Association of three promoter polymorphisms in interleukin-10 gene with cancer susceptibility in the Chinese population: a meta-analysis

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ABSTRACT

Numerous studies have examined the associations of three promoter polymorphisms (-1082A/G, -819T/C and -592A/C) in IL-10 gene with cancer susceptibility in the Chinese population, but the results remain inconclusive. To gain a more precise estimation of this potential association, we conducted the current meta-analysis based on 53 articles, including 26 studies with 4,901 cases and 6,426 controls for the -1082A/G polymorphism, 33 studies with 6,717 cases and 8,550 controls for the -819T/C polymorphism, and 42 studies with 9,934 cases and 13,169 controls for the -592A/C polymorphism. Pooled results indicated that the three promoter polymorphisms in IL-10 gene were significantly associated with an increased overall cancer risk in the Chinese population. Stratification analysis showed that the association was more pronounced for hepatocellular carcinoma and low quality studies for the -1082A/G polymorphism, lung cancer and oral cancer for the -819T/C polymorphism. However, the -592A/C polymorphism was associated with a statistically significant increased risk for lung cancer, oral cancer, hospital-based studies and low quality studies, but a decreased risk for colorectal cancer. We further investigated the significant results using the false-positive report probability (FPRP) test. Interestingly, FPRP test results revealed that only IL-10 -1082A/G polymorphism was truly associated with an increased overall cancer risk. In the subgroup analysis, only the low quality studies, lung cancer and colorectal cancer remained significant at the prior level of 0.1. Although this association needs further confirmation by considering large studies, this meta-analysis suggested an association between IL-10 gene polymorphisms and cancer risk in the Chinese population.

INTRODUCTION

Cancer is still a global public health problem. According to the GLOBOCAN estimates, about 14.1 million new cancer cases and 8.2 million deaths occurred in 2012 worldwide [1]. In China, cancer has become the leading cause of death since 2010, with an estimate of 4292,000 new cancer cases and 2814,000 cancer deaths in 2015 [2]. As a multifactorial disease, it involves both genetic and environmental factors [3]. Accumulating evidence has indicated that inflammation plays a vital role in cancer development [4–6], and approximately 20% of all cancers are associated with chronic inflammation [7].

Interleukin-10 (IL-10) is an anti-inflammatory cytokine with both immunosuppressive and immunostimulatory activities [8]. Although the relationship...
between IL-10 and cancer has been extensively studied, the exact role of IL-10 in cancer is still elusive, since IL-10 have both cancer-promoting and -inhibiting properties [9, 10]. In view of these properties, we hypothesized that IL-10 gene polymorphisms could influence cancer susceptibility.

The IL-10 gene is located on chromosome 1q31-32, and is composed of five exons and four introns. IL-10 gene promoter region is highly polymorphic, and three promoter single nucleotide polymorphisms (SNPs) such as -1082A/G (rs1800896), -819T/C (rs1800871) and -592A/C (rs1800872) have been reported to regulate IL-10 expression [11, 12] and alter the susceptibility to various types of cancers [13–16]. In the Chinese population, numerous case-control studies were performed to investigate the role of IL-10 -1082A/G, -819T/C and -592A/C polymorphisms in cancer risk. However, the results remain inconclusive. Hence, we performed the present meta-analysis to investigate the association between three polymorphisms in IL-10 gene and cancer susceptibility in the Chinese population.

RESULTS

Study characteristics

As shown in Figure 1, 1,596 published records were initially retrieved from PubMed, Embase, Chinese National Knowledge Infrastructure (CNKI) and Wanfang database, and 14 more articles were identified by checking the references in the retrieved publications. After reviewing of the titles and abstracts, 1,535 articles were excluded, leaving only 75 articles for further assessment. Among them, we excluded one study [17] that was covered by another included publication [18], five case-only studies [19–23], five lacking detailed data for further analysis [24–28], and eleven that were considering the deviation from the Hardy-Weinberg equilibrium (HWE) [29–39]. Ultimately, 53 articles were included in the final meta-analysis. Of these 53 articles, 24 articles [40–63] include 26 studies examining IL-10 -1082A/G polymorphism, 28 articles [18, 42, 43, 45, 47, 49, 52, 53, 57–61, 63–77] include 33 studies examining the -819T/C polymorphism, and 39 articles [18, 42, 43, 45, 47, 52, 53, 56–67, 69, 70, 73–76, 78–91] include 42 studies examining the -592A/C polymorphism (Table 1). Of the 53 articles, two publications [18, 45] with three cancer types were considered as three studies and one publication [65] with two cancer types were also considered as two studies.

For the studies assessing three polymorphisms (-1082A/G, -819T/C and -592A/C) [32, 37], two (-1082A/G and -592A/C) [31], only one such as -1082A/G [29, 30, 33–35, 38] or -819T/C [36, 39] polymorphism and cancer...
Table 1: Characteristics of studies included in the meta-analysis

