphism and the risk of cancer.

Methods: An odds ratio (OR) with a 95% confidence interval (CI) was applied to determine a potential association.

Results: A total of 17 case–control publications were selected. This meta-analysis showed that H19 rs2177727 has a significant increased association with cancer risk in allelic, homozygous, heterozygote, dominant and recessive models (T vs C: OR = 1.16, 95% CI = 1.06–1.27, I² = 75.7; TT vs CC: OR = 1.29, 95% CI = 1.06–1.56, I² = 71.6; CT vs CC: OR = 1.15, 95% CI = 1.01–1.31, I² = 75.4; CT + TT vs CC: OR = 1.20, 95% CI = 1.05–1.36, I² = 76.5; TT vs CT + CC: OR = 1.22, 95% CI = 1.02–1.45, I² = 70.6). In the subgroup analysis of smoking status, both smokers and nonsmokers showed an increase in cancer risk in allelic, homozygous, dominant and heterozygote models.

Conclusion: This meta-analysis revealed H19 rs2177727 may influence cancer susceptibility.

Keywords: Cancer risk, H19, rs2177727, Polymorphism, Meta-analysis

Background

Cancer has become a major public health problem and gives the second leading cause of death after cardiovascular and cerebrovascular disease. Therefore, identification of modifiable risk factors to slow cancer progression is crucial. Environmental factors, smoking [1], alcohol consumption [2], human papillomavirus (HPV) [3], and the Epstein-Barr virus (EBV) [4] was known to play a key role in the pathogenesis and tumorigenesis. In addition, single nucleotide polymorphisms (SNPs) were recognized to be associated with cancer development too. For example, CpG rs1909883, rs55247, and rs62382272 play an important role in oncogenesis in breast cancer [5], and the rs874945 in HOX transcript antisense RNA (HOTAIR) gene increases the risk of bladder cancer in Chinese population [6].

H19 (Gene ID: 283120) is an imprinted gene, located on chromosome 11p15.5, close to the insulin-like growth factor 2 (IGF2) gene, which has 6 exons and can produce long non-coding RNA (lncRNA) with a length of 2326 bp. H19 is mainly involved in the development of the embryo, showing high expression in the fetus, rapidly down-regulated after birth, and only continuously expressed in the heart and skeletal muscle in adults. However, H19 was found to be highly expressed in a variety of cancers. Previous studies have demonstrated that increased levels of H19 contributes to melanoma development and progression [7]. In addition, the introduction of the genome-wide association studies (GWAS) allowed for identification of an increased number of H19 SNPs that were associated with various types of cancer. For instance, H19 rs217727 has been reported to significantly increase the risk of gastric cancer [8], and colorectal cancer [9]. In addition, a large number of studies have found that H19 IncRNA tag SNPs (rs217727, rs2839698, rs3741216, rs3741219, rs2107425, rs3024270, rs2735971, rs2071095) are related to the susceptibility of...
cervical cancer [10], breast cancer [11–15], bladder cancer [16–18], gastric cancer [8], lung cancer [19, 20], osteosarcoma [21], pancreatic cancer [22], and oral squamous cell carcinoma [23, 24]. Among them, rs217727 is located in the exon 5 of the H19 gene. Some original studies and previous meta-analyses reported the relationship between H19 rs217727 and cancer risk, but the results were inconsistent. In addition, several recently published studies provide the basis for updating data sets and more accurately evaluating the relationship between H19 rs217727 and cancer risk. Thus, we performed meta-analysis to explore the association between H19 polymorphisms and the risk of cancer.

Methods
For this meta-analysis study, patient consent and ethical approval was not required. We performed this meta-analysis as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [25]. Two independent investigators participated in study selection and data extraction, and any disagreement was solved by discussion and reinterpretation of the data involved.

Selection and exclusion criteria
The eligibility criteria were as follows: (1) case-control studies, in which the relation between H19 rs217727 polymorphism and the risk of cancer was evaluated; (2) 2 or more studies focused on H19 rs217727 polymorphism; (3) the genotype frequency was reported; (4) published as a full-text manuscript in the English language. We excluded meta-analysis, reviews, as well as the articles lack of healthy controls, or polymorphism type not detected.

