Research Article

miR-146a C/G polymorphism increased the risk of head and neck cancer, but overall cancer risk: an analysis of 89 studies

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Several studies have evaluated the association of miR-146a C/G with head and neck cancer (HNC) susceptibility, and overall cancer risk, but with inconclusive outcomes. To drive a more precise estimation, we carried out this meta-analysis. The literature was searched from MEDLINE (mainly PubMed), Embase, the Cochrane Library, and Google Scholar databases to identify eligible studies. A total of 89 studies were included. The results showed that miR-146a C/G was significantly associated with increased HNC risk in dominant model ($I^2=15.6\%$, $P_{\text{heterogeneity}}=0.282$, odds ratio (OR) $=1.088$, 95% confidence interval (CI) $=1.002$–$1.182$, $P=0.044$). However, no cancer risk was detected under all genetic models. By further stratified analysis, we found that rs4919510 mutation contributed to the risk of HNC amongst Asians under homozygote model ($I^2=0$, $P_{\text{heterogeneity}}=0.541$, OR $=1.189$, 95% CI $=1.025$–$1.378$, $P=0.022$), and dominant model ($I^2=0$, $P_{\text{heterogeneity}}=0.959$, OR $=1.155$, 95% CI $=1.016$–$1.312$, $P=0.028$). Simultaneously, in the stratified analysis by source of controls, a significantly increased cancer risk amongst population-based studies was found under homozygote model, dominant model, recessive model, and allele comparison model. However, no significant association was found in the stratified analysis by ethnicity and source of control. The results indicated that miR-146a C/G polymorphism may contribute to the increased HNC susceptibility and could be a promising target to forecast cancer risk for clinical practice. However, no significant association was found in subgroup analysis by ethnicity and source of control. To further confirm these results, well-designed large-scale case–control studies are needed in the future.

Introduction

Cancer, although an age old disease, still poses a formidable challenge to researchers and clinicians. Little is known about its initiation, sustenance, progression and metastasis, and resistance and remission. Due to its morbidity and mortality, cancer is one of the most dreaded diseases and the related fatalities are majorly attributed to delayed diagnosis and treatment. Head and neck cancer (HNC), the sixth most frequent kind of cancer worldwide, is a group of biologically similar cancers that originate from head and neck regions such as oral cavity, pharyngeal cavity, and larynx [1]. Multifactors such as smoking, drinking, betel quid chewing, papilloma virus infection, and exposure to toxic substances are suggested to be the etiological risk factors for HNC [2,3]. Nevertheless, though many individuals are exposed to these external factors, HNC develops only in a small proportion of the exposed people, indicating that intrinsic factors such as genetic polymorphism might play critical roles in its carcinogenic mechanisms.
miRNAs represent a class of evolutionarily conserved, endogenous, single-stranded, non-coding RNA molecules of ~20 nts that regulate gene expression by degrading mRNAs or suppressing translation. miRNAs have been implicated in a wide range of physiologic and pathologic processes, including development, cell differentiation, proliferation, apoptosis, and carcinogenesis [4,5]. Accumulating evidence indicates that the expression of roughly 10–30% of all human genes is regulated by miRNAs [6]. More than half of the known miRNAs are located in cancer-associated genomic regions, and miRNAs are thought to contribute to oncogenesis because they can function either as tumor suppressors or oncogenes [7]. Analyses in human epithelial malignancies have shown that cancers can be distinguished and classified by distinct tumor-specific miRNA signatures [8]. Some of the key dysregulated miRNAs could serve as molecular biomarkers, leading to improved diagnosis and monitoring of cancer treatment response [9–11].

Single nucleotide polymorphisms (SNPs) are a type of common genetic variations associated with population diversity, disease susceptibility, drug metabolism, and genome evolution [12]. SNPs may affect the expression and function of miRNAs, which could therefore contribute to the susceptibility to cancer occurrence and development [13–16]. miR-146a C/G is located in the stem region opposite to the mature miR-146a sequence, which is suspected to have an effect on tumor immune responses and ultimately the development of cancer. In recent years, the polymorphism rs2910164 in miR-146a has attracted wide attention and many studies have been published to explore the association between SNPs of miRNAs and susceptibility to various cancers. But the results were not conclusive and consistent. Since SNPs in miRNAs are closely associated with head and neck cancer (HNC) susceptibility, it is necessary to assess whether these SNP polymorphisms are the risk factors for HNC. It is reported that meta-analysis is a well-established method for combining all the results from the available published information to produce a single estimate for quantitating gene–disease associations more precisely to increase the statistical power [17]. Thus, we performed this meta-analysis of case–control studies to estimate the importance of pre-miR-146a C/G polymorphism for HNC susceptibility.

Materials and methods
Publication search
A comprehensive electronic search was performed to identify articles published up until 12 November 2016 in MEDLINE (mainly PubMed), Embase, the Cochrane Library, and Google Scholar using the following search terms: ‘miR-146a’ or ‘rs2910164’ and ‘head and neck cancer’ or ‘cancer’ or ‘tumor’ or ‘carcinoma’ and ‘polymorphism’ or ‘SNPs’ or ‘variation’. All eligible studies published in English were retrieved, and their bibliographies were checked for additional relevant publications. Review articles and bibliographies of other identified relevant studies were searched by hand to identify any additional eligible studies.

Inclusion and exclusion criteria
Studies included in this meta-analysis had to meet all of the following criteria: (i) case–control study evaluating the association between miR-146a C/G polymorphism and susceptibility to HNC and overall cancer; (ii) sufficient published data for calculating odds ratios (ORs) with corresponding 95% confidence intervals (CIs); (iii) full-text manuscript; and (iv) only the most recent or complete study reporting on the same population of patients was included. Exclusion criteria included: (i) reviews, other meta-analyses, comments, letters, and editorial articles; (ii) not a case–control study; and (iii) no usable data reported.

Data extraction
Information regarding the following aspects was independently retrieved from each study by two reviewers: the first author’s surname, year of publication, country of origin, ethnicity, study design, total number of cases and controls, source of cases and controls, detected sample, genotyping methods, allele and genotype frequencies of cases and controls, and evidence of Hardy–Weinberg equilibrium (HWE) in the controls. In studies including subjects of more than one ethnicity, genotype data were extracted separately for each ethnic group. Data from one publication may contain more than one separate case-control studies. Any discrepancies between the reviewers were resolved through discussion to reach a consensus.

