Association between long non-coding RNA polymorphisms and cancer risk: a meta-analysis

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Several studies have suggested that long non-coding RNA (lncRNA) gene polymorphisms are associated with cancer risk. In the present study, we conducted a meta-analysis related to studies on the association between lncRNA single-nucleotide polymorphisms (SNPs) and the overall risk of cancer. A total of 12 SNPs in five common lncRNA genes were finally included in the meta-analysis. In the lncRNA antisense non-coding RNA (ncRNA) in the INK4 locus (ANRIL), the rs1333048 A/C, rs1016343 T/C, and rs1456315 G/A polymorphisms, but not rs1333045 C/T, were correlated with overall cancer risk. Our study also demonstrated that other SNPs were correlated with overall cancer risk, namely, metastasis-associated lung adenocarcinoma transcript 1 (MALAT1, rs619586 A/G), HOXA distal transcript antisense RNA (HOTTIP, rs1859168 A/C), and highly up-regulated in liver cancer (HULC, rs7763881 A/C). Moreover, four prostate cancer-associated ncRNA1 (PRNCR1, rs16901946 G/A, rs13252298 G/A, rs1016343 T/C, and rs1456315 G/A) SNPs were in association with cancer risk. No association was found between the PRNCR1 (rs7007694 C/T) SNP and the risk of cancer. In conclusion, our results suggest that several studied lncRNA SNPs are associated with cancer risk. Furthermore, our study may shed some light on the biomarkers for predicting cancer risk.

Introduction

As a new class of functional non-coding RNAs (ncRNAs), long ncRNAs (lncRNAs) are made up of over 200 nts and lack the ability of protein coding [1]. Recently, the association between lncRNA and human diseases, especially cancer, has been widely investigated. Compared with other ncRNAs, lncRNAs play an important role in numerous vital activities of cell, including the regulation of epigenetic modifications, cell cycle, cell differentiation, and stress response [2]. The most important function of lncRNA is involvement in the tumorigenesis as proto-oncogene [3] or anti-oncogene [4]. Moreover, the differential expression of lncRNA may facilitate tumor cell proliferation, invasion, and metastasis [5].

Currently, single nucleotide polymorphisms (SNPs) are the most common genetic variants of concern and universally present in lncRNA genes. It is predicted that the expression and function of lncRNAs are affected by SNPs [6]. Studies have also suggested that polymorphism in lncRNA may influence the process of splicing and stability of mRNA conformation, leading to the modification of their interacting partners [7]. To date, several studies have assessed the associations amongst more than 20 lncRNA polymorphisms and susceptibility of cancers, but the results are inconsistent.

In the present study, we conducted a meta-analysis of epidemiological studies to explore the associations between five lncRNA SNPs and overall cancer risk. Furthermore, our study may shed some light on the biomarkers for predicting cancer risk.
Materials and methods

Publication search
A computerized literature search was performed in the Medline, PubMed, Web of Science, and Embase database up to 6 February 2018. The search strategy included the terms ('lncRNA' or 'long non-coding RNA') and ('polymorphisms' or 'variants' or 'variant' or 'SNP') and ('cancer' or 'carcinoma' or 'tumor' or 'neoplasm'). To be eligible for inclusion in the meta-analysis, a study must meet the following criteria: (i) case–control study or cohort study; (ii) assessing the association between lncRNA SNPs and cancer risk; (iii) having an available genotype or allele frequency for estimating an odds ratio (OR) with 95% confidence interval (95% CI) or hazard ratio (HR) with 95% CI; and (iv) genotype frequencies in controls being consistent with those expected from Hardy–Weinberg equilibrium (HWE) (P > 0.05). The exclusion criteria were: (i) duplicate studies; (ii) not relevant to cancer or lncRNA SNPs; or (iii) no available data and the authors could not be contacted.

Data extraction and quality assessment
Two investigators (X.H. and W.Z.) evaluated the eligibility of all retrieved studies and extracted the relevant data independently. Extracted databases were then cross-checked between the two authors to rule out any discrepancy. Disagreement was resolved by consulting with the third investigator (Z.S.). The study quality was assessed in accordance with the Newcastle–Ottawa Scale (NOS) (Supplementary Table S1). Eight items were extracted, and each item scored 1. The total scores ranged from 0 to 8. If the scores were ≥7, then the study was considered to be of high quality.

Statistical analysis
The statistical analysis was performed using STATA 14. Estimates were summarized as ORs with 95% CIs for each study (P < 0.05 was considered statistically significant). The genotype frequencies of the lncRNA polymorphisms for the HWE were calculated for the controls using the chi-square test, and P < 0.05 was considered as significant disequilibrium. The between-study heterogeneity was evaluated by using the chi-square test and the I² statistic. An I² value of > 50% of the I² statistic was considered to indicate significant heterogeneity [8]. When a significant heterogeneity existed across the included studies, a random-effects model was used for the analysis. Otherwise, the fixed-effects model was used. Subgroup analyses were performed to detect the source of heterogeneity. As to genotype comparison, the risks of the heterozygote and variant homozygote compared with the wild-type homozygote were estimated respectively. Then we evaluated the dominant and recessive effects of the variant allele (heterozygote + variant homozygote compared with wild-type homozygote) and variant homozygote compared with heterozygote + wild-type homozygote), respectively. Begg's rank correlation and Egger's linear regression method were used to assess the publication bias statistically. A two-tailed P-value < 0.05 implies a statistically significant publication bias [9,10]. We further conducted sensitivity analyses to substantiate the stability of results and detect the potential source of heterogeneity.