Literature and research strategy
We searched the databases Embase, PubMed, and Web of Science up to January 06, 2019 using the keywords “H19 OR long noncoding RNA H19” AND “cancer OR tumor OR neoplasm” AND “mutation OR variant OR polymorphism”. Studies related to the association of H19 rs217727 polymorphism and cancer risk were obtained. In addition, references and meta-analyses of the studies included were searched manually. The search strategy in PubMed are shown in Additional file 1.

Data extraction and synthesis
Data was extracted and listed on the predesigned data extraction sheet included first author, publication year, country, ethnicity (Asian or Caucasian), source of control, type of cancer, type of polymorphism, number and genotyping distribution of cases and controls, genotyping method, smoking status and P-value of Hardy-Weinberg Equilibrium (HWE) in controls [26]. Authors involved were contacted and asked for data usage, when necessary.

Quality assessment
The quality of the included studies was evaluated by two independent investigators according to the Newcastle Ottawa Scale (NOS) [27]. The points were awarded on selection (case definition adequate, representativeness of the cases, selection of controls, definitions of controls), comparability (comparability of cases and controls on the basis of the design or analysis) and exposure (ascertainment of exposure, uniform method of ascertainment, nonresponse rate) and the total score ranged from 0 to 9. Study with a score of more than 5 was included in the meta-analysis.

Data analysis
We used the OR and 95% CI to present the strength of the association using an allelic model (T vs. C), homozygote model (TT vs. CC), heterozygote model (CT vs. CC), dominant model [(CT + TT) vs. CC] and recessive model [TT vs. (CT + CC)]. Meta-analysis was conducted if 2 or more studies were performed for the same type of polymorphism. Initially, heterogeneity was evaluated by the Chi square-based Q-test, and $I^2$ statistics. A value of $P \geq 0.1$ and $I^2 \leq 50\%$ indicated that heterogeneity was absent, and the fixed-effect model was used. In other occasions, the random-effect model was used. Moreover, subgroup analyses were conducted based on ethnicity, type of cancer, source of controls, sample size, genotyping approach and smoking status. Evaluation of any publication bias was performed by Begg’s and Egger’s tests, when $P < 0.1$, publication bias was considered to exist. Sensitive analysis was performed by elimination of each study to observe the effect of a single study on the pooled OR. Statistical analysis was performed using Stata software version 12.0 (Stata Corporation, College Station, TX, USA).

Results
Study identification
In this meta-analysis, a total of 17 case–control publications [8–14, 16–19, 21–24], including 9166 cancer patients and 10,823 healthy controls were selected. A summary of data retrieval and selection is summarized in Fig. 1.

Characteristics and quality of the study
In these 17 studies, 8 types of cancer were studied, including gastric cancer, breast cancer, lung cancer, bladder cancer, osteosarcoma, cervical cancer, oral squamous cancer, and digestive system tumors. Eight of the studies focused on general population and 9 on hospital data. All studies were performed in Asians, except one in Caucasians. The
summary characteristics are described in Table 1. In addition, the relationship between smoking status and genetic polymorphism has been reported in only 4 studies [8, 17, 23, 24], and the summary characteristics are described in Table 2.

Quality assessment
According to the NOS, detailed quality assessment for each study included are presented in Table 3, the score of each included study is more than 7 points, higher scores were associated with lower risks of bias. The percentage of quality assessment is presented in Fig. 2.