Statistical analysis
We used crude ORs with 95% CIs to explore the association between miR-146a C/G polymorphism and the risk of HNC and overall cancer. Five genetic variation models were analyzed: homozygote model (CC compared with GG), heterogeneity model (GC compared with CC), dominant model (CC + GC compared with GG), recessive model (CC compared with GC + GG), and allele comparison model (C compared with G). P-value of HWE in control
Figure 1. The process of literature research

Results
Characteristics of eligible studies
A total of 721 articles were retrieved after the first search in PubMed, Embase, the Cochrane Library, and Google Scholar. Selection following the specified criteria eliminated 632 studies, leaving 89 individual studies [24-103]. The details of the selection process are presented in Figure 1. The publication years of included articles ranged from 2008 to 2016. The distributions of miR-146a C/G genotype in all studies were in accordance with HWE in the control group. No significant differences were found between cases and controls with respect to gender and age distributions. The modified quality scores of all studies ranged from 9 to 16, with 71% (5/7) of the included studies classified as high quality (≥12). The characteristics of all included studies are summarized in Table 1.

miR-146a C/G polymorphism and HNC risk
In the overall analysis, we pooled 13 separate studies to explore the association between miR-146a C/G polymorphism and the risk of HNC under homozygote, heterozygote, recessive, and allele comparison model. There is no significant association between miR-146a C/G polymorphism and the risk of HNC under homozygote model ($I^2 = 21.6\%$, $P_{\text{heterogeneity}} = 0.226$, OR = 1.113, 95% CI = 0.980–1.263, $P = 0.099$, Figure 2), heterozygote model ($I^2$
Table 1 Characteristics of all eligible studies

| Reference          | Year | Country      | Ethnicity | Cancer type       | Control source | Genotyping method | Sample size | Case | Control |
|--------------------|------|--------------|-----------|-------------------|----------------|-------------------|-------------|------|---------|
|                     |      |              |           |                   |                |                   |             | Cases | Controls |
|                     |      |              |           |                   |                |                   |             | GG   | GC      | CC |
| Horikawa et al. [24]| 2008 | U.S.A.       | Caucasian | Renal cell cancer | PB             | SNPlex assay      | 261         | 235  | 144     | 103 | 14     | 126 | 94  | 15 
| Jazdzewski et al. [25] | 2008 | Finland      | Caucasian | Renal cell cancer | PB             | SNPlex assay      | 206         | 274  | 99      | 104 | 3      | 150 | 105 | 19 
| Jazdzewski et al. [25] | 2008 | Poland       | Caucasian | Renal cell cancer | PB             | SNPlex assay      | 201         | 475  | 115     | 82  | 4      | 286 | 163 | 26 
| Jazdzewski et al. [25] | 2008 | U.S.A.       | Caucasian | Renal cell cancer | PB             | SNPlex assay      | 201         | 152  | 91      | 101 | 9      | 90  | 52  | 10 
| Xu et al. [26]     | 2008 | China        | Asian     | Liver cancer      | HB             | PCR-RFLP          | 479         | 504  | 80      | 241 | 158    | 58  | 249 | 197 |
| Yang et al. [27]   | 2008 | U.S.A.       | Caucasian | Bladder cancer    | PB             | SNPlex assay      | 691         | 674  | 414     | 296 | 59     | 385 | 258 | 31  
| Hoffman et al. [28] | 2009 | U.S.A.       | Caucasian | Breast cancer     | PB             | massARRAY        | 439         | 478  | 234     | 176 | 29     | 273 | 178 | 27  
| Hu et al. [29]     | 2009 | China        | Asian     | Breast cancer     | HB             | PCR-RFLP          | 1009        | 1093 | 165     | 515 | 329    | 180 | 551 | 362 |
| Tian et al. [30]   | 2009 | China        | Asian     | Lung cancer       | PB             | PCR-RFLP          | 1058        | 1035 | 360     | 510 | 188    | 364 | 502 | 169 |
| Catucci et al. [31] | 2010 | Italy        | Caucasian | Breast cancer     | HB             | Sequencing        | 754         | 1243 | 409     | 296 | 59     | 385 | 258 | 31  |
| Catucci et al. [31] | 2010 | Germany      | Caucasian | Breast cancer     | HB             | Sequencing        | 805         | 904  | 451     | 304 | 50     | 536 | 318 | 50  |
| Guo et al. [32]    | 2010 | China        | Caucasian | ESCC              | PB             | SNaPshot          | 444         | 468  | 234     | 190 | 20     | 206 | 220 | 42  |
| Liu et al. [33]    | 2010 | U.S.A.       | Mixed     | SCCHN             | HB             | PCR-RFLP          | 1109        | 1130 | 630     | 411 | 68     | 655 | 405 | 70  |
| Okubo et al. [34]  | 2010 | Japan        | Asian     | Gastric cancer    | PB             | PCR-RFLP          | 552         | 697  | 73      | 243 | 236    | 121 | 322 | 254 |
| Pastrello et al. [35] | 2010 | Italy        | Caucasian | Breast and ovarian cancer | PB | Sequencing | 101 | 155 | 60 | 36 | 5 | 90 | 59 | 6 |
| Srivastava et al. [36] | 2010 | India        | Asian     | Gall bladder cancer | PB            | PCR-RFLP          | 230         | 224  | 129     | 90  | 11     | 138 | 81  | 5   |
| Xu et al. [37]     | 2010 | China        | Asian     | Prostate cancer   | HB             | PCR-RFLP          | 251         | 280  | 68      | 135 | 48     | 54  | 150 | 76  |
| Zeng et al. [38]   | 2010 | China        | Asian     | Gastric cancer    | HB             | PCR-RFLP          | 304         | 304  | 62      | 153 | 89     | 53  | 132 | 119 |
| Akkiz et al. [39]  | 2011 | Turkey       | Caucasian | Liver cancer      | HB             | PCR-RFLP          | 222         | 222  | 137     | 75  | 10     | 144 | 67  | 11  |
| Garcia et al. [40] | 2011 | French       | Caucasian | Breast cancer     | PB             | TaqMan            | 1130        | 596  | 676     | 388 | 66     | 352 | 220 | 24  |
| George et al. [41] | 2011 | India        | Asian     | Prostate cancer   | PB             | PCR-RFLP          | 159         | 230  | 4       | 79  | 7      | 7   | 107 | 116 |
| Hishida et al. [42] | 2011 | Japan        | Asian     | Gastric cancer    | HB             | PCR-RFLP          | 583         | 1637 | 82      | 271 | 230    | 229 | 775 | 633 |
| Mittal et al. [43] | 2011 | India        | Asian     | Bladder cancer    | PB             | PCR-RFLP          | 212         | 250  | 127     | 79  | 6      | 135 | 108 | 7   |
| Permutti-Wey et al. [44] | 2011 | U.S.A.       | Caucasian | Glioma            | PB             | GoldenGate        | 593         | 614  | 345     | 198 | 50     | 375 | 214 | 25  |
| Vinci et al. [45]  | 2011 | Italy        | Caucasian | NSCLC             | PB             | HRMA              | 101         | 129  | 44      | 48  | 9      | 73  | 45  | 11  |
| Yue et al. [46]    | 2011 | China        | Asian     | Cervical cancer   | HB             | PCR-RFLP          | 447         | 443  | 118     | 224 | 105    | 87  | 206 | 150 |
| Zhang et al. [47]  | 2011 | China        | Asian     | Liver cancer      | HB             | PIRA-PCR          | 925         | 1593 | 156     | 450 | 319    | 291 | 725 | 577 |
| Zhou et al. [48]   | 2011 | China        | Asian     | CSCC              | HB             | PCR-RFLP          | 226         | 309  | 43      | 113 | 70     | 34  | 159 | 116 |
| Ma et al. [49]     | 2012 | China        | Asian     | Gastric cancer    | HB             | Sequencing        | 86          | 42   | 20      | 44  | 14     | 6   | 19  | 14  |
| Alishahi et al. [50] | 2012 | Saudi        | Asian     | Breast cancer     | PB             | TaqMan            | 100         | 100  | 2       | 50  | 48     | 3   | 46  | 51  |
| Chu et al. [51]    | 2012 | China        | Asian     | Oral cancer       | HB             | PCR-RFLP          | 470         | 425  | 54      | 242 | 174    | 54  | 196 | 175 |
| Hezova et al. [52] | 2012 | Czech        | Caucasian | Colorectal        | HB             | TaqMan            | 197         | 212  | 115     | 70  | 12     | 124 | 79  | 9   |
| Kim et al. [53]    | 2012 | Korea        | Asian     | Liver cancer      | PB             | PCR-RFLP          | 286         | 201  | 27      | 159 | 100    | 24  | 103 | 74  |
| Lung et al. [54]   | 2012 | China        | Asian     | Nasopharyngeal carcinoma | PB | Trm-shift | 229 | 3631 | 24 | 88 | 117 | 497 | 172 | 1413 |