| Surname [ref] | Year | Cancer type | Control source | Genotype method | Case [11 12 22 All] | Control [11 12 22 All] | MAF | HWE | Score |
|--------------|------|-------------|----------------|-----------------|---------------------|-------------------------|-----|-----|-------|
| -1082A/G polymorphism |
| Wu [40]      | 2002 | Gastric     | HB             | Sequencing      | 135 14 1 150        | 208 11 1 220           | 0.03 | 0.057 | 6     |
| Heneghan [41] | 2003 | HCC         | PB             | Probe           | 86 12 0 98          | 90 7 0 97             | 0.04 | 0.712 | 10    |
| Shih [42]    | 2005 | Lung        | HB             | PCR-RFLP        | 115 39 0 154        | 194 11 0 205           | 0.03 | 0.693 | 8     |
| Wei [43]     | 2007 | NPC         | HB             | PCR-RFLP        | 123 61 14 198       | 167 38 5 210           | 0.11 | 0.124 | 8     |
| Bai [44]     | 2008 | Gastric     | HB             | PCR-RFLP        | 89 22 (AG+GG) 111   | 104 7 (AG+GG) NA        | NA  | 7     |
| Hsing [45]   | 2008 | Gallbladder | PB             | Taqman          | 231 23 1 255        | 624 99 7 730           | 0.08 | 0.173 | 12    |
| Hsing [45]   | 2008 | EHBD        | PB             | Taqman          | 107 18 0 125        | 664 108 7 779          | 0.08 | 0.270 | 12    |
| Hsing [45]   | 2008 | AV          | PB             | Taqman          | 38 9 0 47           | 664 108 7 779          | 0.08 | 0.270 | 12    |
| Hao [46]     | 2008 | Lung        | PB             | Taqman          | 36 7 (AG+GG) 43     | 46 6 (AG+GG) NA        | NA  | 7     |
| Xiao [47]    | 2009 | Gastric     | HB             | PCR-RFLP        | 176 41 3 220        | 593 31 0 624           | 0.03 | 0.525 | 9     |
| Kong [48]    | 2010 | Breast      | HB             | PCR-RFLP        | 285 29 1 315        | 285 35 2 322           | 0.06 | 0.422 | 9     |
| Liu [49]     | 2010 | HCC         | HB             | Taqman          | 131 35 4 170        | 160 24 3 187           | 0.08 | 0.075 | 5     |
| Niu [50]     | 2011 | Prostate    | PB             | Sequencing      | 24 74 (AG+GG) 98    | 42 46 (AG+GG) NA       | NA  | 9     |
| Wang [51]    | 2011 | Cervical    | PB             | PCR-SSP         | 77 85 24 186        | 103 76 21 200          | 0.30 | 0.222 | 8     |
| He [52]      | 2012 | Gastric     | HB             | PCR-RFLP        | 154 42 0 196        | 194 54 0 248           | 0.11 | 0.055 | 9     |
| Chang [53]   | 2013 | HN          | HB             | Taqman          | 289 23 1 313        | 268 27 0 295           | 0.05 | 0.410 | 10    |
| Chen [54]    | 2013 | Bladder     | HB             | AS-PCR          | 374 25 1 400        | 350 48 2 400           | 0.07 | 0.799 | 10    |
| Du [55]      | 2013 | Esophageal  | HB             | PCR             | 95 20 3 118         | 103 15 1 119           | 0.07 | 0.587 | 8     |
| Pan [56]     | 2013 | Gastric     | HB             | MassARRAY       | 263 41 4 308        | 264 41 3 308           | 0.08 | 0.329 | 9     |
| Cheng [57]   | 2015 | NTCL        | HB             | PCR-LDR         | 101 24 0 125        | 237 60 3 300           | 0.11 | 0.710 | 10    |
| Fei [58]     | 2015 | AML         | HB             | PCR-RFLP        | 75 70 22 167        | 159 134 35 328         | 0.31 | 0.398 | 8     |
| Hsu [59]     | 2015 | Oral        | HB             | PCR-SSP         | 130 14 1 145        | 96 16 0 112            | 0.07 | 0.416 | 7     |
| Yang [60]    | 2015 | Esophageal  | HB             | MassARRAY       | 41 106 99 246       | 46 204 242 492         | 0.30 | 0.751 | 9     |
| Bai [61]     | 2016 | Cervical    | HB             | PCR-RFLP        | 74 75 16 165        | 80 72 13 165           | 0.30 | 0.563 | 8     |
| Cai [62]     | 2016 | Colorectal  | HB             | MassARRAY       | 323 50 2 375        | 343 39 0 382           | 0.05 | 0.293 | 9     |
| Peng [63]    | 2016 | HCC         | PB             | PCR-RFLP        | 83 74 16 173        | 96 74 12 182           | 0.27 | 0.653 | 10    |
| -819T/C polymorphism |
| Wu [64]      | 2003 | Gastric     | HB             | Sequencing      | 88 105 27 220       | 127 83 20 230          | 0.27 | 0.231 | 9     |
| Savage [65]  | 2004 | Gastric     | PB             | SBE             | 37 38 9 84          | 170 163 49 382         | 0.34 | 0.315 | 11    |
| Savage [65]  | 2004 | Esophageal  | PB             | SBE             | 53 46 17 116        | 170 163 49 382         | 0.34 | 0.315 | 12    |
| Shih [42]    | 2005 | Lung        | HB             | PCR-RFLP        | 66 58 30 154        | 104 86 15 205          | 0.28 | 0.627 | 8     |
| Wei [43]     | 2007 | NPC         | HB             | PCR-RFLP        | 82 81 35 198        | 94 92 24 210           | 0.33 | 0.836 | 8     |
| Hsing [45]   | 2008 | Gallbladder | PB             | Taqman          | 122 92 23 237       | 311 335 82 728         | 0.34 | 0.564 | 12    |
| Hsing [45]   | 2008 | EHBD        | PB             | Taqman          | 55 52 17 124        | 334 353 90 777         | 0.34 | 0.823 | 12    |
| Hsing [45]   | 2008 | AV          | PB             | Taqman          | 20 6 21 47          | 334 353 90 777         | 0.34 | 0.823 | 12    |
| Yao [66]     | 2008 | Oral        | HB             | PCR-RFLP        | 113 120 47 280      | 129 134 37 300         | 0.35 | 0.809 | 10    |
| Xiao [47]    | 2009 | Gastric     | HB             | PCR-RFLP        | 100 100 20 220      | 272 283 69 624         | 0.34 | 0.719 | 9     |

(Continued)
| Surname [ref] | Year | Cancer type | Control source | Genotype method | Case  | Control  | MAF | HWE | Score |
|--------------|------|-------------|----------------|----------------|-------|----------|-----|-----|-------|
| Liu [67]     | 2010 | Prostate    | HB             | PCR-RFLP       | 120   | 108      | 34  | 262 | 0.31  |
| Liu [49]     | 2010 | HCC         | HB             | Taqman         | 79    | 73       | 18  | 170 | 0.35  |
| Oh [18]      | 2010 | Esophageal  | PB             | Taqman         | 90    | 79       | 27  | 196 | 0.32  |
| Oh [18]      | 2010 | Gastric     | PB             | Taqman         | 81    | 87       | 20  | 188 | 0.32  |
| Oh [18]      | 2010 | HCC         | PB             | Taqman         | 91    | 70       | 25  | 186 | 0.32  |
| Su [68]      | 2010 | Gastric     | HB             | PCR-RFLP       | 18    | 21       | 4   | 43  | 0.28  |
| Bei [69]     | 2011 | HCC         | HB             | Taqman         | 44    | 247      | 298 | 589 | 0.29  |
| Liu [70]     | 2011 | Gastric     | HB             | PCR-RFLP       | 99    | 96       | 39  | 234 | 0.33  |
| He [52]      | 2012 | Gastric     | HB             | PCR-RFLP       | 82    | 96       | 18  | 196 | 0.37  |
| He [71]      | 2012 | Breast      | HB             | MALDI-TOF MS   | 177   | 141      | 29  | 347 | 0.31  |
| Yuan [72]    | 2012 | Gastric     | HB             | MassARRAY      | 108   | 129      | 42  | 279 | 0.32  |
| Zeng [73]    | 2012 | Gastric     | PB             | SBE            | 60    | 80       | 11  | 151 | 0.28  |
| Chang [53]   | 2013 | HN          | HB             | Taqman         | 132   | 153      | 28  | 313 | 0.36  |
| Yao [74]     | 2013 | AML         | HB             | PCR-RFLP       | 68    | 38       | 9   | 115 | 0.34  |
| Cheng [57]   | 2015 | NTCL        | HB             | PCR-LDR        | 57    | 59       | 9   | 125 | 0.34  |
| Fei [58]     | 2015 | AML         | HB             | PCR-RFLP       | 57    | 72       | 38  | 167 | 0.37  |
| Hsu [59]     | 2015 | Oral        | HB             | PCR-SSP        | 33    | 101      | 11  | 145 | 0.30  |
| Yang [60]    | 2015 | Esophageal  | HB             | MassARRAY      | 101   | 105      | 40  | 246 | 0.35  |
| Zhang [75]   | 2015 | Lung        | HB             | PCR-RFLP       | 108   | 135      | 87  | 330 | 0.35  |
| Bai [61]     | 2016 | Cervical    | HB             | PCR-RFLP       | 44    | 76       | 45  | 165 | 0.39  |
| Cui [76]     | 2016 | Osteosarcoma| HB             | PCR-RFLP       | 34    | 120      | 106 | 260 | 0.39  |
| Li [77]      | 2016 | Gastric     | HB             | PCR-RFLP       | 36    | 83       | 38  | 157 | 0.40  |
| Peng [63]    | 2016 | HCC         | PB             | PCR-RFLP       | 74    | 77       | 22  | 173 | 0.31  |