Statistical analysis
As shown in Table 4, H19 rs217727 was found to increase cancer risk in overall analysis under T vs C (OR = 1.16, 95% CI = 1.16–1.60, $I^2 = 13.8$, TT vs CC: OR = 1.96, 95% CI = 1.39–2.75, $I^2 = 0$, CT vs CC: OR = 1.29, 95% CI = 1.05–1.57, $I^2 = 0.4$, CT + TT vs CC: OR = 1.39, 95% CI = 1.14–1.71, $I^2 = 10.9$, TT vs CT + CC: OR = 1.75, 95% CI = 1.26–2.42, $I^2 = 0$) and oral squamous cell carcinoma (T vs C: OR = 1.26, 95% CI = 1.11–1.42, $I^2 = 0$, TT vs CC: OR = 1.63, 95% CI = 1.25–2.12, $I^2 = 0$, CT vs CC: OR = 1.25, 95% CI = 1.04–1.50, $I^2 = 0$, CT + TT vs CC: OR = 1.32, 95% CI = 1.11–1.57, $I^2 = 0$, TT vs CT + CC: OR = 1.42, 95% CI = 1.07–1.88, $I^2 = 28.1$). H19 rs217727 significantly increased the risk of lung cancer in the allelic, homozygote models (T vs C: OR = 1.17, 95% CI = 1.03–1.33, $I^2 = 0$, TT vs CC: OR = 1.15, 95% CI = 1.07–1.24, $I^2 = 29.6$, TT vs CC: OR = 1.29, 95% CI = 1.07–1.45, $I^2 = 70.6$). When stratifying data by ethnicity, genotyping approach and type of cancer, the allelic, homozygote, heterozygote, dominant and recessive models of rs217727 have a positive association with cancer risk in hospital-based controls, as shown in Fig. 3 (T vs C: OR = 1.15, 95% CI = 1.07–1.24, $I^2 = 29.6$, TT vs CC: OR = 1.29, 95% CI = 1.07–1.55, $I^2 = 41.4$, CT vs CC: OR = 1.21, 95% CI = 1.03–1.45, $I^2 = 68.5$, CT + TT vs CC: OR = 1.23, 95% CI = 1.07–1.42, $I^2 = 57.4$). Similarly, a positive relation was observed between the allelic, homozygous, dominant and recessive models and the risk of cancer when the case sample size ≥500 (T vs C: OR = 1.13, 95% CI = 1.04–1.22, $I^2 = 67.1$, TT vs CC: OR = 1.27, 95% CI = 1.08–1.49, $I^2 = 63.6$, CT + TT vs CC: OR = 1.13, 95% CI =
1.01–1.25, \(I^2 = 66.4\), TT vs CT + CC: OR = 1.25, 95% CI = 1.08–1.41, \(I^2 = 56.4\). As shown in Table 5, when stratifying data by smoking status, all the genetic models of rs217727 have a positive association with cancer risk in smokers, as well as in nonsmokers except in recessive model.

### Heterogeneity analysis

In this meta-analysis, heterogeneity was observed, we next performed the stratified analysis to evaluate the source of the heterogeneity. The heterogeneity decreased significantly or disappeared in genotyping approach of MassArray (T vs C: \(P = 0.28, I^2 = 13.8\), TT vs CC: \(P = 0.53, I^2 = 0\), CT vs CC: \(P = 0.32, I^2 = 0.4\), CT + TT vs CC: \(P = 0.29, I^2 = 10.9\), TT vs CT + CC: \(P = 0.66, I^2 = 0\)), oral squamous cell carcinoma (T vs C: \(P = 0.72, I^2 = 0\), TT vs CC: \(P = 0.42, I^2 = 0\), CT vs CC: \(P = 0.65, I^2 = 0\), CT + TT vs CC: \(P = 0.8, I^2 = 0\), TT vs CT + CC: \(P = 0.24, I^2 = 28.1\)) and lung cancer (T vs C: \(P = 0.73, I^2 = 0\), TT vs CC: \(P = 0.27, I^2 = 19.4\), CT vs CC: \(P = 0.18, I^2 = 44.4\)). Furthermore, analyses of control subjects demonstrated that heterogeneity was significantly reduced in hospital-based controls in allelic models (T vs C: \(P = 0.18, I^2 = 29.6\)). Nevertheless, heterogeneity was still present in