Continued over
### Table 1 Characteristics of all eligible studies (Continued)

| Reference        | Year  | Country                  | Ethnicity | Cancer type       | Control Genotyping method | Sample size | Case | Control |
|------------------|-------|--------------------------|-----------|------------------|----------------------------|-------------|------|---------|
|                   |       |                          |           |                  |                             | Cases       | Controls | GG | GC | CC | GG | GC | CC |
| Mihalache et al. [55] | 2012  | Italy and Germany       | Caucasian | Cholangiocarcinoma | HB TaqMan                   | 182         | 350   | 118 | 53 | 11 | 211 | 122 | 17 |
| Min et al. [56]    | 2012  | Korea                    | Asian     | Colorectal        | HB PCR-RFLP                 | 446         | 502   | 62  | 233 | 151 | 69  | 245 | 188 |
| Wang et al. [57]   | 2012  | China                    | Asian     | Bladder cancer    | HB TaqMan                   | 1017        | 1179  | 369 | 456 | 192 | 340 | 571 | 268 |
| Xiang et al. [58]  | 2012  | China                    | Asian     | Liver cancer      | HB PCR-RFLP                 | 100         | 200   | 27  | 45  | 28  | 45  | 100 | 55  |
| Zhou et al. [59]   | 2012  | China                    | Asian     | Liver cancer      | PB PCR-RFLP                 | 186         | 483   | 33  | 86  | 67  | 71  | 254 | 158 |
| Zhou et al. [60]   | 2012  | China                    | Asian     | Gastric cancer    | HB TaqMan                   | 1686        | 1895  | 578 | 822 | 151 | 69  | 245 | 188 |
| Lv et al. [61]     | 2013  | China                    | Asian     | Colorectal cancer | PB PCR-RFLP                 | 353         | 540   | 54  | 230 | 47  | 96  | 274 | 143 |
| Chae et al. [62]   | 2013  | Korea                    | Asian     | Colorectal cancer | PB PCR-RFLP                 | 399         | 568   | 61  | 182 | 156 | 121 | 282 | 165 |
| Ma et al. [63]     | 2013  | China                    | Asian     | TNBC             | HB massARRAY                | 192         | 191   | 35  | 94  | 63  | 34  | 93  | 64  |
| Ma et al. [64]     | 2013  | China                    | Asian     | Colorectal cancer | HB TaqMan                   | 1147        | 1203  | 444 | 534 | 192 | 397 | 614 | 192 |
| Orsos et al. [65]  | 2013  | Hungary                  | Caucasian | SCCHN            | PB PCR-RFLP                 | 468         | 468   | 284 | 168 | 16  | 323 | 136 | 9   |
| Vinci et al. [66]  | 2013  | Italy                    | Caucasian | Colorectal cancer | PB HRMA                     | 160         | 178   | 86  | 57  | 17  | 100 | 65  | 13  |
| Wei et al. [67]    | 2013  | China                    | Asian     | PTC              | PB massARRAY                | 753         | 760   | 136 | 323 | 294 | 138 | 345 | 277 |
| Wei et al. [68]    | 2013  | China                    | Asian     | ESCOC            | HB massARRAY                | 368         | 370   | 67  | 184 | 117 | 67  | 181 | 122 |
| Yamashita et al. [69] | 2013 | Japan                    | Asian     | Melanoma         | PB PCR-RFLP                 | 50          | 107   | 0   | 35  | 16  | 3   | 53  | 51  |
| Zhang et al. [70]  | 2013  | China                    | Asian     | HCC             | PB MassARRAY                | 977         | 997   | 163 | 503 | 331 | 156 | 475 | 367 |
| Ahn et al. [71]    | 2013  | Korea                    | Asian     | Gastric cancer   | HB PCR-RFLP                 | 461         | 447   | 71  | 231 | 159 | 62  | 221 | 164 |
| Song et al. [72]   | 2013  | Korea                    | Asian     | Gastric cancer   | HB PCR-RFLP                 | 1208        | 1166  | 199 | 586 | 423 | 207 | 615 | 344 |
| Wu [73]           | 2014  | China                    | Asian     | Colorectal cancer | HB ASA                      | 175         | 300   | 22  | 59  | 80  | 53  | 120 | 114 |
| Chu et al. [74]    | 2014  | China                    | Asian     | HCC             | HB PCR-RFLP                 | 188         | 337   | 22  | 82  | 84  | 50  | 145 | 141 |
| Cong et al. [75]   | 2014  | China                    | Asian     | HCC             | HB PCR-RFLP                 | 206         | 218   | 27  | 85  | 94  | 17  | 84  | 117 |
| Dikeakos et al. [76] | 2014 | Greece                   | Caucasian | Gastric cancer   | HB PCR-RFLP                 | 163         | 480   | 13  | 45  | 105 | 24  | 149 | 307 |
| Du et al. [77]     | 2014  | China                    | Asian     | Renal            | HB TaqMan assay             | 353         | 362   | 68  | 167 | 118 | 57  | 190 | 115 |
| Hu et al. [78]     | 2014  | China                    | Asian     | Colorectal       | HB PCR-RFLP                 | 200         | 373   | 34  | 82  | 84  | 44  | 187 | 142 |
| Huang et al. [79]  | 2014  | China                    | Asian     | Nasopharyngeal   | HB PCR-RFLP                 | 160         | 200   | 23  | 73  | 64  | 36  | 110 | 54  |
| Jeon et al. [80]   | 2014  | Korea                    | Asian     | Lung            | PB PCR-RFLP                 | 1091        | 1096  | 223 | 500 | 368 | 244 | 540 | 312 |
| Jia et al. [81]    | 2014  | China                    | Asian     | NSCLC           | HB PCR-RFLP                 | 400         | 400   | 64  | 182 | 154 | 76  | 200 | 124 |
| Kupcinskas et al. [82] | 2014 | Germany, Lithuania, Latvia | Caucasian | Gastric cancer | HB TaqMan assay             | 362         | 347   | 252 | 94  | 16  | 223 | 108 | 16  |
| Kupcinskas et al. [83] | 2014 | Lithuania, Latvia       | Caucasian | Colorectal      | HB TaqMan assay             | 192         | 424   | 140 | 50  | 2   | 275 | 134 | 15  |
| Mao et al. [84]    | 2014  | China                    | Asian     | Colorectal       | PB SNPscan system           | 547         | 561   | 70  | 291 | 186 | 85  | 271 | 205 |
| Nikolic et al. [85] | 2014 | Serbia                   | Caucasian | Prostate        | HB TaqMan assay             | 286         | 199   | 184 | 90  | 12  | 129 | 63  | 7   |
| Palmieri et al. [86] | 2014 | Italy                    | Caucasian | OSCC            | HB TaqMan assay             | 337         | 88    | 197 | 121 | 19  | 50  | 31  | 7   |
| Palmieri et al. [86] | 2014 | Italy                    | Caucasian | OSCC            | HB TaqMan assay             | 337         | 206   | 197 | 121 | 19  | 105 | 84  | 17  |
| Palmieri et al. [86] | 2014 | Italy                    | Caucasian | OSCC            | HB TaqMan assay             | 337         | 543   | 197 | 121 | 19  | 297 | 206 | 40  |