Results
Characteristics of the eligible studies
Finally, a total of 234 articles were included in the meta-analysis, 42 case–control studies that met our inclusion criteria were included in quantitative analysis, and 17 of them involving 9548 cases and 9828 controls were included in our meta-analysis (Figure 1). Table 1 lists the characteristics of the eligible studies. Amongst the 17 case–control studies, the control groups of 9 were hospital-based and 8 were population-based. Genotyping methods included tetra-primer amplification refractory mutation system (T-ARMS)-PCR (2), MALDI-TOF MS (1), PCR-restriction fragment length polymorphism (RFLP) (5), created restriction site (CRS)-RFLP (1), TaqMan (3), MassARRAY (4), multiplex PCR-based Invader assay (1), and SNPlex Genotyping System (1) (Table 1). Table 2 presents the genotype frequency distributions of a total 19 SNPs in five lncRNA genes (antisense ncRNA in the INK4 locus (ANRIL), metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), HOXA distal transcript antisense RNA (HOTTIP), highly up-regulated in liver cancer (HULC), and prostate cancer-associated ncRNA 1 (PRNCR1)) involved in the 17 eligible studies. After removal of those records for which P<0.05, seven SNPs were found to be only based on one single eligible study. They were ANRIL rs2151280, MALAT1 rs3200401, MALAT1 rs79277113, MALAT1 rs1194338, HOTTIP rs5883064, PRNCR1 rs7841060, and PRNCR1 rs7463708. Therefore, the remaining 12 lncRNA SNPs were included in our final calculation (Table 2).
Quantitative data synthesis of 12 SNPs in five highly studied lncRNA genes

Four SNPs in ANRIL
First, we calculated the pooled ORs of all eligible studies to estimate the association between the four SNPs in ANRIL and overall cancer risk. The rs133045 C/T polymorphism was not associated with cancer; and the rs133048 A/C, rs4977574 A/G, and rs10757278 A/G polymorphisms were associated with overall cancer risk. The rs133048 A/C polymorphism was associated with increased overall risk of cancer in all genetic models (C compared with A: $P=0.000, OR = 2.06, 95\% CI = 1.64–2.57$; CC compared with AA: $P=0.000, OR = 4.26, 95\% CI = 2.67–6.78$; AC compared with AA: $P=0.049, OR = 1.45, 95\% CI = 1.00–2.10$; dominant model: $P=0.001, OR = 1.80, 95\% CI = 1.28–2.51$; recessive model: $P=0.000, OR = 2.01, 95\% CI = 1.42–2.84$). For the rs4977574 A/G polymorphism, both the heterozygote type AG and the dominant model were associated with decreased overall risk of cancer compared with the wild-type AA (AG compared with AA: $P=0.006, OR = 0.62, 95\% CI = 0.44–0.87$; dominant model: $P=0.007, OR = 0.64, 95\% CI = 0.46–0.88$). However, both the mutation type GG and the allelic model were associated with increased overall risk of cancer (GG compared with AA: $P=0.000, OR = 2.40, 95\% CI = 1.60–3.59$; G compared with A: $P=0.000, OR = 1.68, 95\% CI = 1.35–2.08$). For the rs10757278 A/G polymorphism, the heterozygote type AG, the dominant model, and the recessive model were associated with increased overall risk of cancer (AG compared with AA: $P=0.000, OR = 2.13, 95\% CI = 1.45–3.12$; dominant model: $P=0.000, OR = 2.58, 95\% CI = 1.80–3.69$; recessive model: $P=0.000, OR = 2.64, 95\% CI = 1.79–3.88$). Nevertheless, the allelic model was associated with decreased overall risk of cancer (G compared with A: $P=0.030, OR = 0.77, 95\% CI = 0.60–0.97$, Table 3).

One SNP in MALAT1
The meta-analysis showed that MALAT1 rs619586 A/G polymorphism was associated with overall cancer risk. For the rs619586 A/G polymorphism, the allelic model, the heterozygote type AG and the dominant model were associated
### Table 1 Characteristics of eligible studies

| Number | First author          | Year | Country | Ethnicity | Sample size | Genotyping method            | Adjusted factors | Citation |
|--------|-----------------------|------|---------|-----------|-------------|-----------------------------|-----------------|----------|
| 1      | Khorshidi et al.      | 2017 | Iran    | Asian     | 382         | MassARRAY                  | Age, sex, BMI   | [11]     |
| 2      | Kang et al.           | 2016 | China   | Asian     | 380         | PCR-RFLP                  | Age, sex, drinking | [12]     |
| 3      | Chung et al.          | 2017 | Japan   | Asian     | 2014        | MALDI-TOF MS               | Age, sex, BMI, smoking | [13]     |
| 4      | Li et al.             | 2017 | China   | Asian     | 2017        | MassARRAY                  | Age, sex, smoking, and HBV chronic infection | [14]     |
| 5      | Duan et al.           | 2017 | China   | Asian     | 470         | PCR-RFLP                  | Age, sex, BMI, smoking and alcohol drinking | [15]     |
| 6      | Gong et al.           | 2017 | China   | Asian     | 213         | MassARRAY                  | Age, sex, BMI, smoking, and alcohol drinking | [16]     |
| 7      | Hu et al.             | 2017 | China   | Asian     | 213         | TaqMan Assay-PCR           | Age, sex, BMI, smoking and alcohol drinking | [17]     |
| 8      | Shaker et al.         | 2017 | Egypt   | Caucasian | 120         | TaqMan Assay-PCR           | Age, sex, BMI, smoking and alcohol drinking | [18]     |
| 9      | He et al.             | 2017 | China   | Asian     | 194         | TaqMan Assay-PCR           | Age, sex, BMI, smoking and alcohol drinking | [19]     |
| 10     | Duan et al.           | 2017 | China   | Asian     | 740         | MassARRAY                  | Age, sex, BMI, smoking and alcohol drinking | [20]     |
| 11     | Li et al.             | 2017 | China   | Asian     | 394         | PCR-RFLP                  | Age, sex, BMI, smoking and alcohol drinking | [21]     |
| 12     | Shaker et al.         | 2017 | Egypt   | Caucasian | 830         | PCR-RFLP                  | Age, sex, BMI, smoking and alcohol drinking | [22]     |
| 13     | Li et al.             | 2017 | China   | Asian     | 595         | PCR-RFLP                  | Age, sex, BMI, smoking and alcohol drinking | [23]     |
| 14     | Chung et al.          | 2010 | Japan   | Asian     | 1500        | MassARRAY                  | Age, sex, BMI, smoking and alcohol drinking | [24]     |
| 15     | Salinas et al.        | 2008 | U.S.A.  | Caucasian | 1209        | MassARRAY                  | Age, sex, BMI, smoking and alcohol drinking | [25]     |
| 16     | Zheng et al.          | 2010 | China   | Asian     | 155         | MassARRAY                  | Age, sex, BMI, smoking and alcohol drinking | [26]     |