-592A/C polymorphism

| Surname [ref] | Year | Cancer type | Control source | Genotype method | Case  | Control  | MAF | HWE | Score |
|--------------|------|-------------|----------------|----------------|-------|----------|-----|-----|-------|
| Wu [64]      | 2003 | Gastric     | HB             | Sequencing     | 88    | 105      | 27  | 220 | 0.27  |
| Savage [65]  | 2004 | Gastric     | PB             | SBE            | 9     | 39       | 36  | 84  | 0.34  |
| Shih [42]    | 2005 | Lung        | HB             | PCR-RFLP       | 66    | 70       | 18  | 154 | 0.25  |
| Tseng [78]   | 2006 | HCC         | HB             | MALDI-TOF MS   | 93    | 84       | 31  | 208 | 0.31  |
| Wei [43]     | 2007 | NPC         | HB             | PCR-RFLP       | 82    | 81       | 35  | 198 | 0.33  |
| Hsing [45]   | 2008 | Gallbladder | PB             | Taqman         | 121   | 91       | 23  | 235 | 0.34  |
| Yao [66]     | 2008 | Oral        | HB             | PCR-RFLP       | 113   | 120      | 47  | 280 | 0.35  |
| Xiao [47]    | 2009 | Gastric     | HB             | PCR-RFLP       | 100   | 100      | 20  | 220 | 0.34  |
| Liu [67]     | 2010 | Prostate    | HB             | PCR-RFLP       | 120   | 108      | 34  | 262 | 0.31  |
| Oh [18]      | 2010 | Esophageal  | PB             | SNPlex         | 81    | 72       | 26  | 179 | 0.32  |
| Oh [18]      | 2010 | Gastric     | PB             | SNPlex         | 77    | 81       | 20  | 178 | 0.32  |
| Oh [18]      | 2010 | HCC         | PB             | SNPlex         | 82    | 68       | 19  | 169 | 0.32  |
| Xiong [79]   | 2010 | Cervical    | HB             | PCR-RFLP       | 35    | 23       | 12  | 70  | 0.32  |
| Bei [69]     | 2011 | HCC         | HB             | Taqman         | 42    | 248      | 299 | 589 | 0.29  |

(Continued)
| Surname [ref] | Year | Cancer type | Control source | Genotype method | Case | Control | MAF | HWE | Score |
|--------------|------|-------------|----------------|---------------|-----|---------|-----|-----|-------|
| Liang [80]   | 2011 | Lung        | HB             | PCR-RFLP      | 69  | 65      | 116 | 7   | 0.24  |
| Liu [70]     | 2011 | Gastric     | HB             | PCR-RFLP      | 99  | 106     | 234 | 7   | 0.33  |
| Yu [81]      | 2011 | Cervical    | PB             | PCR-RFLP      | 59  | 52      | 103 | 11  | 0.36  |
| He [52]      | 2012 | Gastric     | HB             | PCR-RFLP      | 82  | 92      | 196 | 24  | 0.37  |
| Zeng [73]    | 2012 | Gastric     | PB             | SBE           | 59  | 80      | 151 | 7   | 0.26  |
| Zhang [82]   | 2012 | NHL         | PB             | Taqman        | 226 | 269     | 604 | 3   | 0.57  |
| Chang [53]   | 2013 | HN          | HB             | Taqman        | 134 | 137     | 27  | 13  | 0.32  |
| Pan [56]     | 2013 | Gastric     | HB             | MassARRAY     | 144 | 142     | 36  | 31  | 0.32  |
| Sun [83]     | 2013 | Esophageal  | HB             | SNPscan       | 162 | 191     | 356 | 36  | 0.28  |
| Tsai [84]    | 2013 | NPC         | HB             | PCR-RFLP      | 93  | 261     | 17  | 56  | 0.30  |
| Yao [74]     | 2013 | AML         | HB             | PCR-RFLP      | 68  | 56      | 115 | 18  | 0.36  |
| Bei [85]     | 2014 | HCC         | HB             | Taqman        | 356 | 392     | 52  | 79  | 0.30  |
| Hsia [86]    | 2014 | Lung        | HB             | PCR-RFLP      | 173 | 368     | 40  | 71  | 0.29  |
| Kuo [87]     | 2014 | Gastric     | HB             | PCR-RFLP      | 186 | 180     | 38  | 35  | 0.30  |
| Yu [88]      | 2014 | Colorectal  | PB             | PCR-RFLP      | 153 | 118     | 31  | 29  | 0.31  |
| Cheng [57]   | 2015 | NTCL        | HB             | PCR-LDR       | 57  | 138     | 9  | 30  | 0.33  |
| Fei [58]     | 2015 | AML         | HB             | PCR-RFLP      | 54  | 126     | 39  | 59  | 0.40  |
| Hsu [59]     | 2015 | Oral        | HB             | PCR-SSP       | 33  | 53      | 11  | 8  | 0.30  |
| Yang [60]    | 2015 | Esophageal  | HB             | MassARRAY     | 85  | 185     | 45  | 79  | 0.39  |
| Yin [89]     | 2015 | Gastric     | HB             | SNPscan       | 112 | 235     | 20  | 42  | 0.29  |
| Zhang [75]   | 2015 | Lung        | HB             | PCR-RFLP      | 64  | 85      | 110 | 75  | 0.49  |
| Bai [61]     | 2016 | Cervical    | HB             | PCR-RFLP      | 63  | 70      | 82  | 16  | 0.33  |
| Cai [62]     | 2016 | Colorectal  | HB             | MassARRAY     | 221 | 184     | 26  | 40  | 0.31  |
| Chang [90]   | 2016 | RCC         | HB             | PCR-RFLP      | 61  | 371     | 27  | 24  | 0.50  |
| Cui [76]     | 2016 | Osteosarcoma| HB             | PCR-RFLP      | 108 | 100     | 27  | 32  | 0.57  |
| Peng [63]    | 2016 | HCC         | PB             | PCR-RFLP      | 57  | 79      | 81  | 22  | 0.52  |
| Ma [91]      | 2016 | Gastric     | HB             | PCR-RFLP      | 67  | 71      | 17  | 12  | 0.50  |

MAF: minor allele frequency; HWE: Hardy-Weinberg equilibrium; HB: hospital based; PB: population based; NA: not applicable; HCC: hepatocellular carcinoma; NPC: nasopharyngeal carcinoma; EHBD: extrahepatic bile duct; AV: ampulla of vater; HN: head and neck; NTCL: NK/T-cell lymphoma; AML: acute myeloid leukemia; NHL: non-Hodgkin’s lymphoma; RCC: renal cell carcinoma; PCR-RFLP: polymorphism chain reaction restriction fragment length polymorphism; PCR-SSP: polymerase chain reaction sequence-specific primer; AS-PCR: allele-specific polymorphism chain reaction; PCR-LDR: polymorphism chain reaction-ligase detection reaction; SBE: single base extension; MALDI-TOF MS: matrix-assisted laser desorption/ionization-time-of-flight mass spectrometry.

1 Heneghan [41], Shih [42], Hsing [44] (extrahepatic bile duct cancer and ampulla of vater cancer), Xiao [47], He [52], Chang [53], Cheng [57], Hsu [59] and Cui [76] were only calculated for the heterozygous model, dominant model and allele comparison for the IL-10 -1082A/G polymorphism, and the number of GG genotype was zero.

2 Bai [44], Hao [46] and Niu [50] were only calculated for the dominant model.

Risk but no other IL-10 gene polymorphisms, the genotypes distribution in the controls were deviated from HWE, thus, these studies were excluded in the final analysis. Sixteen studies were also deviated from HWE, but the genotypes distribution in the controls of eight studies [18, 64-67, 70, 73, 76] were consistent with that expected from the HWE for both -819T/C and -592A/C polymorphisms, five [81, 84, 86, 87, 90] for the -592A/C polymorphism and three [41, 48, 54] for the -1082A/G polymorphism, thus, these studies were included in the final analysis. For those studies [18, 45, 65] with the same control subjects, the control numbers were calculated once in the total number. Overall, 26 studies with 4,901 cases and 6,426 controls for the -1082A/G polymorphism, 33 studies with 6,717 cases and 8,550 controls for the -819T/C polymorphism, and 42 studies with 9,934 cases and 13,169 controls for...
the -592A/C polymorphism were considered in this meta-analysis. Sample sizes for cases of the included studies ranged from 43 to 400 for the -1082A/G polymorphism, 43 to 589 for the -819T/C polymorphism, and 70 to 720 for the -592A/C polymorphism.