### Table 1 Characteristics of included studies in the meta-analysis (rs217727 C>T)

| Author       | Year | Country | Ethnicity | Sample size (case/control) | Source of control | Cancer site and type | Genotype distribution | Genotyping method | \(P\) for HWE |
|--------------|------|---------|-----------|----------------------------|-------------------|----------------------|----------------------|-------------------|---------------|
| Jin [10]     | 2016 | China   | Asian     | 246/284                    | PB                | cervical cancer      | 117 103 26 169 99 16 | MassArray         | 0.74          |
| Li [9]       | 2016 | China   | Asian     | 1147/1203                  | PB                | colorectal cancer    | 480 514 153 456 570 177 | TaqMan            | 0.959         |
| Xia [11]     | 2016 | China   | Asian     | 464/467                    | PB                | breast cancer        | 160 156 148 139 212 116 | CRS-RFLP          | 0.052         |
| Hua [17]     | 2016 | China   | Asian     | 1046/1394                  | HB                | bladder cancer       | 431 467 148 573 665 156 | TaqMan            | 0.074         |
| Yang [8]     | 2015 | China   | Asian     | 500/500                    | HB                | gastric cancer       | 160 252 88 193 244 63  | TaqMan            | 0.296         |
| Verhaegh [16]| 2008 | Netherlands | Caucasian     | 177/204                    | PB                | bladder cancer       | 114 59 4 115 80 9      | PCR-RFLP          | 0.288         |
| Hu [22]      | 2017 | China   | Asian     | 416/416                    | HB                | pancreatic cancer    | 133 200 83 128 196 92  | TaqMan            | 0.302         |
| Guo [23]     | 2017 | China   | Asian     | 362/740                    | PB                | oral squamous cell carcinoma | 101 181 80 255 348 137 | BeadChip         | 0.342         |
| Lin [12]     | 2017 | China   | Asian     | 1005/1020                  | HB                | breast cancer        | 403 471 131 465 450 105 | SNPscan           | 0.801         |
| He [21]      | 2017 | China   | Asian     | 193/383                    | HB                | osteosarcoma         | 79 102 12 195 165 23   | TaqMan            | 0.121         |
| Hassanzarei [13]| 2017 | Iran     | Asian     | 230/240                    | PB                | breast cancer        | 71 132 27 125 113 2    | PCR-RFLP          | 0             |
| Li [18]      | 2018 | China   | Asian     | 200/200                    | PB                | bladder cancer       | 51 140 9 84 90 26      | TaqMan            | 0.806         |
| Yuan [24]    | 2018 | China   | Asian     | 431/984                    | PB                | oral squamous cell carcinoma | 186 194 51 488 423 73 | MassArray         | 0.151         |
| Cui [14]     | 2018 | China   | Asian     | 1488/1675                  | PB                | breast cancer        | 611 692 185 685 773 217 | TaqMan            | 0.963         |
| Li [19]      | 2018 | China   | Asian     | 555/618                    | HB                | lung cancer          | 210 250 95 246 305 67  | TaqMan            | 0.053         |
| Abdollahzadeh [15]| 2018 | Iran     | Asian     | 150/100                    | HB                | breast cancer        | 116 29 5 86 14 0      | PCR-RFLP          | 0.452         |
| Yin [20]     | 2018 | China   | Asian     | 556/395                    | HB                | lung cancer          | 204 264 88 165 172 58  | TaqMan            | 0.232         |

### Table 2 Smoking status: characteristics of studies included in the meta-analysis

| Author       | Year | Cancer site and type | Smokers | Non-smokers |
|--------------|------|----------------------|---------|-------------|
| Hua [17]     | 2016 | bladder cancer       | 187 308 73 250 229 52 | 219 257 75 368 391 104 |
| Yang [8]     | 2015 | gastric cancer       | 44 60 20 49 68 24 | 116 186 74 | 144 167 48 |
| Guo [23]     | 2017 | oral squamous cell carcinoma | 35 75 30 81 131 49 | 66 106 50 | 174 217 88 |
| Yuan [24]    | 2018 | oral squamous cell carcinoma | 79 76 18 179 138 26 | 107 118 33 | 309 285 47 |
| Yin [20]     | 2018 | lung cancer          | 0 0 0 0 0 | 204 264 88 165 172 58 |
### Table 3 Quality score assessment