Continued over
Table 1 Characteristics of all eligible studies (Continued)

| Reference            | Year | Country | Ethnicity | Cancer type | Control source | Genotyping method | Sample size | Case | Control |
|----------------------|------|---------|-----------|-------------|----------------|-------------------|-------------|------|---------|
| Chen et al.1 [103]   | 2016 | Taiwan  | Asian     | OSCC        | HB             | TaqMan assay      | 512         | 668  | 71      |
| Chen et al.2 [103]   | 2016 | Taiwan  | Asian     | PSCC        | HB             | TaqMan assay      | 146         | 668  | 16      |
| Chen et al.3 [103]   | 2016 | Taiwan  | Asian     | OPSCC       | HB             | TaqMan assay      | 658         | 668  | 87      |
| Li et al. [95]       | 2015 | China   | Asian     | HCC         | HB             | PCR-RFLP          | 266         | 266  | 151     |
| Shen et al. [96]     | 2015 | China   | Asian     | HCC         | HB             | SNaPshot multiplex assay | 1400     | 2185 | 220     |
| Yan et al. [97]      | 2015 | China   | Asian     | HCC         | HB             | PCR-RFLP          | 274         | 328  | 35      |
| Yin et al. [98]      | 2015 | China   | Asian     | Lung cancer | HB             | PCR-RFLP          | 575         | 608  | 97      |
| Xia et al. [96]      | 2015 | China   | Asian     | Gastric cancer | HB             | TaqMan assay      | 1125        | 1196 | 192     |
| Hashemi et al. [100] | 2016 | Iran    | Caucasian | Prostate cancer | HB             | T-ARMS-PCR assay | 169         | 182  | 25      |
| Jiang et al. [101]   | 2016 | China   | Asian     | Gastric cancer | HB             | MassARRAY         | 898         | 992  | 154     |
| Miao et al. [102]    | 2016 | China   | Asian     | HNSCC       | HB             | Illumina Infinum1 human exome BeadChip | 576       | 1552 | 497     |
| Parlayan et al.1 [87]| 2014 | Japan   | Asian     | Gastric     | HB             | TaqMan assay      | 160         | 524  | 20      |
| Parlayan et al.2 [87]| 2014 | Japan   | Asian     | Lung        | HB             | TaqMan assay      | 148         | 524  | 25      |
| Parlayan et al.3 [87]| 2014 | Japan   | Asian     | Prostate    | HB             | TaqMan assay      | 89          | 524  | 11      |
| Pu et al. [88]       | 2014 | China   | Asian     | Gastric     | HB             | PCR-RFLP          | 197         | 513  | 36      |
| Qu et al. [89]       | 2014 | China   | Asian     | ESCC        | HB             | Allele-specific PCR | 381       | 426  | 62      |
| Dikaiakos et al. [90]| 2015 | Greece  | Caucasian | Colorectal  | HB             | TaqMan assay      | 157         | 299  | 8       |
| Gomez-Lira et al. [91]| 2015 | Italy   | Caucasian | Melanoma    | HB             | PCR-RFLP          | 224         | 264  | 107     |
| Qu et al. [92]       | 2015 | China   | Asian     | Breast cancer | PB             | PCR-RFLP          | 321         | 290  | 146     |
| Zhu et al. [83]      | 2015 | China   | Asian     | ESCC        | HB             | PCR-RFLP          | 248         | 300  | 82      |
| Deng et al. [94]     | 2015 | China   | Asian     | Bladder cancer | HB             | PCR-RFLP          | 159         | 258  | 26      |
| Wang et al. [87]     | 2014 | China   | Asian     | Lung cancer | HB             | PCR-RFLP          | 148         | 668  | 71      |
| Qu et al. [93]       | 2014 | China   | Asian     | ESCC        | HB             | All-in-One PCR     | 381         | 426  | 62      |
| Yan et al. [97]      | 2014 | Japan   | Asian     | Prostate    | HB             | TaqMan assay      | 89          | 524  | 11      |
| Yin et al. [98]      | 2014 | Japan   | Asian     | Lung cancer | HB             | PCR-RFLP          | 197         | 513  | 36      |
| Xia et al. [96]      | 2014 | Japan   | Asian     | Gastric cancer | HB             | TaqMan assay      | 89          | 524  | 11      |
| Hashemi et al. [100] | 2016 | Iran    | Caucasian | Prostate cancer | HB             | T-ARMS-PCR assay | 169         | 182  | 25      |
| Jiang et al. [101]   | 2016 | China   | Asian     | Gastric cancer | HB             | MassARRAY         | 898         | 992  | 154     |
| Miao et al. [102]    | 2016 | China   | Asian     | HNSCC       | HB             | Illumina Infinum1 human exome BeadChip | 576       | 1552 | 497     |