As regards the -1082A/G polymorphism, five studies focused on gastric cancer [40, 44, 47, 52, 56], three on hepatocellular carcinoma [41, 49, 63], two studies for each of the following cancer types, such as lung cancer [42, 46], cervical cancer [51, 61] and esophageal cancer [55, 60], and the other cancer types with one study per each cancer type. As regards the -819T/C polymorphism, 10 studies focused on gastric cancer [18, 47, 52, 64, 65, 68, 70, 72, 73, 77], four on hepatocellular carcinoma [18, 49, 63, 69], three on esophageal cancer [18, 60, 65], two studies for each of the following cancer types, such as lung cancer [42, 75], oral cancer [59, 66] and acute myeloid leukemia [58, 74], and the other cancer types with one study per each cancer type. As regards the -592A/C polymorphism, 11 studies focused on gastric cancer [18, 47, 52, 56, 64, 65, 70, 73, 87, 89, 91], five on hepatocellular carcinoma [18, 63, 69, 78, 85], four studies for each of the following cancer types, such as lung cancer [42, 75, 80, 86] and esophageal cancer [18, 60, 65, 83], three on cervical cancer [61, 79, 81], two studies for each of the following cancer types, such as nasopharyngeal carcinoma [43, 84], oral cancer [59, 66], acute myeloid leukemia [58, 74] and colorectal cancer [62, 88], and the other cancer types with one study per each cancer type. Among all studies, 18 were hospital-based and eight were population-based associated to the -1082A/G polymorphism, 23 were hospital-based and 10 were population-based associated to the -819T/C polymorphism, 31 were hospital-based and 11 were population-based associated to the -592A/C polymorphism. Furthermore, 18 studies were rated as low quality (quality score ≤ 9) and eight were considered as high quality (quality score > 9) for the -1082A/G polymorphism, 16 were low quality and 17 were high quality studies for the -819T/C polymorphism, 21 were low quality and 21 were high quality studies for the -592A/C polymorphism. Controls were matched for age and sex in most studies, and cases were mostly histologically confirmed.

**Meta-analysis results**

The main results regarding the association between *IL-10* -1082A/G polymorphism and cancer risk are shown in Table 2 and Figure 2. A significant association was found between *IL-10* -1082A/G polymorphism and overall cancer risk [dominant: odds ratio (OR) = 1.32, 95% confidence interval (CI) = 1.04-1.67, *P* < 0.001]. In the subgroup analysis, a statistically significant association was found for hepatocellular carcinoma (heterozygous: OR = 1.40, 95% CI = 1.01-1.94, *P* = 0.043; dominant: OR = 1.43, 95% CI = 1.04-1.95, *P* = 0.497 and allele comparison: OR = 1.35, 95% CI = 1.04-1.75, *P* = 0.480) and low quality studies (heterozygous: OR = 1.42, 95% CI = 1.05-1.91, *P* = 0.001; dominant: OR = 1.56, 95% CI = 1.17-2.08, *P* < 0.001 and allele comparison: OR = 1.43, 95% CI = 1.08-1.88, *P* < 0.001).

The overall results regarding the association between *IL-10* -819T/C polymorphism and cancer risk are shown in Table 2. A significant association was found between *IL-10* -819T/C polymorphism and overall cancer risk (homozygous: OR = 1.19, 95% CI = 1.00-1.41, *P* < 0.001; recessive: OR = 1.17, 95% CI = 1.00-1.36, *P* < 0.001 and allele comparison: OR = 1.08, 95% CI = 1.00-1.18, *P* < 0.001). In the subgroup analysis, a statistically significant association was found for lung cancer (homozygous: OR = 2.66, 95% CI = 1.84-3.84, *P* = 0.569; recessive: OR = 2.40, 95% CI = 1.71-3.37, *P* = 0.399; dominant: OR = 1.49, 95% CI = 1.16-1.92, *P* = 0.633 and allele comparison: OR = 1.59, 95% CI = 1.33-1.91, *P* = 0.920) and oral cancer (homozygous: OR = 1.58, 95% CI = 1.01-2.46, *P* = 0.464).

The detailed results regarding the association between *IL-10* -592A/C polymorphism and cancer risk are shown in Table 2. A significant association was found between *IL-10* -592A/C polymorphism and increased overall cancer risk (homozygous: OR = 1.13, 95% CI = 1.00-1.28, *P* = 0.001). In the subgroup analysis, a statistically significant increased risk was found for lung cancer (homozygous: OR = 1.64, 95% CI = 1.19-2.24, *P* = 0.301; recessive: OR = 1.52, 95% CI = 1.20-1.93, *P* = 0.402; dominant: OR = 1.27, 95% CI = 1.01-1.60, *P* = 0.198 and allele comparison: OR = 1.27, 95% CI = 1.06-1.52, *P* = 0.149), oral cancer (homozygous: OR = 1.58, 95% CI = 1.01-2.46, *P* = 0.464), hospital-based studies (allele comparison: OR = 1.07, 95% CI = 1.00-1.15, *P* < 0.001) and low quality studies (homozygous: OR = 1.23, 95% CI = 1.02-1.49, *P* = 0.012 and recessive: OR = 1.21, 95% CI = 1.05-1.40, *P* = 0.193). In contrast, a significantly decreased risk was observed for colorectal cancer (homozygous: OR = 0.58, 95% CI = 0.40-0.85, *P* = 0.694; heterozygous: OR = 0.66, 95% CI = 0.53-0.83, *P* = 0.882; dominant: OR = 0.65, 95% CI = 0.52-0.80, *P* = 0.994 and allele comparison: OR = 0.72, 95% CI = 0.61-0.85, *P* = 0.750).

**Heterogeneity and sensitivity analysis**

Substantial heterogeneities were found among all studies regarding *IL-10* -1082A/G polymorphism and overall cancer risk (homozygous: *P* = 0.025; heterozygous: *P* < 0.001; dominant: *P* < 0.001 and allele comparison: *P* < 0.001), but not under the recessive model (*P* = 0.242) (Table 2). Considerable heterogeneities were also observed for the -819T/C (all *P* < 0.001) and -592A/C (homozygous: *P* = 0.001; recessive: *P* = 0.035; dominant: *P* < 0.001 and allele comparison: *P* < 0.001) polymorphisms. Therefore,
Table 2: Meta-analysis of the association between *IL-10* polymorphisms and cancer risk