Abbreviations: BMI, body mass index; HB, hospital based; NM, not mentioned; PB, population based.

with decreased overall risk of cancer compared with the wild-type AA (G compared with A: P=0.003, OR=0.77, 95% CI = 0.65–0.92; AG compared with AA: P=0.009, OR=0.78, 95% CI = 0.65–0.94; dominant model: P=0.004, OR=0.77, 95% CI = 0.64–0.92, Table 3).

#### One SNP in HOTTIP

Our results suggested that the HOTTIP rs1859168 A/C polymorphism was associated with increased overall risk of cancer in all genetic models (G compared with A: P=0.000, OR=1.32, 95% CI = 1.19–1.45; CC compared with AA: P=0.000, OR=1.54, 95% CI = 1.27–1.87; AC compared with AA: P=0.006, OR=1.24, 95% CI = 1.06–1.45; dominant model: P=0.000, OR=1.37, 95% CI = 1.19–1.59; recessive model: P=0.000, OR=1.49, 95% CI = 1.26–1.76, Table 3).

#### One SNP in HULC

In the present study, the allelic model, the heterozygote type AC, and the dominant model of HULC rs7763881 A/C polymorphism were associated with increased overall risk of cancer compared with the wild-type AA (A compared with A: P=0.040, OR=0.91, 95% CI = 0.83–0.99; AC compared with AA: P=0.000, OR=0.74, 95% CI = 0.63–0.86; dominant model: P=0.000, OR=0.77, 95% CI = 0.66–0.89, Table 3).

#### Five SNPs in PRNCR1

The pooled OR and stratified analyses showed that amongst the five PRNCR1 SNPs included in the meta-analysis, only rs16901946 G/A, rs13252298 G/A, rs1016343 T/C, and rs1456315 G/A were associated with cancer risk, while the association of the rs7007694 C/T was not statistically significant (P>0.05).
Table 2 Genotype frequency distributions of lncRNA SNPs studied in included studies

| First author     | Year   | lncRNA SNPs | Type of cancer | Sample size | Case | Control | Homozygote wild | Heterozygote variant | P for HWE | Quality score |
|------------------|--------|-------------|----------------|-------------|------|---------|-----------------|----------------------|-----------|--------------|
| Khorshidi et al. | 2017   | ANRIL rs1333045 (C/T) | Breast cancer | 122         | 31   | 52      | 39              | 57                   | 100       |              |
|                  |        | ANRIL rs1333048 (A/C) | Breast cancer | 122         | 39   | 52      | 32              | 51                   | 97        |              |
|                  |        | ANRIL rs4977574 (A/G) | Breast cancer | 122         | 61   | 44      | 17              | 81                   | 93        |              |
|                  |        | ANRIL rs10757278 (AG) | | 122         | 22   | 42      | 22              | 74                   | 100       | 26           |
| Kang et al.      | 2015   | ANRIL rs2151280 (C/T) | ESCC          | 380         | 57   | 153     | 161             | 43                   | 173       | 154          |
| Taheri et al.    | 2017   | ANRIL rs1333045 (C/T) | Prostate cancer | 125         | 41   | 61      | 23              | 75                   | 102       | 43           |
|                  |        | ANRIL rs1333048 (A/C) | Prostate cancer | 148         | 35   | 65      | 58              | 101                  | 88        | 31           |
| Peng et al.      | 2017   | MALAT1 rs200446 (T/C) | Breast cancer | 487         | 357  | 120     | 10              | 338                  | 145       | 6            |
| Peng et al.      | 2017   | MALAT1 rs619586 (A/G) | Breast cancer | 487         | 415  | 65      | 7               | 396                  | 93        | 10           |
| Khorshidi et al. | 2017   | HOTTIP rs5883064 (C/T) | Lung cancer  | 491         | 161  | 252     | 78              | 89                   | 87        | 30           |
| He et al.        | 2017   | PRNCR1 rs16901946 (A/G) | Gastric cancer | 494         | 238  | 238     | 175             | 98                   | 79        | 10           |
| Shakeri et al.   | 2017   | HULC rs7763884 (A/G) | CRC            | 120         | 32   | 88      | 32              | 12                   | 84        | 0            |
| He et al.        | 2017   | PRNCR1 rs16901946 (A/G) | Gastric cancer | 1300        | 1094 | 189     | 5               | 1115                 | 205       | 10           |
| U et al.         | 2012   | MALAT1 rs619586 (A/G) | HCC            | 1300        | 1344 | 1094    | 189             | 5                    | 1115      | 205          |
| Hu et al.        | 2017   | HOTTIP rs1859168 (A/C) | Lung cancer  | 491         | 251  | 251     | 148             | 364                  | 421       | 136          |
| Dong et al.      | 2017   | HOTTIP rs1859168 (A/C) | Lung cancer  | 491         | 210  | 151     | 156             | 86                   | 94        | 31           |
| Kang et al.      | 2015   | HULC rs763981 (A/G) | | 380         | 122  | 122     | 122             | 99                   | 195       | 81           |
| Li et al.        | 2013   | PRNCR1 rs1016343 (C/T) | Gastric cancer | 219         | 125  | 92      | 2               | 230                  | 136       | 29           |
| Li et al.        | 2013   | PRNCR1 rs16901946 (A/G) | Gastric cancer | 1300        | 1344 | 1094    | 189             | 5                    | 1115      | 205          |
| Sattarifard et al.| 2017   | PRNCR1 rs1325298 (A/G) | Prostate cancer | 178         | 179  | 33      | 32              | 140                  | 176       | 78           |
| Li et al.        | 2013   | PRNCR1 rs1016343 (C/T) | CRC            | 313         | 195  | 195     | 195             | 31                   | 195       | 195          |
| First author | Year | lncRNA | SNPs          | Type of cancer | Sample size | Case  | Control | Case  | Control | Homozygote wild | Heterozygote | Heterozygote variant | Heterozygote variant | P for HWE | Quality score |
|--------------|------|--------|---------------|----------------|-------------|-------|---------|-------|---------|------------------|--------------|---------------------|---------------------|-----------|---------------|
| Chung et al. | 2010 | PRNCR1 | rs1016343 (C/T) | Prostate cancer | 1504 1554   | 650   | 667     | 185   | 841     | 608              | 68          | 103                 | 68                  | 0.624     | 7             |
|              |      |        | rs13252298 (A/G) | Prostate cancer | 1504 1554   | 808   | 556     | 137   | 609     | 737              | 204         | 0.416               | 609                 |           |               |
|              |      |        | rs16901946 (A/G) | Prostate cancer | 1504 1554   | 690   | 637     | 177   | 783     | 645              | 126         | 0.671               | 783                 |           |               |
|              |      |        | rs1456315 (A/G) | Prostate cancer | 1504 1554   | 905   | 495     | 104   | 663     | 703              | 187         | 0.975               | 663                 |           |               |
|              |      |        | rs7007694 (C/T) | Prostate cancer | 1504 1554   | 656   | 650     | 191   | 700     | 684              | 170         | 0.880               | 700                 |           |               |
| Salinas et al. | 2008 | PRNCR1 | rs1456315 (A/G) | Prostate cancer | 1308 1266 | 464   | 598     | 192   | 401     | 605              | 227         | 0.964               | 401                 |           |               |
|              |      |        | rs1016343 (C/T) | Prostate cancer | 1253 1233 | 711   | 454     | 88    | 706     | 385              | 52          | 0.529               | 706                 |           |               |
| Zheng et al. | 2010 | PRNCR1 | rs1016343 (C/T) | Prostate cancer | 284 147    | 76    | 159     | 49    | 66      | 65               | 16          | 0.999               | 66                  |           |               |