| Abbreviations: BC, breast cancer; CRC, colorectal cancer; GC, gastric cancer; HCC, hepatocellular carcinoma; HNSCC, squamous cell carcinoma of the head and neck; HRMA, high resolution melting analysis; LC, lung cancer; NSCLC, non-small-cell lung carcinoma; OPSCC, squamous cell carcinoma of the oral cavity, oropharynx, and hypopharynx; OSCC, oral squamous cell carcinoma; PB, population-based; $P_{\text{heterogeneity}}$, $P$-value of HWE; $P_{\text{homozygous}}$, recessive model ($I^2 = 66.3\%$, $P_{\text{heterogeneity}}<0.01$, OR = 1.068, 95% CI = 0.896–1.272, $P=0.465$); $P_{\text{heterogeneity}}$, $P$-value of HWE; $P_{\text{homozygous}}$, dominant model ($I^2 = 15.6\%$, $P_{\text{heterogeneity}}=0.282$, OR = 1.088, 95% CI = 1.002–1.182, $P=0.044$); $P_{\text{heterogeneity}}$, $P$-value of HWE; $P_{\text{homozygous}}$, heterozygous model ($I^2 = 36.7\%$, $P_{\text{heterogeneity}}=0.177$, OR = 0.919, 95% CI = 0.716–1.180, $P=0.509$). |
Figure 2. Forest plot of the association between miR-146a rs2910164 polymorphism and HNC risk (under homozygote model)

![Figure 2. Forest plot of the association between miR-146a rs2910164 polymorphism and HNC risk (under homozygote model)](image)

| Study ID | OR (95% CI) | Weight |
|----------|-------------|--------|
| Liu et al. [24] | 1.01 (0.71, 1.43) | 13.63 |
| Chu et al.a [25] | 0.99 (0.65, 1.53) | 9.10 |
| Lung et al.b [26] | 1.49 (0.75, 2.96) | 2.86 |
| Lung et al.c [26] | 1.65 (1.05, 2.60) | 7.34 |
| Orsos et al. [27] | 2.02 (0.86, 4.68) | 1.78 |
| Huang et al. [29] | 1.86 (0.98, 3.51) | 3.09 |
| Palmieri et al.a [30] | 0.69 (0.27, 1.73) | 2.22 |
| Palmieri et al.b [30] | 0.60 (0.30, 1.19) | 4.36 |
| Palmieri et al.c [30] | 0.72 (0.40, 1.27) | 6.27 |
| Miao et al. [31] | 1.08 (0.79, 1.46) | 17.34 |
| Chen et al.a [32] | 1.07 (0.75, 1.52) | 13.15 |
| Chen et al.b [32] | 1.25 (0.69, 2.29) | 4.31 |
| Chen et al.c [32] | 1.10 (0.79, 1.54) | 14.56 |
| Overall (I-squared = 21.6%, P = 0.228) | 1.11 (0.98, 1.26) | 100.00 |

Figure 3. Forest plot of the association between miR-146a rs2910164 polymorphism and HNC risk (under heterozygote model)

![Figure 3. Forest plot of the association between miR-146a rs2910164 polymorphism and HNC risk (under heterozygote model)](image)

| Study ID | OR (95% CI) | Weight |
|----------|-------------|--------|
| Liu et al. [24] | 1.06 (0.89, 1.26) | 26.52 |
| Chu et al.a [25] | 1.23 (0.81, 1.88) | 4.23 |
| Lung et al.b [26] | 0.77 (0.39, 1.51) | 2.09 |
| Lung et al.c [26] | 1.02 (0.64, 1.62) | 3.90 |
| Orsos et al. [27] | 1.40 (1.07, 1.85) | 9.26 |
| Huang et al. [29] | 1.04 (0.57, 1.89) | 2.28 |
| Palmieri et al.a [30] | 0.99 (0.60, 1.64) | 3.34 |
| Palmieri et al.b [30] | 0.77 (0.53, 1.11) | 7.13 |
| Palmieri et al.c [30] | 0.89 (0.66, 1.38) | 10.80 |
| Miao et al. [31] | 1.05 (0.63, 1.73) | 14.98 |
| Chen et al.a [32] | 1.19 (0.64, 1.96) | 6.42 |
| Chen et al.b [32] | 1.69 (0.94, 3.03) | 2.09 |
| Chen et al.c [32] | 1.28 (0.93, 1.78) | 6.95 |
| Overall (I-squared = 14.2%, P = 0.301) | 1.08 (0.99, 1.19) | 100.00 |
**Figure 4.** Forest plot of the association between miR-146a rs2910164 polymorphism and HNC risk (under recessive model)

**Figure 5.** Forest plot of the association between miR-146a rs2910164 polymorphism and HNC risk (under allele comparison model)
Figure 6. Forest plot of the association between miR-146a rs2910164 polymorphism and HNC risk (under dominant model)