| Variables | No. of studies | Sample size (case/controls) | Homozygous | Heterozygous | Recessive | Dominant | Allele comparison |
|-----------|----------------|----------------------------|-------------|--------------|-----------|----------|-------------------|
|           |                |                            | OR (95% CI) | p_{het}      | OR (95% CI) | p_{het}  | OR (95% CI) | p_{het}         |
|           |                |                            | OR (95% CI) | p_{het}      | OR (95% CI) | p_{het}  | OR (95% CI) | p_{het}         |
|           |                |                            | OR (95% CI) | p_{het}      | OR (95% CI) | p_{het}  | OR (95% CI) | p_{het}         |
|           |                |                            | OR (95% CI) | p_{het}      | OR (95% CI) | p_{het}  | OR (95% CI) | p_{het}         |
| -1082A/G  |                |                            |             |              |           |          |             |                |
| All       | 26             | 4,901/6,426                | 1.21 (0.80-1.85) | 0.025 | 1.22 (0.97-1.54) | <0.001 | 1.12 (0.84-1.48) | 0.242 | **1.32 (1.04-1.67)** | <0.001 | 1.22 (0.99-1.51) | <0.001 |
| Cancer type |              |                            |             |              |           |          |             |                |
| Gastric   | 5              | 985/1,511                  | 1.38 (0.37-5.20) | 0.930 | 1.70 (0.79-3.66) | <0.001 | 1.37 (0.36-5.13) | 0.953 | 1.97 (0.97-3.99) | <0.001 | 1.72 (0.79-3.71) | <0.001 |
| HCC       | 3              | 441/466                    | 1.56 (0.77-3.18) | 0.950 | **1.40 (1.01-1.94)** | 0.433 | 1.45 (0.73-2.90) | 0.978 | **1.43 (1.04-1.95)** | 0.497 | **1.35 (1.04-1.75)** | 0.480 |
| Lung a     | 2              | 197/257                    | NA           | NA           | NA       | NA       | 3.24 (0.84-12.54) | 0.047 | NA                | NA             |                |
| Cervical  | 2              | 351/365                    | 1.45 (0.87-2.40) | 0.792 | 1.31 (0.96-1.79) | 0.371 | 1.26 (0.78-2.04) | 0.991 | 1.33 (0.99-1.79) | 0.386 | 1.24 (0.99-1.55) | 0.490 |
| Esophageal | 2              | 364/611                    | 0.88 (0.14-5.40) | 0.099 | 0.88 (0.36-2.14) | 0.041 | 0.94 (0.29-3.01) | 0.205 | 0.87 (0.29-2.56) | 0.009 | 1.00 (0.44-2.26) | 0.015 |
| Others    | 12             | 2,563/3,216                | 1.30 (0.59-2.85) | 0.168 | 0.96 (0.74-1.25) | 0.002 | 1.30 (0.68-2.46) | 0.280 | 1.05 (0.78-1.41) | <0.001 | 0.97 (0.74-1.27) | <0.001 |
| Source of control         |              |                            |             |              |           |          |             |                |
| PB        | 8              | 1,025/1,398                | 1.42 (0.87-2.33) | 0.454 | 1.13 (0.84-1.53) | 0.114 | 1.25 (0.78-2.01) | 0.538 | 1.29 (0.92-1.80) | 0.013 | 1.07 (0.82-1.41) | 0.078 |
| HB        | 18             | 3,876/5,028                | 1.20 (0.69-2.09) | 0.018 | 1.25 (0.93-1.68) | <0.001 | 1.13 (0.78-1.64) | 0.183 | 1.33 (0.98-1.80) | <0.001 | 1.27 (0.97-1.68) | <0.001 |
| Score     |                |                            |             |              |           |          |             |                |
| Low       | 18             | 3,365/4,373                | 1.29 (0.78-2.12) | 0.012 | **1.42 (1.05-1.91)** | <0.001 | 1.16 (0.83-1.63) | 0.160 | **1.56 (1.17-2.08)** | <0.001 | **1.43 (1.08-1.88)** | <0.001 |
| High      | 8              | 1,536/2,053                | 1.13 (0.52-2.48) | 0.349 | 0.89 (0.68-1.17) | 0.073 | 1.15 (0.57-2.31) | 0.417 | 0.88 (0.67-1.67) | 0.059 | 0.88 (0.68-1.14) | 0.047 |
| -819T/C   |                |                            |             |              |           |          |             |                |
| All       | 33             | 6,717/8,550                | **1.19 (1.00-1.41)** | <0.001 | 1.04 (0.93-1.16) | <0.001 | **1.17 (1.00-1.36)** | <0.001 | 1.08 (0.97-1.20) | <0.001 | **1.08 (1.00-1.18)** | <0.001 |
| Cancer type |              |                            |             |              |           |          |             |                |
| Gastric   | 10             | 1,772/2,142                | 1.08 (0.79-1.47) | 0.021 | 1.15 (0.95-1.38) | 0.046 | 1.01 (0.81-1.27) | 0.196 | 1.14 (0.93-1.40) | 0.007 | 1.08 (0.92-1.27) | 0.002 |
| HCC       | 4              | 1,118/1,344                | 1.14 (0.86-1.51) | 0.744 | 0.96 (0.78-1.19) | 0.396 | 1.04 (0.86-1.26) | 0.668 | 1.00 (0.82-1.22) | 0.412 | 1.01 (0.90-1.15) | 0.549 |

(Continued)
| Variables | No. of studies | Sample size (case/controls) | Homozygous | Heterozygous | Recessive | Dominant | Allele comparison |
|-----------|---------------|-----------------------------|------------|--------------|-----------|----------|------------------|
|           |               |                             | OR (95% CI) | p<sub>het</sub> | OR (95% CI) | p<sub>het</sub> | OR (95% CI) | p<sub>het</sub> | OR (95% CI) | p<sub>het</sub> |
| Esophageal| 3             | 558/873                     | 1.23 (0.90-1.67) | 0.940 | 1.02 (0.82-1.27) | 0.741 | 1.21 (0.91-1.61) | 0.966 | 1.07 (0.87-1.31) | 0.763 | 1.09 (0.94-1.27) | 0.852 |
| Lung      | 2             | 484/541                     | 2.66 (1.84-3.84) | 0.569 | 1.18 (0.90-1.56) | 0.560 | 2.40 (1.71-3.37) | 0.399 | 1.49 (1.16-1.92) | 0.633 | 1.59 (1.33-1.91) | 0.920 |
| Oral      | 2             | 425/412                     | 1.58 (1.01-2.46) | 0.464 | 1.77 (0.58-5.37) | 0.001 | 1.35 (0.89-2.06) | 0.583 | 1.80 (0.67-4.82) | 0.002 | 1.38 (0.94-2.02) | 0.080 |
| AML       | 2             | 282/465                     | 0.87 (0.22-3.48) | 0.006 | 0.80 (0.32-2.01) | 0.007 | 0.98 (0.38-2.53) | 0.046 | 0.82 (0.29-2.34) | 0.001 | 0.88 (0.38-2.03) | <0.001 |
| Others    | 10            | 2,078/2,773                 | 1.08 (0.76-1.53) | <0.001 | 0.91 (0.76-1.09) | 0.047 | 1.14 (0.79-1.65) | <0.001 | 0.95 (0.82-1.11) | 0.117 | 1.10 (0.87-1.18) | 0.001 |
| Source of control | | | | | | | | | | | | |
| PB        | 10            | 1,502/1,872                 | 1.24 (0.93-1.65) | 0.035 | 0.96 (0.79-1.16) | 0.035 | 1.31 (0.92-1.86) | <0.001 | 1.01 (0.88-1.16) | 0.248 | 1.08 (0.95-1.24) | 0.031 |
| HB        | 23            | 5,215/6,678                 | 1.17 (0.94-1.44) | <0.001 | 1.08 (0.95-1.22) | 0.001 | 1.12 (0.95-1.33) | <0.001 | 1.10 (0.96-1.27) | <0.001 | 1.08 (0.97-1.20) | <0.001 |
| Score | | | | | | | | | | | | |
| Low       | 16            | 3,039/4,160                 | 1.21 (0.89-1.64) | <0.001 | 1.07 (0.89-1.29) | <0.001 | 1.18 (0.92-1.51) | <0.001 | 1.11 (0.91-1.36) | <0.001 | 1.10 (0.94-1.29) | <0.001 |
| High      | 17            | 3,678/4,390                 | 1.17 (0.98-1.39) | 0.075 | 1.01 (0.89-1.13) | 0.097 | 1.16 (0.95-1.42) | 0.001 | 1.03 (0.94-1.12) | 0.409 | 1.05 (0.97-1.14) | 0.089 |
| -592A/C   |               |                             | CC vs.AA | 0.047 | AC vs.AA | 0.047 | CC vs.(AA+AC) | 0.047 | (AC+CC) vs.AA | 0.047 | C vs.A | 0.047 |
| All       | 42            | 9,934/13,169                | 1.13 (1.00-1.28) | 0.001 | 1.04 (0.96-1.13) | 0.001 | 1.10 (0.99-1.13) | 0.035 | 1.06 (0.97-1.15) | <0.001 | 1.05 (0.99-1.12) | <0.001 |
| Cancer type |            |                             | | | | | | | | | | | |
| Gastric   | 11            | 2,324/2,775                 | 1.18 (0.96-1.44) | 0.289 | 1.08 (0.94-1.23) | 0.200 | 1.11 (0.94-1.32) | 0.562 | 1.10 (0.95-1.27) | 0.093 | 1.08 (0.97-1.21) | 0.080 |
| HCC       | 5             | 1,859/2,109                 | 1.20 (0.82-1.75) | 0.032 | 1.09 (0.94-1.27) | 0.650 | 1.10 (0.80-1.50) | 0.039 | 1.09 (0.94-1.27) | 0.373 | 1.08 (0.93-1.24) | 0.094 |
| Esophageal| 4             | 900/1,243                   | 1.18 (0.90-1.54) | 0.637 | 1.13 (0.93-1.36) | 0.399 | 1.11 (0.88-1.39) | 0.498 | 1.15 (0.96-1.37) | 0.582 | 1.10 (0.97-1.25) | 0.702 |
| Lung      | 4             | 958/1,377                   | 1.64 (1.19-2.24) | 0.301 | 1.17 (0.94-1.45) | 0.285 | 1.52 (1.20-1.93) | 0.402 | 1.27 (1.01-1.60) | 0.198 | 1.27 (1.06-1.52) | 0.149 |
| Cervical  | 3             | 338/388                     | 0.89 (0.35-2.24) | 0.031 | 0.91 (0.67-1.25) | 0.431 | 0.94 (0.41-2.19) | 0.042 | 0.89 (0.60-1.32) | 0.174 | 0.91 (0.60-1.38) | 0.034 |