Abbreviations: CRC, colorectal cancer; EOC, epithelial ovarian cancer; ESCC, esophageal squamous cell carcinoma; HCC, hepatocellular carcinoma.

1Not included due to the limited number of studies for this lncRNA locus.
2Not included because the $P$ of the HWE was $<0.05$. 

Table 2: Genotype frequency distributions of lncRNA SNPs studied in included studies (Continued)
Table 3 Meta-analysis of the association between common SNPs and cancer risk

| Stratification | n | Allelic model | Mutation homozygote compared with wild-type | Heterozygote compared with wild-type | Dominant model | Recessive model |
|----------------|---|---------------|---------------------------------------------|-----------------------------------|----------------|----------------|
|                |   | OR (95% CI)   | P    | I² (%) | OR (95% CI)   | P    | I² (%) | OR (95% CI)   | P    | I² (%) |
| ANRIL          |   |               |      |        |               |      |        |               |      |        |
| rs1333048 (A/C) | 2 | 2.06 (1.64–2.57) | 0.001 | 94.3   | 4.26 (2.67–6.78) | 0.0001 | 93.1   | 1.45 (1.00–2.10) | 0.0491 | 93.0   | 1.80 (1.28–2.51) | 0.001 | 95.7   | 2.01 (1.42–2.94) | 0.000 | 92.7   |
| rs4977574 (A/G) | 2 | 1.68 (1.35–2.08) | 0.0001 | 96.7   | 2.40 (1.60–3.59) | 0.0001 | 96.1   | 0.62 (0.44–0.87) | 0.006 | 0.001 | 0.64 (0.46–0.88) | 0.007 | 0.001 | 0.91 (0.57–1.46) | 0.693 | 0.001 |
| rs1075728 (A/G) | 2 | 0.77 (0.60–0.97) | 0.030 | 0.001 | 0.72 (0.43–1.16) | 0.192 | 0.0   | 2.13 (1.45–3.12) | 0.001 | 90.7   | 2.58 (1.80–3.69) | 0.001 | 93.9   | 2.64 (1.79–3.88) | 0.000 | 82.7   |
| rs1333046 (C/T) | 2 | 1.15 (0.92–1.43) | 0.236 | 27.7   | 1.29 (0.83–1.99) | 0.260 | 26.5   | 1.03 (0.71–1.48) | 0.874 | 0.0   | 1.11 (0.79–1.56) | 0.556 | 0.0   | 1.30 (0.89–1.88) | 0.175 | 60.4   |
| MALAT1         |   |               |      |        |               |      |        |               |      |        |
| rs195986 (A/G) | 2 | 0.77 (0.65–0.92) | 0.003 | 9.7    | 0.58 (0.28–1.20) | 0.141 | 0.0    | 0.78 (0.65–0.94) | 0.009 | 33.5   | 0.77 (0.64–0.92) | 0.004 | 27.9   | 0.61 (0.30–1.26) | 0.180 | 0.001 |
| HOTTIP         | 3 | 1.32 (1.19–1.45) | 0.0001 | 75.2   | 1.54 (1.27–1.87) | 0.0001 | 81.8   | 1.24 (1.06–1.45) | 0.006 | 96.4   | 1.37 (1.19–1.59) | 0.0001 | 94.3   | 1.49 (1.26–1.76) | 0.000 | 0.001 |
| HULC           | 3 | 0.91 (0.83–0.99) | 0.040 | 0.0    | 0.86 (0.71–1.05) | 0.132 | 0.0    | 0.74 (0.63–0.86) | 0.000 | 41.3   | 0.77 (0.66–0.89) | 0.000 | 45.2   | 1.02 (0.87–1.21) | 0.776 | 0.001 |
| PRNCR1         |   |               |      |        |               |      |        |               |      |        |
| rs16901946 (G/A) | 3 | 1.15 (1.06–1.25) | 0.001 | 66.4   | 1.26 (1.06–1.50) | 0.008 | 82.6   | 1.15 (1.03–1.28) | 0.017 | 0.0    | 1.17 (1.06–1.30) | 0.003 | 21.6   | 1.21 (1.03–1.43) | 0.019 | 81.7   |
| Type of cancer  |   |               |      |        |               |      |        |               |      |        |
| Gastric cancer |   |               |      |        |               |      |        |               |      |        |