| Studies       | Case definition adequate | Representativeness of the cases | Selection of controls | Definition of controls | Comparability of cases and controls on the basis of the design or analysis | Exposure | Uniform method of ascertainment | Nonresponderate | Total |
|---------------|--------------------------|--------------------------------|-----------------------|------------------------|--------------------------------------------------------------------------------|---------|---------------------------------|------------------|-------|
| Jin [10]      | *                        | *                              | *                     |                        | **                                                                             | *       |                                 |                  | 9     |
| Li [9]        | *                        | *                              | *                     |                        | **                                                                             | *       |                                 |                  | 9     |
| Xia [11]      | *                        | *                              | *                     |                        | **                                                                             | *       |                                 |                  | 9     |
| Hua [17]      | *                        | *                              | 0                     |                        | **                                                                             | *       |                                 |                  | 7     |
| Yang [8]      | *                        | *                              | 0                     |                        | **                                                                             | *       |                                 |                  | 8     |
| Verhaegh [16] | *                        | *                              | *                     |                        | **                                                                             | *       |                                 |                  | 9     |
| Hu [22]       | *                        | *                              | 0                     |                        | **                                                                             | *       |                                 |                  | 8     |
| Guo [23]      | *                        | *                              | *                     |                        | **                                                                             | *       |                                 |                  | 8     |
| Lin [12]      | *                        | *                              | 0                     |                        | *                                                                             | *       |                                 |                  | 7     |
| He2 [1]       | *                        | *                              | 0                     |                        | **                                                                             | *       |                                 |                  | 8     |
| Hassanzarei [13] | *                      | *                              | *                     |                        | **                                                                             | *       |                                 |                  | 7     |
| Li [18]       | *                        | *                              | 0                     |                        | **                                                                             | *       |                                 |                  | 8     |
| Yuan [24]     | *                        | *                              | *                     |                        | **                                                                             | *       |                                 |                  | 8     |
| Cui [14]      | *                        | *                              | *                     |                        | *                                                                             | *       |                                 |                  | 7     |
| Li [19]       | *                        | *                              | 0                     |                        | **                                                                             | *       |                                 |                  | 8     |
| Abdollahzadeh [15] | *                     | *                              | 0                     |                        | **                                                                             | *       |                                 |                  | 8     |
| Yin [20]      | *                        | *                              | 0                     |                        | **                                                                             | *       |                                 |                  | 8     |

*indicates a score of 1, **indicates a score of 2. The total score ranged from 0 to 9

![Graph of quality assessments](Image)
Table 4: Overall and subgroups meta-analysis of H19 rs217727 (C > T) polymorphism and cancer risk