(Continued)
the random-effect model was used to generate wider CIs. Sensitivity analysis was conducted and the results indicated that each individual study did not influence the pooled ORs obviously (data not shown).

**Publication bias**

The funnel plot was symmetric for the -1082A/G (Figure 3), -819T/C and -592A/C polymorphisms, indicating no presence of publication bias, which was further supported by the Egger’s test for the -1082A/G polymorphism (homozygous: $P = 0.428$; heterozygous: $P = 0.395$; recessive: $P = 0.168$; dominant: $P = 0.223$ and allele comparison: $P = 0.179$), -819T/C polymorphism (homozygous: $P = 0.589$; heterozygous: $P = 0.777$; recessive: $P = 0.616$; dominant: $P = 0.797$ and allele comparison: $P = 0.576$), and -592A/C polymorphism (homozygous: $P = 0.727$; heterozygous: $P = 0.763$; recessive: $P = 0.748$; dominant: $P = 0.474$ and allele comparison: $P = 0.677$).

**False-positive report probability (FPRP) test analysis**

The significant findings were assessed using the FPRP test and the results are shown in Table 3. With a prior probability of 0.1, assuming that the OR for a specific genotype was 0.67/1.50 (protection/risk), with statistical power of 0.857, the FPRP value was 0.179 for the -1082A/G polymorphism and cancer risk under the dominant model, and a positive association was also found for low quality studies (dominant: FPRP = 0.053 and allele comparison: FPRP = 0.129). As regards the -819T/C polymorphism, a positive association was found

| Variables | No. of studies | Sample size (case/controls) | Homozygous | Heterozygous | Recessive | Dominant | Allele comparison |
|-----------|----------------|-----------------------------|------------|-------------|-----------|-----------|------------------|
| NPC       | 2              | 374/732                     | 1.19 (0.62-2.31) | 0.116 | 0.95 (0.72-1.25) | 0.697 | 1.22 (0.66-2.25) | 0.125 | 0.99 (0.77-1.29) | 0.346 | 1.05 (0.78-1.42) | 0.129 |
| Oral      | 2              | 425/412                     | 1.58 (1.01-2.46) | 0.464 | 1.77 (0.58-5.37) | 0.001 | 1.35 (0.89-2.06) | 0.583 | 1.80 (0.67-4.82) | 0.002 | 1.38 (0.94-2.02) | 0.080 |
| AML       | 2              | 282/465                     | 0.84 (0.23-3.05) | 0.011 | 0.79 (0.33-1.90) | 0.010 | 0.95 (0.40-2.27) | 0.064 | 0.80 (0.30-2.16) | 0.002 | 0.86 (0.39-1.88) | 0.001 |
| Colorectal | 2             | 673/673                     | 0.58 (0.40-0.85) | 0.694 | 0.66 (0.53-0.83) | 0.882 | 0.70 (0.49-1.01) | 0.599 | 0.65 (0.52-0.80) | 0.994 | 0.72 (0.61-0.85) | 0.750 |
| Others    | 7              | 1,801/2,995                 | 0.98 (0.77-1.24) | 0.313 | 1.01 (0.86-1.17) | 0.246 | 0.98 (0.80-1.21) | 0.437 | 1.00 (0.86-1.16) | 0.185 | 0.99 (0.88-1.11) | 0.187 |
| Source of control | | | | | | | | | | | | |
| PB        | 11             | 2,203/2,780                 | 1.08 (0.82-1.43) | 0.011 | 0.96 (0.82-1.13) | 0.056 | 1.08 (0.89-1.33) | 0.117 | 0.99 (0.82-1.18) | 0.004 | 1.01 (0.87-1.16) | 0.001 |
| HB        | 31             | 7,731/10,389                | 1.14 (0.99-1.31) | 0.009 | 1.07 (0.97-1.17) | 0.004 | 1.10 (0.98-1.24) | 0.054 | 1.09 (0.99-1.20) | <0.001 | 1.07 (1.00-1.15) | <0.001 |
| Score     | | | | | | | | | | | | |
| Low       | 21             | 4,240/6,041                 | 1.23 (1.02-1.49) | 0.012 | 1.03 (0.90-1.19) | <0.001 | 1.21 (1.05-1.40) | 0.193 | 1.08 (0.93-1.25) | <0.001 | 1.09 (0.98-1.21) | <0.001 |
| High      | 21             | 5,694/7,128                 | 1.05 (0.89-1.23) | 0.023 | 1.05 (0.96-1.15) | 0.161 | 1.02 (0.89-1.16) | 0.100 | 1.05 (0.95-1.15) | 0.033 | 1.03 (0.95-1.11) | 0.007 |

Het: heterogeneity; NA: not applicable; HCC: hepatocellular carcinoma; NPC: nasopharyngeal carcinoma; AML: acute myeloid leukemia; PB: population based; HB: hospital based.