| rs13252298 (G/A) | 4 | 0.78 (0.72–0.85) | 0.0001 | 89.2   | 0.68 (0.56–0.81) | 0.0001 | 81.6   | 0.69 (0.62–0.77) | 0.0001 | 85.1   | 0.81 (0.73–0.90) | 0.0001 | 73.7   | 0.85 (0.72–1.01) | 0.005 | 82.7   |
| Type of cancer  |   |               |      |        |               |      |        |               |      |        |
| Gastric cancer |   |               |      |        |               |      |        |               |      |        |
| rs7007648 (C/T) | 5 | 1.03 (0.95–1.12) | 0.522 | 69.0   | 1.19 (0.98–1.45) | 0.086 | 58.4   | 0.96 (0.86–1.07) | 0.443 | 42.5   | 0.99 (0.89–1.10) | 0.848 | 61.0   | 1.19 (0.98–1.44) | 0.070 | 49.9   |
| Type of cancer  |   |               |      |        |               |      |        |               |      |        |
| Prostate cancer |   |               |      |        |               |      |        |               |      |        |
| rs1016343 (T/C) | 5 | 1.31 (1.22–1.41) | 0.0001 | 85.2   | 1.67 (1.41–1.97) | 0.0001 | 86.0   | 1.35 (1.22–1.49) | 0.000 | 47.2   | 1.41 (1.28–1.55) | 0.0001 | 73.1   | 1.42 (1.21–1.66) | 0.000 | 84.5   |
| Ethnicity      |   |               |      |        |               |      |        |               |      |        |
| Asian          | 4 | 1.30 (1.19–1.41) | 0.0001 | 88.7   | 1.60 (1.33–1.94) | 0.0001 | 89.3   | 1.37 (1.21–1.54) | 0.0001 | 59.8   | 1.42 (1.26–1.59) | 0.0001 | 79.8   | 1.35 (1.13–1.61) | 0.001 | 87.7   |
| Type of cancer  |   |               |      |        |               |      |        |               |      |        |
| Prostate cancer |   |               |      |        |               |      |        |               |      |        |
| rs1456315 (G/A) | 4 | 0.72 (0.66–0.79) | 0.000 | 95.7   | 0.48 (0.39–0.60) | 0.000 | 66.4   | 0.71 (0.63–0.80) | 0.000 | 96.4   | 0.66 (0.61–0.76) | 0.000 | 96.6   | 0.60 (0.49–0.75) | 0.000 | 84.2   |
| Ethnicity      |   |               |      |        |               |      |        |               |      |        |
| Asian          | 4 | 0.75 (0.70–0.81) | 0.0001 | 97.2   | 0.56 (0.47–0.67) | 0.000 | 90.7   | 0.73 (0.66–0.82) | 0.000 | 97.6   | 0.69 (0.63–0.77) | 0.000 | 97.8   | 0.68 (0.58–0.80) | 0.000 | 81.6   |

The results are in bold if P < 0.05.

1P was calculated by random model.
The rs16901946 G/A polymorphism was associated with increased overall risk of cancer in all genetic models (A compared with G: \( P=0.001, \ OR = 1.15, \ 95\% \ CI = 1.06–1.25 \); AA compared with GG: \( P=0.008, \ OR = 1.26, \ 95\% \ CI = 1.06–1.50 \); AG compared with GG: \( P=0.017, \ OR = 1.15, \ 95\% \ CI = 1.03–1.28 \); dominant model: \( P=0.003, \ OR = 1.17, \ 95\% \ CI = 1.06–1.30 \); recessive model: \( P=0.019, \ OR = 1.21, \ 95\% \ CI = 1.03–1.43 \)).

For the rs13252298 G/A polymorphism, the allelic model, the mutation type AA, the heterozygote type AG, and the dominant model were associated with decreased overall risk of cancer compared with the wild-type GG (A compared with G: \( P=0.000, \ OR = 0.78, \ 95\% \ CI = 0.72–0.85 \); AA compared with GG: \( P=0.000, \ OR = 0.68, \ 95\% \ CI = 0.56–0.81 \); AG compared with GG: \( P=0.000, \ OR = 0.69, \ 95\% \ CI = 0.62–0.77 \); dominant model: \( P=0.000, \ OR = 0.81, \ 95\% \ CI = 0.73–0.90 \)).