| Overall and subgroups | NO. | T versus C | TT versus CC | CT versus CC | CT + TT versus CC | TT versus CT + CC |
|-----------------------|-----|------------|--------------|--------------|------------------|------------------|
|                       |     | OR (95% CI)| PQ | I² (%) | OR (95% CI) | PQ | I² (%) | OR (95% CI) | PQ | I² (%) | OR (95% CI) | PQ | I² (%) |
| Total                 | 17  | 1.16      | 0  | 75.7  | 1.29 (1.06, 1.56) | 0  | 71.6  | 1.15 (1.01, 1.31) | 0  | 75.4  | 1.20 (1.05, 1.36) | 0  | 76.5  | 1.22 (1.02, 1.45) |
| Ethnicity             |     |           |    |        |              |    |        |              |    |        |              |    |        |
| Asians                | 16  | 1.18      | 0  | 75.3  | 1.32 (1.09, 1.59) | 0  | 72.1  | 1.18 (1.03, 1.34) | 0  | 75.9  | 1.23 (1.08, 1.39) | 0  | 76.4  | 1.24 (1.04, 1.47) |
| Caucasians            | 1   | 0.74      | NA | NA     | 0.45 (0.13, 1.50) | NA | NA     | 0.74 (0.49, 1.14) | NA | NA     | 0.71 (0.47, 1.08) | NA | NA     |
| Method                |     |           |    |        |              |    |        |              |    |        |              |    |        |
| TaqMan                | 9   | 1.07      | 0.01  | 60.6  | 1.12 (0.92, 1.36) | 0.01  | 63.2  | 1.12 (0.96, 1.31) | 0  | 74.1  | 1.12 (0.98, 1.29) | 0  | 72.6  | 1.06 (0.87, 1.31) |
| MassArray             | 2   | 1.36      | 0.28  | 13.8  | 1.96 (1.39, 2.75) | 0.53  | 0     | 1.29 (1.05, 1.57) | 0.32  | 0.4  | 1.39 (1.14, 1.71) | 0.29  | 0.9  | 1.75 (1.26, 2.42) |
| PCR-RFLP             | 3   | 1.44      | 0.00  | 79.9  | 4.14 (0.21, 80.14) | 0     | 89    | 1.32 (0.66, 2.64) | 0  | 83.7  | 1.45 (0.63, 3.35) | 0  | 89.4  | 3.60 (0.26, 49.72) |
| Others                | 3   | 1.17      | 0.4  | 0     | 1.33 (1.11, 1.61) | 0.42  | 0     | 1.01 (0.68, 1.51) | 0  | 86    | 1.12 (0.84, 1.49) | 0.01  | 77    | 1.33 (1.12, 1.57) |
| Cancer type           |     |           |    |        |              |    |        |              |    |        |              |    |        |
| Breast cancer         | 5   | 1.29      | 0  | 86.8  | 1.56 (0.95, 2.56) | 0  | 83    | 1.15 (0.84, 1.55) | 0  | 84.2  | 1.27 (0.94, 1.71) | 0  | 85.7  | 1.48 (0.98, 2.26) |
| Bladder cancer        | 3   | 1.01      | 0.1  | 56.8  | 0.80 (0.40, 1.61) | 0.06  | 64    | 1.20 (0.64, 2.23) | 0  | 90.1  | 1.13 (0.68, 1.88) | 0  | 85.9  | 0.63 (0.22, 1.80) |
| Digestive system cancer | 3  | 1.02      | 0.04  | 81.6  | 1.05 (0.68, 1.62) | 0.01  | 79.8  | 1.00 (0.79, 1.26) | 0.08  | 61    | 1.01 (0.77, 1.34) | 0.02  | 76.1  | 1.03 (0.76, 1.41) |
| Osteosarcoma          | 1   | 1.27      | NA   | NA     | 1.29 (0.61, 2.71) | NA   | NA     | 1.53 (1.07, 2.19) | NA   | NA     | 1.50 (1.05, 2.12) | NA   | NA     |
| Cervical cancer       | 1   | 1.53      | NA   | NA     | 2.35 (1.21, 4.57) | NA   | NA     | 1.50 (1.05, 2.16) | NA   | NA     | 1.62 (1.15, 2.29) | NA   | NA     |
| Oral squamous cell carcinoma | 2 | 1.26      | 0.72  | 0     | 1.63 (1.25, 2.12) | 0.42  | 0     | 1.25 (1.04, 1.50) | 0.65  | 0     | 1.32 (1.11, 1.57) | 0.8   | 0     | 1.42 (1.07, 1.88) |
| Lung cancer           | 2   | 1.17      | 0.73  | 0     | 1.44 (1.07, 1.94) | 0.27  | 19.4  | 1.08 (0.84, 1.39) | 0.18  | 44.4  | 1.15 (0.97, 1.37) | 0.47  | 0     | 1.37 (0.89, 2.11) |
| Source of controls    |     |           |    |        |              |    |        |              |    |        |              |    |        |
| Population-based      | 8   | 1.16      | 0  | 86.5  | 1.36 (0.96, 1.93) | 0  | 82.4  | 1.08 (0.87, 1.33) | 0  | 80.9  | 1.15 (0.92, 1.43) | 0  | 84.7  | 1.30 (0.98, 1.73) |
| Hospital-based        | 9   | 1.15      | 0.18  | 29.6  | 1.29 (1.07, 1.55) | 0.09  | 41.4  | 1.21 (1.03, 1.45) | 0  | 68.5  | 1.23 (1.07, 1.42) | 0.02  | 57.4  | 1.16 (0.93, 1.46) |
| Case sample size      |     |           |    |        |              |    |        |              |    |        |              |    |        |
| ≥ 500                | 13  | 1.13      | 0  | 67.1  | 1.27 (1.08, 1.06) | 0  | 63.6  | 1.08 (0.96, 1.13) | 0  | 65.2  | 1.13 (0.98, 1.13) | 0  | 66.4  | 1.25 (1.08, 1.43) |
other subgroups. In Table 4, an overview of all analyses is presented.