* Lung cancer was only calculated for the dominant model.
for lung cancer (homozygous: FPRP = 0.001; recessive: FPRP = 0.001; dominant: FPRP = 0.034 and allele comparison: FPRP < 0.001). As regards the -592A/C polymorphism, noteworthy findings were observed for lung cancer (homozygous: FPRP = 0.055; recessive: FPRP = 0.011 and allele comparison: FPRP = 0.078), colorectal cancer (homozygous: FPRP = 0.165; heterozygous: FPRP = 0.007; dominant: FPRP = 0.001 and allele comparison: FPRP = 0.001) and low quality studies (recessive: FPRP = 0.086). However, greater FPRP values were observed for other significant findings, which need validation in further studies.

**DISCUSSION**

In this meta-analysis, we comprehensively investigated the associations between three promoter variants (-1082A/G, -819T/C and -592A/C) in *IL-10* gene and cancer risk in the Chinese population through 53 articles. The results revealed that all the three *IL-10* gene polymorphisms we considered were associated with an increased overall cancer risk. Stratification analysis showed that the association between the -1082A/G polymorphism and cancer risk was more evident for hepatocellular carcinoma and low quality studies, the association between the -819T/C polymorphism and cancer risk was more obvious for lung cancer and oral cancer. However, the -592A/C polymorphism showed a statistically significant increased risk for lung cancer, oral cancer, hospital-based studies and low quality studies, but a decreased risk for colorectal cancer. To our knowledge, this is so far the first meta-analysis that has assessed multiple promoter polymorphisms in *IL-10* gene with cancer risk in the Chinese population.

Three meta-analyses including international studies have investigated the association of *IL-10* -1082A/G, -819T/C and -592A/C polymorphisms with overall cancer susceptibility. The study carried out by Wang et al. [92] analyzed *IL-10* -1082A/G polymorphism, consisting 61 international studies with a total of 14,499 cases and

**Figure 2:** Forest plot for overall cancer risk associated with the *IL-10* -1082A/G polymorphism by a dominant model. For each study, the estimated OR and its 95% CI are plotted with a box and a horizontal line. ◊, pooled ORs and its 95% CIs.
16,967 controls, in which no significant association was found between this polymorphism and overall cancer risk. Another meta-analysis [93] including 15,942 cases and 22,336 controls investigated IL-10 -819C/T polymorphism and cancer risk, without finding any significant association between this polymorphism and overall cancer risk. The study carried out by Ding et al. [94] considered IL-10 -592C/A polymorphism, in which a decreased risk of overall cancer was found with the AA genotype. Other meta-analyses with international studies have assessed the association between polymorphisms in IL-10 gene and susceptibility to some types of cancer. For example, two studies [95, 96] revealed no significant association between IL-10 -1082A/G, -819T/C and -592A/C polymorphisms with non-Hodgkin lymphoma susceptibility. Some of the significant associations found in the previous studies were not validated in our meta-analysis, for example, IL-10 -1082A/G polymorphism was associated with an increased lung cancer risk [92]. We also found some significant associations that were not observed in previous analyses. For instance, we found that IL-10 -592A/C polymorphism was associated with a decreased colorectal cancer risk. The discrepancy occurred because our analysis was carried out only in the Chinese population, suggesting that the polymorphisms on cancer risk might vary among different study subjects’ ethnicity or lifestyle factors.

To make our significant findings more noteworthy, FPRP analysis was performed. Interestingly, FPRP test results revealed that only the association between IL-10 -1082A/G polymorphism and overall cancer risk remained significant at the prior probability level of 0.1. In the subgroup analysis, only the low quality studies, lung cancer and colorectal cancer remained significant. Other findings were false-positive, which might be due to the limited sample size.

Our present meta-analysis has some highlights. First, it identified the significant association between IL-10 -1082A/G, -819T/C and -592A/C polymorphisms and an increased overall cancer risk in the Chinese population. Second, the quality of each included study was evaluated by the quality score criteria. Third, no publication bias was detected in the study, indicating the robustness of the results. Finally, the significant findings were further validated using the FPRP test, making the results more authentic. However, some possible limitations should be considered. First, the total sample size in each individual study was less than 1000 in all but four studies [69, 82, 85, 86], which might reflect a difficulty to evaluate the real association. Second, our results were based on unadjusted estimates, which might cause confounding bias. Third, in the subgroup analysis by cancer type, only two studies were included for some types of cancer, which might affect the detection of the real association. Finally, the potential gene-gene, and gene-environment interactions were not assessed due to the lack of information in the original studies.

Figure 3: Begg’s funnel plot for the IL-10 -1082A/G polymorphism and overall cancer risk by a dominant model.
Table 3: False-positive report probability values for associations between cancer risk and *IL-10* polymorphisms

| Genotype              | Crude OR (95% CI) | P-value* | Statistical power* | Prior probability | 0.25 | 0.1 | 0.01 | 0.001 | 0.0001 |
|-----------------------|-------------------|----------|--------------------|-------------------|------|-----|------|-------|--------|
| -1082A/G              |                   |          |                    |                   |      |     |      |       |        |
| All                   |                   |          |                    |                   |      |     |      |       |        |
| Dominant              | 1.32 (1.04-1.67)  | 0.021    | 0.857              | 0.068             | 0.179| 0.705| 0.960| 0.996 |
| Cancer type-          |                   |          |                    |                   |      |     |      |       |        |
| HCC                   |                   |          |                    |                   |      |     |      |       |        |
| Heterozygous          | 1.40 (1.01-1.94)  | 0.043    | 0.661              | 0.164             | 0.371| 0.866| 0.985| 0.998 |
| Dominant              | 1.43 (1.04-1.95)  | 0.024    | 0.619              | 0.103             | 0.257| 0.792| 0.975| 0.997 |
| Allele comparison     | 1.35 (1.04-1.75)  | 0.023    | 0.787              | 0.082             | 0.211| 0.747| 0.967| 0.997 |
| Quality score-        |                   |          |                    |                   |      |     |      |       |        |
| low                   |                   |          |                    |                   |      |     |      |       |        |
| Heterozygous          | 1.42 (1.05-1.91)  | 0.020    | 0.641              | 0.087             | 0.223| 0.759| 0.970| 0.997 |
| Dominant              | 1.56 (1.17-2.08)  | 0.002    | 0.395              | 0.018             | 0.053| 0.380| 0.861| 0.984 |
| Allele comparison     | 1.43 (1.08-1.88)  | 0.010    | 0.634              | 0.047             | 0.129| 0.619| 0.942| 0.994 |
| -819T/C               |                   |          |                    |                   |      |     |      |       |        |
| All                   |                   |          |                    |                   |      |     |      |       |        |
| Homozygous            | 1.19 (1.00-1.41)  | 0.044    | 0.996              | 0.118             | 0.286| 0.815| 0.978| 0.998 |
| Recessive             | 1.17 (1.00-1.36)  | 0.041    | 0.999              | 0.109             | 0.269| 0.802| 0.976| 0.998 |
| Allele comparison     | 1.08 (1.00-1.18)  | 0.088    | 1.000              | 0.210             | 0.443| 0.898| 0.989| 0.999 |
| Cancer type-          |                   |          |                    |                   |      |     |      |       |        |
| lung cancer           |                   |          |                    |                   |      |     |      |       |        |
| Homozygous            | 2.66 (1.84-3.84)  | <0.001   | 0.001              | <0.001            | 0.001| 0.015| 0.137| 0.613 |
| Recessive             | 2.40 (1.71-3.37)  | <0.001   | 0.003              | <0.001            | 0.001| 0.013| 0.114| 0.564 |
| Dominant              | 1.49 (1.16-1.92)  | 0.002    | 0.521              | 0.012             | 0.034| 0.281| 0.797| 0.975 |
| Allele comparison     | 1.59 (1.33-1.91)  | <0.001   | 0.267              | <0.001            | <0.001| 0.003| 0.026|        |
| Cancer type-          |                   |          |                    |                   |      |     |      |       |        |
| oral cancer           |                   |          |                    |                   |      |     |      |       |        |
| Homozygous            | 1.58 (1.01-2.46)  | 0.043    | 0.409              | 0.239             | 0.485| 0.912| 0.991| 0.999 |
| -592A/C               |                   |          |                    |                   |      |     |      |       |        |
| All                   |                   |          |                    |                   |      |     |      |       |        |
| Homozygous            | 1.13 (1.00-1.28)  | 0.055    | 1.000              | 0.141             | 0.330| 0.844| 0.982| 0.998 |
| Cancer type-          |                   |          |                    |                   |      |     |      |       |        |
| lung cancer           |                   |          |                    |                   |      |     |      |       |        |
| Homozygous            | 1.64 (1.19-2.24)  | 0.002    | 0.287              | 0.019             | 0.055| 0.392| 0.867| 0.985 |
| Recessive             | 1.52 (1.20-1.93)  | 0.001    | 0.457              | 0.004             | 0.011| 0.113| 0.563| 0.928 |
| Dominant              | 1.27 (1.01-1.60)  | 0.043    | 0.921              | 0.122             | 0.294| 0.821| 0.979| 0.998 |
| Allele comparison     | 1.27 (1.06-1.52)  | 0.009    | 0.965              | 0.028             | 0.078| 0.484| 0.904| 0.990 |