Additionally, the rs1016343 T/C polymorphism was associated with increased overall risk of cancer in all genetic models (C compared with T: \( P=0.000, \ OR = 1.31, \ 95\% \ CI = 1.22–1.41 \); CC compared with TT: \( P=0.000, \ OR = 1.67, \ 95\% \ CI = 1.41–1.97 \); CT compared with TT: \( P=0.000, \ OR = 1.35, \ 95\% \ CI = 1.22–1.49 \); dominant model: \( P=0.000, \ OR = 1.41, \ 95\% \ CI = 1.28–1.55 \); recessive model: \( P=0.000, \ OR = 1.42, \ 95\% \ CI = 1.21–1.66 \)).

The rs1456315 G/A polymorphism was associated with decreased overall risk of cancer in all genetic models (A compared with G: \( P=0.000, \ OR = 0.77, \ 95\% \ CI = 0.72–0.83 \); AA compared with GG: \( P=0.000, \ OR = 0.59, \ 95\% \ CI = 0.49–0.69 \); AG compared with GG: \( P=0.000, \ OR = 0.76, \ 95\% \ CI = 0.68–0.83 \); dominant model: \( P=0.000, \ OR = 0.72, \ 95\% \ CI = 0.66–0.79 \); recessive model: \( P=0.000, \ OR = 0.69, \ 95\% \ CI = 0.59–0.81 \), Table 3).

Due to heterogeneity, we performed stratified analyses based on ethnicity and cancer type. Stratified analyses based on cancer type showed a significant association between the rs16901946 G/A polymorphism and increased risk of gastric cancer in the heterozygote type AG and the dominant model. In the Asian subgroup, the rs1016343 T/C polymorphism was associated with increased cancer risk in all genetic models. When stratified with cancer type, a significant association between the rs1456315 G/A polymorphism and decreased risk of prostate cancer was observed in our study (Table 3).

**Heterogeneity**

There was interstudy heterogeneity (slight, moderate, or severe) in the overall comparison and the subgroup analyses (Table 3). We subsequently performed sensitivity analyses to explore the influence of an individual study on the pooled results by estimating the sensitivity before and after the removal of the study from the analysis. Some ORs and 95% CIs ranged from insignificantly to statistically significant after individual studies were removed (Supplementary Table S2).

**Publication bias**

We used Begg’s test and Egger’s test to evaluate potential publication bias of the included studies. No statistically significant publication bias was indicated in any of the genetic models for all IncRNA SNPs (Table 4).

**Discussion**

It is known to all that over 20 IncRNA polymorphisms are associated with susceptibility of cancer. In recent studies, most of meta-analyses were conducted to focus on the association between IncRNA HOTAIR [27,28] or IncRNA ZNRD1-AS1 [28] or IncRNA POLR2E [29] or IncRNA H19 [28,30] polymorphisms and cancer risk. For example, the study of Lv et al. [28] included only four common IncRNA genes such as H19, HOTAIR, ZNRD1-AS1, and PRNCR1. However, more IncRNA polymorphisms with larger sample sizes are warranted. Therefore, a total of 12 SNPs in five common IncRNA genes were finally included in our study. In addition, our study was the first meta-analysis to show the significant association between the IncRNA ANRIL, MALAT1, HOTTIP, and HULC polymorphisms and cancer risk. Compared with the studies of Lv et al. [28] and Chu et al. [29], we decided to include more eligible studies related to IncRNA PRNCR1 genes according to the inclusion and exclusion criteria. Therefore, we included a larger size of cancer patients with more SNPs of IncRNA PRNCR1 into our study to confirm the results. More importantly, discussions about underlying mechanisms of each gene and the related polymorphisms were included in our study. It might help readers better understand the function of different IncRNA genes in cancer. Our study provides theoretical bases and research clues for future studies.

**The ANRIL SNPs**

Chromosome region 9p21 is a hotspot for disease-associated polymorphisms and encodes three tumor suppressors, namely p16INK4a, p14ARF, and p15INK4b, and the IncRNA ANRIL [31]. ANRIL is 3.8-kb long and expressed on the reverse strand. It has been shown to bind to and recruit polycomb repression complex 2 (PRC2) to repress the expression...
Table 4: The results of Begg's and Egger's test for the publication bias