gote model ($I^2 = 52.7\%, P_{\text{heterogeneity}} = 0.076$, OR = 1.040, 95% CI = 0.922–1.173, $P = 0.521$, Table 2), dominant model ($I^2 = 58.6\%, P_{\text{heterogeneity}} = 0.034$, OR = 1.027, 95% CI = 0.857–1.232, $P = 0.772$, Table 2), recessive model ($I^2 = 10.9\%, P_{\text{heterogeneity}} = 0.344$, OR = 0.919, 95% CI = 0.719–1.174, $P = 0.449$, Table 2), and allele comparison model ($I^2 = 69\%, P_{\text{heterogeneity}} = 0.012$, OR = 0.981, 95% CI = 0.814–1.183, $P = 0.843$, Table 2). Simultaneously, no associations were detected amongst Asians under heterozygote model ($I^2 = 0$, $P_{\text{heterogeneity}} = 0.713$, OR = 1.142, 95% CI = 0.997–1.308, $P = 0.054$, Table 2), recessive model ($I^2 = 76.5\%, P_{\text{heterogeneity}} < 0.01$, OR = 1.133, 95% CI = 0.914–1.404, $P = 0.254$, Table 2), and allele comparison model ($I^2 = 57.6\%, P_{\text{heterogeneity}} = 0.021$, OR = 1.103, 95% CI = 0.988–1.233, $P = 0.082$, Table 2), while slight association was found amongst Asians under homozygote model ($I^2 = 0$, $P_{\text{heterogeneity}} = 0.541$, OR = 1.189, 95% CI = 1.025–1.378, $P = 0.022$, Table 2) and dominant model ($I^2 = 0$, $P_{\text{heterogeneity}} = 0.959$, OR = 1.155, 95% CI = 1.016–1.312, $P = 0.028$, Table 2). In the stratified analysis by source of controls, a significantly increased cancer risk amongst population-based studies was found under homozygote model ($I^2 = 0$, $P_{\text{heterogeneity}} = 0.855$, OR = 1.668, 95% CI = 1.183–2.352, $P = 0.004$, Table 2), dominant model ($I^2 = 0$, $P_{\text{heterogeneity}} = 0.674$, OR = 1.359, 95% CI = 1.095–1.687, $P = 0.005$, Table 2), recessive model ($I^2 = 0$, $P_{\text{heterogeneity}} = 0.874$, OR = 1.697, 95% CI = 1.367–2.107, $P < 0.001$, Table 2), and allele comparison model ($I^2 = 0$, $P_{\text{heterogeneity}} = 0.991$, OR = 1.394, 95% CI = 1.215–1.599, $P < 0.001$, Table 2), while no association was found amongst population-based studies under heterozygote model ($I^2 = 3.5\%$, $P_{\text{heterogeneity}} = 0.408$, OR = 1.219, 95% CI = 0.974–1.526, $P = 0.083$, Table 2). Meanwhile, no significant association was found amongst hospital-based studies under homozygote model ($I^2 = 0$, $P_{\text{heterogeneity}} = 0.471$, OR = 1.113, 95% CI = 0.980–1.263, $P = 0.603$, Table 2), heterozygote model ($I^2 = 40.5\%$, $P_{\text{heterogeneity}} = 0.186$, OR = 1.060, 95% CI = 0.961–1.169, $P = 0.248$, Table 2), dominant model ($I^2 = 0$, $P_{\text{heterogeneity}} = 0.462$, OR = 1.047, 95% CI = 0.957–1.144, $P = 0.318$, Table 2), recessive model ($I^2 = 26\%$, $P_{\text{heterogeneity}} = 0.204$, OR = 0.941, 95% CI = 0.849–1.043, $P = 0.247$, Table 2), and allele comparison model ($I^2 = 19.8\%$, $P_{\text{heterogeneity}} = 0.261$, OR = 0.994, 95% CI = 0.935–1.056, $P = 0.837$, Table 2). Results of the meta-analyses are presented in Table 2.
Table 2: Meta-analysis on the association between miR-146a rs2910164 polymorphism and HNC risk

| Variables          | Study number | Statistic model | Test of heterogeneity | Test of association | Publication bias |
|--------------------|--------------|-----------------|-----------------------|---------------------|-----------------|
|                    |              |                 | $P$  | $I^2$ | OR (95% CI) | $P$   | $P_{\text{Begg's}}$ | $P_{\text{Egger's}}$ |
| Homozygote model   |              |                 |                 |                     |                 |       |                     |                     |
| Total              | 13           | Fixed           | 0.226 | 21.6 | 1.113 (0.980–1.263) | 0.099 | 1.000 | 0.793 |
| Ethnicity          |              |                 |                 |                     |                 |       |                     |                     |
| Caucasian          | 5            | Fixed           | 0.177 | 36.7 | 0.919 (0.716–1.180) | 0.509 |       |                     |
| Asian              | 8            | Fixed           | 0.541 | 0    | 1.189 (1.025–1.378) | 0.022 |       |                     |
| Source of control  |              |                 |                 |                     |                 |       |                     |                     |
| Population-based study | 3        | Fixed           | 0.855 | 0    | 1.668 (1.183–2.352) | 0.004 |       |                     |
| Hospital-based study | 10       | Fixed           | 0.471 | 0    | 1.113 (0.980–1.263) | 0.603 |       |                     |
| Heterozygote model |              |                 |                 |                     |                 |       |                     |                     |
| Total              | 13           | Fixed           | 0.301 | 14.2 | 1.084 (0.991–1.186) | 0.079 | 0.855 | 0.968 |
| Ethnicity          |              |                 |                 |                     |                 |       |                     |                     |
| Caucasian          | 5            | Fixed           | 0.076 | 52.7 | 1.040 (0.922–1.173) | 0.521 |       |                     |
| Asian              | 8            | Fixed           | 0.713 | 0    | 1.142 (0.997–1.308) | 0.054 |       |                     |
| Source of control  |              |                 |                 |                     |                 |       |                     |                     |
| Population-based study | 3        | Fixed           | 0.408 | 3.5  | 1.219 (0.974–1.526) | 0.083 |       |                     |
| Hospital-based study | 10       | Fixed           | 0.186 | 40.5 | 1.060 (0.961–1.169) | 0.248 |       |                     |
| Dominant model     |              |                 |                 |                     |                 |       |                     |                     |
| Total              | 14           | Fixed           | 0.282 | 15.6 | 1.088 (1.002–1.182) | 0.044 | 0.661 | 0.549 |
| Ethnicity          |              |                 |                 |                     |                 |       |                     |                     |
| Caucasian          | 6            | Random          | 0.034 | 58.6 | 1.027 (0.857–1.232) | 0.772 |       |                     |
| Asian              | 8            | Fixed           | 0.959 | 0    | 1.155 (1.016–1.312) | 0.028 |       |                     |
| Source of control  |              |                 |                 |                     |                 |       |                     |                     |
| Population-based study | 3        | Fixed           | 0.674 | 0    | 1.359 (1.095–1.687) | 0.005 |       |                     |
| Hospital-based study | 10       | Fixed           | 0.462 | 0    | 1.047 (0.957–1.144) | 0.318 |       |                     |
| Recessive model    |              |                 |                 |                     |                 |       |                     |                     |
| Total              | 13           | Random          | <0.01 | 66.3 | 1.068 (0.896–1.272) | 0.465 | 0.76  | 0.784 |
| Ethnicity          |              |                 |                 |                     |                 |       |                     |                     |
| Caucasian          | 5            | Fixed           | 0.344 | 10.9 | 0.919 (0.719–1.174) | 0.449 |       |                     |
| Asian              | 8            | Random          | <0.01 | 76.5 | 1.133 (0.914–1.404) | 0.254 |       |                     |
| Source of control  |              |                 |                 |                     |                 |       |                     |                     |
| Population-based study | 3        | Fixed           | 0.874 | 0    | 1.697 (1.367–2.107) | <0.001 |       |                     |
| Hospital-based study | 10       | Fixed           | 0.204 | 26   | 0.941 (0.849–1.043) | 0.247 |       |                     |
| Allele comparison model |         |                 |                 |                     |                 |       |                     |                     |
| Total              | 13           | Random          | 0.002 | 61   | 1.061 (0.966–1.166) | 0.214 | 0.855 | 0.587 |
| Ethnicity          |              |                 |                 |                     |                 |       |                     |                     |
| Caucasian          | 5            | Random          | 0.012 | 69   | 0.981 (0.814–1.183) | 0.843 |       |                     |
| Asian              | 8            | Random          | 0.021 | 57.6 | 1.103 (0.988–1.233) | 0.082 |       |                     |
| Source of control  |              |                 |                 |                     |                 |       |                     |                     |
| Population-based study | 3        | Fixed           | 0.991 | 0    | 1.394 (1.215–1.599) | <0.001 |       |                     |
| Hospital-based study | 10       | Fixed           | 0.261 | 19.8 | 0.994 (0.935–1.056) | 0.837 |       |                     |