(Continued)
In conclusion, this meta-analysis suggested an association between IL-10 gene polymorphisms and cancer risk in the Chinese population, especially for lung cancer, colorectal cancer and low quality studies. Well-designed studies with large sample size are required to verify our findings.

**MATERIALS AND METHODS**

**Search strategy**

A systematic literature search was conducted in PubMed, Embase, CNKI and Wanfang database using the following MeSH terms and their synonyms: (“interleukin-10” or “interleukin 10” or “IL-10” or “IL 10”) AND (“polymorphism, single nucleotide” [MeSH] or “SNP” or “single nucleotide polymorphism” or “polymorphism” or “variant” or “variation”) AND (“neoplasms” [MeSH] or “neoplasia” or “neoplasm” or “tumor” or “malignancy” or “cancer”), up to 19 January, 2017. In addition, review articles and references of the selected articles were manually searched to identify additional relevant articles. Only the most recent publications or the ones with most participants were included in the final meta-analysis in cases of overlapping data.

| Genotype                  | Crude OR (95% CI) | P-value* | Statistical power* | Prior probability |
|---------------------------|-------------------|----------|--------------------|-------------------|
|                           |                   |          |                    | 0.25  | 0.1   | 0.01  | 0.001 | 0.0001 |
| Cancer type-              |                   |          |                    |       |       |       |       |        |
| oral cancer               |                   |          |                    |       |       |       |       |        |
| Homozygous                | 1.58 (1.01-2.46)  | 0.043    | 0.409              | 0.239 | 0.485 | 0.912 | 0.991 | 0.999  |
| Cancer type-              |                   |          |                    |       |       |       |       |        |
| colorectal cancer         |                   |          |                    |       |       |       |       |        |
| Homozygous                | 0.58 (0.40-0.85)  | 0.005    | 0.238              | 0.062 | 0.165 | 0.685 | 0.956 | 0.995  |
| Heterozygous              | 0.66 (0.53-0.83)  | <0.001   | 0.466              | 0.002 | 0.007 | 0.075 | 0.449 | 0.891  |
| Dominant                  | 0.65 (0.52-0.80)  | <0.001   | 0.406              | <0.001| 0.001 | 0.012 | 0.105 | 0.541  |
| Allele comparison         | 0.72 (0.61-0.85)  | <0.001   | 0.818              | <0.001| 0.001 | 0.013 | 0.113 | 0.562  |
| Control source-           |                   |          |                    |       |       |       |       |        |
| HB                        |                   |          |                    |       |       |       |       |        |
| Allele comparison         | 1.07 (1.00-1.15)  | 0.066    | 1.000              | 0.165 | 0.372 | 0.867 | 0.985 | 0.998  |
| Quality score-            |                   |          |                    |       |       |       |       |        |
| low                       |                   |          |                    |       |       |       |       |        |
| Homozygous                | 1.23 (1.02-1.49)  | 0.034    | 0.979              | 0.095 | 0.240 | 0.777 | 0.972 | 0.997  |
| Recessive                 | 1.21 (1.05-1.40)  | 0.010    | 0.998              | 0.030 | 0.086 | 0.508 | 0.913 | 0.991  |

HCC: hepatocellular carcinoma; HB: hospital based.

*Chi-square test was used to calculate the genotype frequency distributions.

*Statistical power was calculated using the number of observations in the subgroup and the OR and P values in this table.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) studies investigating the association between IL-10 -1082A/G, -819T/C and -592A/C polymorphisms with cancer risk in Chinese populations; (2) case-control studies; (3) studies providing sufficient data for calculation of ORs and 95% CIs. Studies were excluded if any of the following aspects existed: (1) not a case-control study; (2) duplicate publications; (3) studies without available genotype data; (4) review articles, meta-analyses, conference abstracts or editorial articles; and (5) genotype frequencies in the controls departure from HWE.

Data extraction

Two investigators independently extracted the relevant data from all included studies based on the inclusion criteria listed above. Disagreement was resolved by discussion with a third investigator. The following information was extracted from each included study: first author’s surname, publication year, cancer type, control source (hospital-based or population-based), genotyping methods, and number of cases and controls with different genotypes.
Quality assessment

Two independent investigators assessed the qualities of all included studies according to the criteria from a previous meta-analysis [97]. Quality scores of studies ranged from 0 (lowest) to 15 (highest), and the studies with scores > 9 were considered of high quality.

Statistical analysis

The strength of association between IL-10 -1082A/G, -819T/C and -592A/C polymorphisms and cancer risk was assessed by calculating the ORs and the corresponding 95% CIs. The pooled ORs were calculated for the homozygous model, heterozygous model, recessive model, dominant model and an allele comparison. The between-study heterogeneity was quantified by chi-square based Q test and the fixed-effects model (the Mantel-Haenszel method) [98] was used when no significant heterogeneity was observed (P > 0.1); otherwise, the random-effects model (the DerSimonian and Laird method) [99] was adopted. Subgroup analysis was performed by cancer type (if one cancer type contained less than two studies, it was merged into the “other cancers” group), control source (hospital-based studies and population-based studies), and quality scores (≤ 9 and > 9). Sensitivity analysis was performed to assess results stability. Publication bias was examined using Begg’s funnel plot and Egger’s linear regression test.

The FPRP was calculated to examine the significant associations found in the present meta-analysis. FPRP was calculated with 0.2 as a FPRP threshold and a prior probability of 0.1 was assigned to detect an OR of 0.67/1.50 (protective/risk effects) for an association with the genotypes under investigation [100]. FPRP values below threshold 0.2 were considered as noteworthy associations. All the statistical tests were performed using STATA version 12.0 (Stata Corporation, College Station, TX). All the P values were two-sided, and P < 0.05 were considered statistically significant.

Author contributions

Ping Wang, Junling An and Yanfeng Zhu performed the research study and collected the data; Ping Wang, Xuedong Wan and Hongzhen Zhang analyzed the data; Shoumin Xi and Sanqiang Li designed the research study; Ping Wang wrote the paper. All authors read and approve the final manuscript.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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