| Comparison type                          | Begg's test | Egger's test |
|------------------------------------------|-------------|--------------|
|                                          | Z-value     | P-value      | Z-value     | P-value      |
| **ANRIL rs1333048 (A/C)**                |             |              |             |              |
| Allelic model                            | 0.00        | 1.000        | NA          | NA          |
| Mutation homozygote compared with wild-type | 0.00        | 1.000        | NA          | NA          |
| Heterozygote compared with wild-type     | 0.00        | 1.000        | NA          | NA          |
| Dominant model                           | 0.00        | 1.000        | NA          | NA          |
| Recessive model                          | 0.00        | 1.000        | NA          | NA          |
| **ANRIL rs4977574 (A/G)**                |             |              |             |              |
| Allelic model                            | 0.00        | 1.000        | NA          | NA          |
| Mutation homozygote compared with wild-type | 0.00        | 1.000        | NA          | NA          |
| Heterozygote compared with wild-type     | 0.00        | 1.000        | NA          | NA          |
| Dominant model                           | 0.00        | 1.000        | NA          | NA          |
| Recessive model                          | 0.00        | 1.000        | NA          | NA          |
| **ANRIL rs10757278 (A/G)**               |             |              |             |              |
| Allelic model                            | 0.00        | 1.000        | NA          | NA          |
| Mutation homozygote compared with wild-type | 0.00        | 1.000        | NA          | NA          |
| Heterozygote compared with wild-type     | 0.00        | 1.000        | NA          | NA          |
| Dominant model                           | 0.00        | 1.000        | NA          | NA          |
| Recessive model                          | 0.00        | 1.000        | NA          | NA          |
| **ANRIL rs1333045 (C/T)**                |             |              |             |              |
| Allelic model                            | 0.00        | 1.000        | NA          | NA          |
| Mutation homozygote compared with wild-type | 0.00        | 1.000        | NA          | NA          |
| Heterozygote compared with wild-type     | 0.00        | 1.000        | NA          | NA          |
| Dominant model                           | 0.00        | 1.000        | NA          | NA          |
| Recessive model                          | 0.00        | 1.000        | NA          | NA          |
| **MALAT1 rs619586 (A/G)**                |             |              |             |              |
| Allelic model                            | 0.00        | 1.000        | NA          | NA          |
| Mutation homozygote compared with wild-type | 0.00        | 1.000        | NA          | NA          |
| Heterozygote compared with wild-type     | 0.00        | 1.000        | NA          | NA          |
| Dominant model                           | 0.00        | 1.000        | NA          | NA          |
| Recessive model                          | 0.00        | 1.000        | NA          | NA          |
| **HOTTIP rs1859168 (A/C)**               |             |              |             |              |
| Allelic model                            | 0.00        | 1.000        | −0.86       | 0.548       |
| Mutation homozygote compared with wild-type | 0.00        | 1.000        | −0.46       | 0.725       |
| Heterozygote compared with wild-type     | 0.00        | 1.000        | −1.02       | 0.494       |
| Dominant model                           | 0.00        | 1.000        | −0.91       | 0.531       |
| Recessive model                          | 0.00        | 1.000        | −0.75       | 0.590       |
| **HULC rs7763881 (A/C)**                 |             |              |             |              |
| Allelic model                            | 1.04        | 0.296        | −3.13       | 0.197       |
| Mutation homozygote compared with wild-type | 0.00        | 1.000        | NA          | NA          |
| Heterozygote compared with wild-type     | 1.04        | 0.296        | −9.06       | 0.070       |
| Dominant model                           | 1.04        | 0.296        | −5.60       | 0.113       |
| Recessive model                          | 0.00        | 1.000        | NA          | NA          |
| **PRNCR1 rs16901946 (G/A)**              |             |              |             |              |
| Allelic model                            | 0.34        | 0.734        | −0.71       | 0.553       |
| Mutation homozygote compared with wild-type | 0.34        | 0.734        | −0.71       | 0.553       |
| Heterozygote compared with wild-type     | −0.34       | 1.000        | 0.38        | 0.742       |
| Dominant model                           | −0.34       | 1.000        | −0.27       | 0.810       |
| Recessive model                          | 0.34        | 0.734        | −0.19       | 0.867       |
| **PRNCR1 rs13252298 (G/A)**              |             |              |             |              |
| Allelic model                            | 1.22        | 0.221        | 3.30        | 0.046       |
| Mutation homozygote compared with wild-type | 1.71        | 0.086        | 3.34        | 0.044       |
| Heterozygote compared with wild-type     | 0.24        | 0.806        | 1.07        | 0.363       |
| Dominant model                           | 0.73        | 0.462        | 0.70        | 0.535       |
| Recessive model                          | 1.71        | 0.086        | 1.82        | 0.166       |
Table 4 The results of Begg’s and Egger’s test for the publication bias (Continued)

| Comparison type                                      | Begg’s test | Egger’s test |
|------------------------------------------------------|-------------|--------------|
|                                                      | Z-value     | P-value       | Z-value     | P-value       |
| PRNCR1 rs7007694 (C/T)                               |             |              |             |              |
| Allelic model                                        | 0.73        | 0.462        | −1.42       | 0.251         |
| Mutation homozygote compared with wild-type          | −0.34       | 1.000        | −0.10       | 0.933         |
| Heterozygote compared with wild-type                 | 1.71        | 0.086        | −1.96       | 0.145         |
| Dominant model                                       | 1.22        | 0.221        | −1.70       | 0.188         |
| Recessive model                                      | −0.34       | 1.000        | −0.04       | 0.974         |
| PRNCR1 rs1016343 (T/C)                               |             |              |             |              |
| Allelic model                                        | 0.24        | 0.806        | −0.87       | 0.450         |
| Mutation homozygote compared with wild-type          | 0.24        | 0.806        | −0.83       | 0.467         |
| Heterozygote compared with wild-type                 | −0.24       | 1.000        | 0.25        | 0.820         |
| Dominant model                                       | −0.24       | 1.000        | −0.15       | 0.888         |
| Recessive model                                      | 0.73        | 0.462        | −1.29       | 0.288         |
| PRNCR1 rs1456315 (G/A)                               |             |              |             |              |
| Allelic model                                        | 1.22        | 0.221        | 1.74        | 0.181         |
| Mutation homozygote compared with wild-type          | −0.24       | 1.000        | 0.27        | 0.810         |
| Heterozygote compared with wild-type                 | 1.71        | 0.086        | 2.07        | 0.130         |
| Dominant model                                       | 1.71        | 0.086        | 2.10        | 0.127         |
| Recessive model                                      | −0.24       | 1.000        | 0.20        | 0.862         |

Abbreviation: NA, not available.

The MALAT1 SNPs
MALAT1 is located in chromosome 11q13, which is over 8000 nts long. It is enriched in nuclear speckles in interphase cells and concentrates in mitotic interchromatin granule clusters. And it is co-localized with pre-mRNA-splicing factor SF2/ASF and CC3 antigen in the nuclear speckles [38]. It is reported that lncRNA MALAT1 could regulate the expression through modulating transcription and the processing of post-transcriptional pre-mRNA in various genes [39]. Zhuo et al. [40] suggested that rs619586 SNP could bind with miR-214 directly and suppress the expression of MALAT1. Several studies revealed that MALAT1 has an elevated expression and was associated with a higher risk and poorer survival in many kinds of cancers [41]. Our study showed that MALAT1 rs619586 A/G polymorphism was potential predictive biomarker of overall cancer risk.