Values of $P<0.05$ were considered statistically significant.

**miR-146a C/G polymorphism and overall cancer risk**

Furthermore, we explored the association between the pre-miR-146a C/G polymorphism and overall cancer risk. We first analyzed the heterogeneity by Q-test and $I^2$-squared in any of the genetic models. Significant statistical heterogeneity was identified in the homozygote model ($I^2=57.1\%$), heterozygote model ($I^2=55.1\%$, $P_{\text{heterogeneity}}<0.001$), dominant model ($I^2=46.4\%$, $P_{\text{heterogeneity}}<0.001$), recessive model ($I^2=60.9\%$, $P_{\text{heterogeneity}}<0.001$), and allele comparison model ($I^2=58.8\%$, $P_{\text{heterogeneity}}<0.001$), so that random-effects model was used in all genetic models. Overall, significant association was not identified in all genetic models (homozygote model: OR =1.005, 95% CI =0.931–1.084, $P=0.901$, Figure 7; heterozygote model: OR =1.009, 95% CI =0.951–1.070, $P=0.766$, Figure 8; dominant model: OR =0.998, 95% CI =0.951–1.047, $P=0.932$, Figure 9; recessive model: OR =1.005, 95% CI =0.931–1.084, $P=0.901$, Figure 7).
Figure 7. Forest plot of the association between miR-146a rs2910164 polymorphism and overall risk (under homozygote model)
Figure 8. Forest plot of the association between miR-146a rs2910164 polymorphism and overall cancer risk (under heterozygote model)
Figure 9. Forest plot of the association between miR-146a rs2910164 polymorphism and HNC risk (under dominant model).

=0.946–1.066, P=0.880, Figure 10, and allele comparison model: OR =0.999, 95% CI =0.965–1.035, P=0.970, Figure 11). Subgroup analysis was performed according to ethnicity. The same result was found, that is, no significant association was detected in all genetic models amongst Caucasians, Asians, and mixed populations. All the results are listed in Table 3.
Figure 10. Forest plot of the association between miR-146a rs2910164 polymorphism and overall cancer risk (under recessive model)
Figure 11. Forest plot of the association between miR-146a rs2910164 polymorphism and overall cancer risk (under allele comparison model)
Table 3 Meta-analysis on the association between miR-146a rs2910164 polymorphism and overall cancer risk