Sensitivity analysis and publication bias
Sensitivity analysis was performed by omitting each and every included studies. As shown in Fig. 4, the results indicated that the pooled ORs were not subjective to change, which indicated the stability of our study. To assess the publication bias for the studies, both the Egger’s test and Begg’s funnel plot were performed. Publication bias was found in allelic model ($P = 0.04$), heterozygote model ($P = 0.05$), dominant model ($P = 0.03$). Trim and fill

**Table 4** Overall and subgroups meta-analysis of H19 rs217727 (C > T) polymorphism and cancer risk (Continued)

| Overall and subgroups | NO. | T versus C | TT versus CC | CT versus CC | CT + TT versus CC | TT versus CT + CC |
|-----------------------|-----|------------|--------------|--------------|-------------------|------------------|
|                       |     | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) |
| $< 500$               | 4   | 1.36 (0.83, 2.29) | 0.871 (0.31, 2.29) | 15.7 (0.88, 2.80) | 1.60 (0.87, 2.92) | 85.8 (0.87, 2.92) |
|                       |     | 1.49        | 1.20         | 1.41         | 1.41         |

*Including colorectal cancer, gastric cancer and pancreatic cancer

![Fig. 3 Forest plots for H19 rs217727 polymorphism associated with risk of cancer in subgroup analysis under hospital-based controls. a Allelic model (T vs. C), b homozygote model (TT vs. CC), c Heterozygote model (CT vs. CC), d Dominant model (CT + TT vs. CC)
Table 5  Smoking status: Meta-analysis of the association between the H19 rs217727 polymorphism and cancer risk

| Smoking status | NO. | T versus C | | TT versus CC | | CT versus CC | | CT + TT versus CC | | TT versus CT + CC |
|---------------|-----|-----------|---|-------------|---|-------------|---|-------------|---|-------------|
|               |     | OR (95% CI) | P (%) | OR (95% CI) | P (%) | OR (95% CI) | P (%) | OR (95% CI) | P (%) | OR (95% CI) | P (%) |
| smokers       | 4   | 1.29 (1.14, 1.46) | 0.19 | 1.55 (1.17, 2.03) | 0.41 | 1.48 (1.23, 1.77) | 0.14 | 1.49 (1.26, 1.78) | 0.11 | 1.25 (0.97, 1.61) | 0.77 |
| nonsmokers    | 5   | 1.21 (1.11, 1.32) | 0.41 | 1.46 (1.22, 1.76) | 0.28 | 1.21 (1.07, 1.38) | 0.84 | 1.27 (1.12, 1.43) | 0.64 | 1.31 (1.10, 1.55) | 0.33 |
method was used to identify and correct the publication bias. Before and after the trim, ORs does not change, which indicates that despite the publication bias in this study, the publication bias has little impact, and the research results are robust and reliable. The trim and fill method’s funnel plot is shown in Fig. 5.

Discussion

In recent years, many studies have focused on the relationship between genotype and phenotype, and the personalized prevention and treatment of cancer based on genetic information is the current research trend and hotspot [28]. SNP is the most common type of gene polymorphism, which may affect gene expression and function through indirect influence of related transcription factors or micro-RNAs, and further participate in the occurrence and development of tumors. LncRNA H19 has been widely recognized for its aberrant expression profile and role in carcinogenesis, and it is suggested to be a novel biomarker for the diagnosis of cancer [29, 30]. In addition, numerous studies have focused on the relation between H19 SNPs and cancer susceptibility. A study conducted by Yang et al. revealed that the TT + CT genotype of rs2839698 could increase the risk of hepatocellular cancer [31]. In terms of H19 rs217727, it was found to increase the risk of breast cancer [12, 13, 15]. Further functional experiments found that the expression level of H19 in breast cancer tissues was higher than that in normal tissues, and rs217727 CT or TT genotype was helpful to improve the expression level of H19 (P<0.001, 12]. However, no significant correlation was found in the study conducted by Xia et al. [11]. Furthermore, a study [17] included 1049 cancer cases and 1399 controls, showed that the AA genotype increased the risk of bladder cancer up to 1.31 times compared with the GG/GA genotype. Similarly, a positive relation was also found in gastric cancer [8] and cervical cancer [10]. However, in another study it was demonstrated that rs217727 did not associate with risk of colorectal cancer in additive model [9]. The results were inconsistent and inconclusive, and might be due to the limited sample size, the difference in genetic background, or the type of cancer. Therefore, in this study, we performed meta-analysis to comprehensively evaluate the association between H19 SNPs and susceptibility to cancer.
In the current meta-analysis, which included 17 case-control studies, people with the T, TT, CT and CT + TT genotypes of SNP rs217727 got a higher risk of cancer. Similarly, subgroup analysis based on ethnicity, type of cancer and genotyping method showed an increased risk for all genetic models in Asian, oral squamous cell carcinoma and genotyping approach according to MassArray. In addition, the risk of lung cancer increased in the allelic, homozygote models, and for breast cancer, the risk increased in the allelic model. The significant association was also found in allelic, homozygote, heterozygote and dominant models in the subgroup of hospital-based controls, as well as in allelic, homozygote, dominant and recessive models in the subgroup with a sample size of more than 500. Overall, the study revealed that H19 rs217727 might increase the risk of cancer. Interestingly, we also found that smoking was not significantly associated with the development of cancer in H19 rs217727.