The HOTTIP SNPs
HOTTIP is an antisense non-coding transcript located at the 5’-end of the HOXA gene cluster. The previous study showed that rs1859168 might change the expression level of HOTTIP by affecting transcription factor binding sites [17]. Furthermore, RNAfold web server also revealed that rs1859168 could alter the centroid secondary structure and minimum free energy. It might also influence the folding of HOTTIP and its function [17]. Further studies are warranted to explore the specific mechanisms. Our results suggested that the HOTTIP rs1859168 A/C polymorphism was associated with increased overall risk of cancer. Although the detailed mechanisms underlying the association of SNP in HOTTIP with cancer susceptibility are unclear, these findings could provide a new insight into understanding the genetic factors of cancer susceptibility and carcinogenesis.
The HULC SNPs
The IncRNA HULC is approximately 1.6 k nucleotide long and contains two exons but not translated [42]. Some studies have reported that HULC is highly up-regulated in hepatocellular carcinoma (HCC) and colorectal cancer (CRC) that metastasized to livers [42,43]. Rs7763881 SNP changing from A to C in HULC gene was located in the 6p24.3 region. Based on the Hapmap database, all the SNPs in HULC are in high linkage disequilibrium (LD). For example, rs7763881 was in complete LD with rs1328867 ($r^2 = 1$), which is located in the promoter region of HULC. Additionally, the wild-type allele T of rs1328867 is predicted to bind with some transcription factors including C-Myc [15]. It has been identified that C-Myc is critical in the regulation of the growth, differentiation, and apoptosis of both normal and neoplastic liver cells [44]. In conclusion, HULC rs7763881 A/C polymorphism was associated with decreased overall risk of cancer.

The PRNCR1 SNPs
The IncRNA PRNCR1, also referred to as PCAT8 and CARLo3, is transcribed from the ‘gene desert’ region of chromosome 8q24 (128.14–128.28 Mb) [24]. It has been stated that PRNCR1 is involved in the development of prostate cancer by activating androgen receptor (AR) [45]. Moreover, IncRNA PRNCR1 SNPs were observed to be risk of diverse cancers [21-23]. It might affect the predicted secondary structure of PRNCR1 mRNA, altering the stability of PRNCR1 or the mRNA conformation, and giving rise to the modification of its interacting partners [24]. All the PRNCR1 polymorphisms in the exon region might result in the mechanism [28]. More specific mechanisms are warranted to be explored in further studies. Amongst the five PRNCR1 SNPs included in our study, rs16901946 G/A, rs13252298 G/A, rs1016343 T/C, and rs1456315 G/A could be predictive biomarkers of cancer risk.

Limitations
Although this meta-analysis revealed the significant association between IncRNA polymorphisms and cancer risk, however, some limitations still should be acknowledged. First, the number of subjects in the included studies is relatively small, which might result in a lack of statistical power and prevent a meaningful analysis of the results. Second, in stratified analyses based on ethnicity and cancer type, we failed to perform further subgroup analysis because of limited relevant reports. Third, only English articles were included in our study and it may result in publication bias. Finally, study of the association between IncRNA polymorphisms and cancer risk remains an emerging field, we concluded only representative SNPs in our study. Therefore, additional prospective studies with larger sample sizes including other polymorphisms are warranted.

Summary and future directions
We systematically reviewed studies on the association between IncRNA SNPs and overall cancer risk, and used the available data to perform a meta-analysis of 19 SNPs in five common IncRNA genes. The results suggest that the association between IncRNA SNPs and cancer risk can be categorized into four types: (i) complete association, where polymorphisms are significantly associated with risk of overall cancer in all genetic models, including ANRIL rs1333048, HOTTIP rs1859168, PRNCR1 rs16901946, PRNCR1 rs1016343, and PRNCR1 rs1456315; (ii) ANRIL rs4977574, ANRIL rs10757278, MALAT1 rs619586, HULC rs7763881, and PRNCR1 rs13252298 polymorphisms are only associated with cancer risk in some genetic models; (iii) no association, where the association of polymorphisms with cancer risk are not statistically significant, including ANRIL rs1333045 and PRNCR1 rs7007694; (iv) failed to be quantitatively synthesized due to limited studies. Therefore, the IncRNA SNPs provide more alternatives for biomarkers that can predict cancer risk.

More attention should be paid to several research directions in the future studies. First, more IncRNA polymorphisms and other aspects of cancer including chemotherapeutic susceptibility, metastasis, and relapse should be explored. Second, functional studies are needed to clarify the underlying mechanisms of IncRNA polymorphism in the tumorigenesis. Finally, the extensive clinical application of IncRNA polymorphisms requires further study.

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Competing interests
The authors declare that there are no competing interests associated with the manuscript.
Author contribution
Z.S. and X.H. conceived and designed the study. X.H. and W.Z. performed data collection and management. X.H. performed data analysis. Z.S. and X.H. wrote the paper. All the authors reviewed the manuscript.

Abbreviations
ANRIL, antisense non-coding RNA in the INK4 locus; CRS, created restriction site; HOTTIP, HOXA distal transcript antisense RNA; HULC, highly up-regulated in liver cancer; HWE, Hardy–Weinberg equilibrium; LD, linkage disequilibrium; IncRNA, long non-coding RNA; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; ncRNA, non-coding RNA; NOS, Newcastle–Ottawa scale; OR, odds ratio; PRNCR1, prostate cancer-associated non-coding RNA 1; RFLP, restriction fragment length polymorphism; SNP, single-nucleotide polymorphism; T-ARMS, tetra-primer amplification refractory mutation system; 95% CI, 95% confidence interval.

Appendix A: supplementary data
Supplementary data associated with this article can be found, in the online version.
Supplementary Table S1. Quality assessment of eligible studies NOS.
Supplementary Table S2. The results of ORs and 95% CI of sensitivity analysis.

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