| Variables                  | Study number | Statistic model | Test of heterogeneity | Test of association | Publication bias |
|----------------------------|--------------|-----------------|-----------------------|---------------------|-----------------|
|                            |              |                 | \( P \) | \( I^2 \) | OR (95% CI) | \( P \) | \( P_{\text{Begg's}} \) | \( P_{\text{Egger's}} \) |
| **Homozygote model**       |              |                 |                |                    |                |              |                  |                    |
| Total                      | 89           | Random          | <0.001         | 57.1               | 1.005 (0.931–1.084) | 0.901 | 0.568          | 0.889          |
| Ethnicity                  |              |                 |                |                    |                |              |                  |                    |
| Caucasian                  | 28           | Random          | 0.004          | 46.9               | 0.919 (0.716–1.180) | 0.756 |                |                |
| Asian                      | 60           | Random          | <0.001         | 61.4               | 0.995 (0.915–1.083) | 0.913 |                |                |
| Mixed population           | 1            | Random          |               |                    | 1.01 (0.711–1.435)  | 0.966 |                |                |
| Source of control          |              |                 |                |                    |                |              |                  |                    |
| Population-based study     | 29           | Random          | <0.001         | 54.6               | 1.134 (0.972–1.323) | 0.109 |                |                |
| Hospital-based study       | 60           | Random          | <0.001         | 55.4               | 0.960 (0.882–1.045) | 0.347 |                |                |
| **Heterozygote model**     |              |                 |                |                    |                |              |                  |                    |
| Total                      | 89           | Random          | <0.001         | 55.1               | 1.009 (0.951–1.070) | 0.766 | 0.918          | 0.836          |
| Ethnicity                  |              |                 |                |                    |                |              |                  |                    |
| Caucasian                  | 28           | Random          | 0.010          | 42.7               | 1.072 (0.902–1.273) | 0.430 |                |                |
| Asian                      | 60           | Random          | <0.001         | 59.3               | 0.994 (0.934–1.057) | 0.839 |                |                |
| Mixed population           | 1            | Random          |               |                    | 0.957 (0.667–1.373) | 0.812 |                |                |
| Source of control          |              |                 |                |                    |                |              |                  |                    |
| Population-based study     | 29           | Random          | <0.001         | 72.9               | 1.013 (0.863–1.187) | 0.878 |                |                |
| Hospital-based study       | 60           | Random          | 0.005          | 25                 | 0.997 (0.944–1.052) | 0.906 |                |                |
| **Dominant model**         |              |                 |                |                    |                |              |                  |                    |
| Total                      | 89           | Random          | <0.001         | 46.4               | 0.998 (0.951–1.047) | 0.932 | 0.632          | 0.349          |
| Ethnicity                  |              |                 |                |                    |                |              |                  |                    |
| Caucasian                  | 28           | Random          | 0.003          | 48                 | 1.012 (0.929–1.104) | 0.781 |                |                |
| Asian                      | 60           | Random          | <0.001         | 46.9               | 0.989 (0.932–1.051) | 0.731 |                |                |
| Mixed population           | 1            | Random          |               |                    | 1.048 (0.887–1.240) | 0.580 |                |                |
| Source of control          |              |                 |                |                    |                |              |                  |                    |
| Population-based study     | 29           | Random          | 0.034          | 35.1               | 1.083 (0.983–1.168) | 0.420 |                |                |
| Hospital-based study       | 60           | Random          | <0.001         | 46.7               | 0.957 (0.903–1.015) | 0.143 |                |                |
| **Recessive model**        |              |                 |                |                    |                |              |                  |                    |
| Total                      | 89           | Random          | <0.001         | 60.9               | 1.005 (0.946–1.066) | 0.880 | 0.975          | 0.817          |
| Ethnicity                  |              |                 |                |                    |                |              |                  |                    |
| Caucasian                  | 28           | Random          | 0.034          | 35.1               | 1.083 (1.003–1.168) | 0.467 |                |                |
| Asian                      | 60           | Random          | <0.001         | 46.7               | 0.957 (0.903–1.015) | 0.743 |                |                |
| Mixed population           | 1            | Random          |               |                    | 0.989 (0.701–1.436) | 0.951 |                |                |
| Source of control          |              |                 |                |                    |                |              |                  |                    |
| Population-based study     | 29           | Random          | <0.001         | 72.3               | 1.041 (0.895–1.210) | 0.605 |                |                |
| Hospital-based study       | 60           | Random          | <0.001         | 50.3               | 0.986 (0.929–1.046) | 0.643 |                |                |
| **Allele comparison model**|              |                 |                |                    |                |              |                  |                    |
| Total                      | 89           | Random          | <0.001         | 60.8               | 0.999 (0.965–1.035) | 0.970 | 0.790          | 0.757          |
| Ethnicity                  |              |                 |                |                    |                |              |                  |                    |
| Caucasian                  | 28           | Random          | 0.002          | 49.8               | 1.022 (0.954–1.095) | 0.542 |                |                |
| Asian                      | 60           | Random          | <0.001         | 65.1               | 0.991 (0.950–1.032) | 0.665 |                |                |
| Mixed population           | 1            | Random          |               |                    | 1.030 (0.899–1.181) | 0.670 |                |                |
| Source of control          |              |                 |                |                    |                |              |                  |                    |
| Population-based study     | 29           | Random          | <0.001         | 57.7               | 1.053 (0.988–1.122) | 0.112 |                |                |
| Hospital-based study       | 60           | Random          | <0.001         | 60.1               | 0.977 (0.938–1.017) | 0.252 |                |                |

**Publication bias**

Egger’s test and Begg’s test were used to investigate the publication bias in the literature in all the genetic models. No publication bias was detected by Begg’s and Egger’s tests. The shapes of the funnel plots (not shown) did not identify obvious asymmetry in any of the comparison models, and plot symmetries are evidenced by \( P \)-values greater than 0.05. Accordingly, no publication bias was evident in the meta-analysis (Tables 2 and 3).
Sensitivity analysis
We performed sensitivity analysis by sequential omission of individual studies, and the results showed that the significance of the pooled ORs for miR-146a rs2910164 polymorphism was not excessively influenced, suggesting the stability and reliability of the results in the present meta-analysis (not shown).

Discussion
It is well known that genetic mutations are responsible for cancer occurrence [104]. SNPs, as the most common genetic sequence variation, could affect the function of a series of miRNAs by altering the formation of the primary transcript, miRNA maturation, or miRNA–mRNA interactions [105,106]. Thus, genetic susceptibility to cancer, particularly from SNPs, has been a research focus in the scientific community. Previously, variations of the pre-miR-146a C/G gene have drawn increasing attention in cancer etiologies, and altered expression levels have been observed in inflammatory diseases as well as in cancers [107,108]. The results of the present meta-analysis confirm that miR-146a C/G polymorphism is associated with HNC risk. This risk is significant amongst the individuals with a dominant genotype model. In the stratified analysis by ethnicity, significant analysis was detected amongst Asians under homozygote and dominant model, while no association was found amongst Caucasians under all genetic models. Furthermore, significant association was found in population-based studies under homozygote, dominant, recessive, and allele comparison models. However, no significant association was detected in hospital-based studies under all genetic models. Moreover, no significant association was found between this gene polymorphism and overall cancer risk. Furthermore, in the stratified analyses by ethnicity and source of control, no significant association was detected in the subgroup analyses of source of control.

To the best of our knowledge, the present study is the first and most comprehensive one to date to assess the relationship between miR-146a C/G polymorphism and HNC risk, and the most comprehensive one to date to explore the association between this gene polymorphism and overall cancer risk. Nevertheless, our meta-analysis also has some limitations common to these types of studies. First, relatively large heterogeneity was observed across all the studies involved despite the use of strict criteria for study inclusion and precise data extraction. So, we performed subgroup analyses to explore the possible source of heterogeneity. Second, the majority of studies included in this meta-analysis were mainly Caucasians and Asians. Thus, the inherent genetic and geographic differences require more data from different ethnic group to increase the statistical power. Third, the low sample size in some of the included studies likely influences the statistical power for evaluating the association between the miR-146a C/G polymorphism and HNC risk, especially in subgroup analyses. Fourth, lack of original data from the reviewed studies limited our further evaluation of potential interactions, considering that gene-to-gene and gene-to-environment interactions might modulate cancer risk. As a result, a more precise analysis stratified by variable host factors could be performed. Last, although the results for publication bias were not statistically significant, publication bias may still exist, because only published studies were included in this meta-analysis.

In conclusion, the meta-analysis presented here indicates that miR-146a C/G polymorphism more is likely contribute to the susceptibility to HNC, and overall cancer risk. Further well-designed studies with large sample size are needed to confirm these findings.

Author contribution
Xiaolei Z. contributed to the study design. D.S. and Xiaoyan Z. contributed to the literature search, data extraction, and the assessment of methodology quality. D.S. contributed to the statistical analysis and drafting of the manuscript. Xiaolei Z. contributed to the revising of the manuscript. All authors approved the final version of manuscript.

Competing interests
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Abbreviations
Cl, confidence interval; HNC, head and neck cancer; HWE, Hardy–Weinberg equilibrium; OR, odds ratio; SNP, single nucleotide polymorphism.
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