Our results differ from those previously published [32–35]. Lv et al. [32] and Li et al. [35] included 5 studies and concluded that the rs217727 C > T might not be associated with the risk of cancer. Chu et al [33] used differently 3 genetic models, and the pooled results showed that the heterozygote and dominant model of rs217727 appeared to be a protective factor to cancer in hospital-based controls, as well as in the subgroup of population-based controls. Lu’s study, which included 4 literatures, subgroup analyses only stratified by genotyping approach and failed to reveal the relationship between rs217727 C > T and cancer risk [34]. The increased sample size and newly incorporated studies in our study may explain this difference. For the relation observed in subgroup meta-analysis, but not in overall meta-analysis, there are several possibilities to explain this difference, such as differences in genetic background, and the complex process of cancer formation. Interestingly, we also found that H19 rs217727 was associated with a neoplastic predisposition, and had little to do with smoking.

Our meta-analysis has several limitations, which should be addressed. First, despite the comprehensive analysis that has been performed to determine a possible relation, potential covariates (age, sex, drinking status, and smoking status) cannot be extracted from all included cases. Thus, the pooled results were based on unadjusted data. Second, the sample size of this study is still limited, which may reduce the power of analysis. Therefore, the data should be validated in a larger study. Third, only English databases were used in our search, which may affect our results. If literatures of other languages were included in this study, it would be possible that additional estimations could have been conducted. Finally, after subgroup analyses, heterogeneity could still be observed in a variety of SNPs, therefore, our conclusions should be treated with caution.

Conclusions

LncRNA H19 rs217727 could increase cancer risk in overall population, as well as in Asians, subgroups for genotyping based on MassArray, oral squamous cell carcinoma, lung cancer, breast cancer, hospital-based controls and subgroups with a case sample size ≥500. Because of the limitations in our study, well-designed studies with a larger sample size, and adjusted risk factors are required to further confirm the conclusions.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s12881-019-0904-x.

Additional file 1. PubMed search strategy.

Abbreviations

CI: Confidence interval; EBV: Epstein-Barr virus; GWAS: Genome-wide association studies; HOTAIR: HOX transcript antisense RNA; HPV: Human papillomavirus.
Acknowledgements
Not applicable.

Authors’ contributions
QL obtained funding and designed the study. XW and JLZ performed the analysis and interpretation of the data, and wrote the manuscript. FC, KH and SHS performed the analysis and interpretation of data. YXL, XMC, FJG, YNP provided technical support for the analysis and critical revision of the manuscript. All authors have read and approved the final version of the manuscript.

Funding
1. The National Natural Science Foundation of China (No.81860469) provided ideas for the direction of the topic.
2. The University Excellent Science and Technology Innovation Talent Support Plan Fund of Guizhou Province (Qian Jiao He KY zi [2015]495) provided help for literature retrieval and literature screening.
3. The Key Technologies & R&D Program of Guizhou (Qian Ke He LH zi [2016]7479, Qian Ke He LH ZI [2015]7485) and Science Foundation Project of Guizhou provincial health and family planning commission (gzwjxj2107–1-024) provided help for data extraction and synthesis.
4. The Scientific research project of Sichuan provincial health and Family Planning Commission (18PJ115) provided help for quality assessment and funds for language modification of the manuscript.

Availability of data and materials
The datasets generated and analyzed during the present study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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Received: 12 April 2019 Accepted: 2 October 2019

Published online: 21 November 2019

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