Research Article

An updated meta-analysis of the association between fibroblast growth factor receptor 4 polymorphisms and susceptibility to cancer

Abdolkarim Moazeni-Roodi1,2, Sahel Sarabandi3, Shima Karami3, Mohammad Hashemi3,4,* and Saeid Ghavami5,6

1Tropical and Communicable Diseases Research Centre, Iranshahr University of Medical Sciences, Iranshahr, Iran; 2Department of Clinical Biochemistry, Iranshahr University of Medical Sciences, Iranshahr, Iran; 3Department of Clinical Biochemistry, School of Medicine, Zahedan University of Medical Sciences, Zahedan, Iran; 4Genetics of Non-Communicable Disease Research Center, Zahedan University of Medical Sciences, Zahedan, Iran; 5Department of Human Anatomy and Cell Science, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, MB, Canada; 6Research Institute in Oncology and Hematology, CancerCare Manitoba, University of Manitoba, Winnipeg, Canada

Correspondence: Saeid Ghavami (saeid.ghavami@umanitoba.ca)

Fibroblast growth factor receptor 4 (FGFR4) is a cell surface receptor tyrosine kinases (RTKs) for FGFs. Several studies have focused on the association between FGFR4 polymorphisms and cancer development. This meta-analysis aimed to estimate the association between FGFR4 rs351855 (Gly388Arg), rs1966265 (Val10Ile), rs7708357, rs2011077, and rs376618 polymorphisms and cancer risk. Eligible studies were identified from electronic databases. All statistical analyses were achieved with the STATA 14.0 software. Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were used to quantitatively estimate the association. Overall, no significant association was found among rs351855, rs2011077, and rs376618 polymorphisms with the risk of overall cancer. The rs1966265 polymorphism significantly decreased the risk of cancer in recessive (OR = 0.87, 95% CI = 0.78–0.97, P = 0.009, TT vs CT+CC) genetic model. Whereas the rs7708357 polymorphism was positively associated with cancer risk in dominant (OR = 1.17, 95% CI = 1.02–1.36, P = 0.028) genetic model. Stratified analysis revealed that rs351855 variant significantly increased the risk of prostate cancer in heterozygous (OR = 1.16, 95% CI = 1.02–1.32, P = 0.025 AG vs GG), dominant (OR = 1.20, 95% CI = 1.06–1.35, P = 0.004, AG+AA vs GG), and allele (OR = 1.22, 95% CI = 1.06–1.41, P = 0.005, A vs G) genetic models.

In summary, the findings of this meta-analysis indicate that rs1966265, rs7708357, and rs351855 polymorphisms are correlated to cancer development. Further well-designed studies are necessary to draw more precise conclusions.

Introduction

Cancer poses a major health problem in both developing and developed countries [1–3]. There were approximately 18.1 million new cases and 9.6 million cancer deaths in 2018 [4]. The exact mechanism of cancer development is not clear yet. Mounting evidence have indicated that cancer development and progression is influenced by environmental and genetic factors [3,5–7].

The human fibroblast growth factor receptors (FGFRs), a subfamily of cell surface receptor tyrosine kinases (RTKs), consist of four closely related family members (FGFR1–4) [8]. FGFR activation by various fibroblast growth factors (FGFs) triggers a cascade that leads to the activation of multiple signal transduction pathways, including the Ras/Raf/MapK, PI3K/Akt, STAT, and PLCγ, which can promote cell survival,
cell proliferation, tissue development, differentiation, angiogenesis, epithelial-to-mesenchymal transition (EMT), angiogenesis, and can thereby involve in carcinogenesis [9–11].

The human FGFR4 gene, also termed as cluster of differentiation 334 (CD334), is mapped to chromosome 5 (5q 35.1) [12] and is highly polymorphic. A common nonsynonymous single nucleotide polymorphism (SNP) at codon 388 (rs351855 G>A) in exon 9, which results in a change of glycine to arginine (Gly388Arg), was recognized in the transmembrane domain of the FGFR4 receptor [13]. Several studies investigated the relationship between FGFR4 gene rs351855 G>A polymorphism and numerous types of cancer including breast cancer [13–18], cervical cancer [19–21], colon cancer [13,18,22], gastric cancer [23], prostate cancer [24–27], head and neck squamous cell carcinoma (HNSCC) [28,29], oral squamous cell carcinoma (OSCC) [30,31], lung cancer [32–34], hepatocellular carcinoma [35–37], sarcoma [38], skin cancer [39], neuroblastoma [40], non-Hodgkin’s lymphoma [41], and glioma [42]. There are few direct reports about the effect of FGFR4 polymorphism on the gene expression. FGFR4 rs351855 polymorphism induced higher expression of FGFR4 protein and worse prognosis in breast cancer [43]. It has been reported that the rate of degradation of the Arg388 receptor was slower than the Gly388 receptor in neuroblastoma cells and also initiated internalization of the receptor into multivesicular structures (Rev1-1) [40]. In another investigation, the researchers showed that expression of the FGFR4 Arg388 protein activated the extracellular signal-related kinase pathway with subsequent expression of several genes which were associated with the aggressive form of prostate cancer [44], (Rev1-1). Researchers have reported that there was no significant difference between different genotypes of FGFR4 in gastric cancer [45]. Interestingly in the lung normal tissue, genotype-dependent transcriptional profile is present [46]. In the past few years, there were few epidemiological analysis and meta-analysis focusing on FGFR4 in uterine leiomyomata [47], hip bone geometry [48–50], and all types of cancer [31,51]. Our current meta-analysis covers Gly388Arg rs351855 G>A and Val10Ile rs1966265 polymorphism in FGFR4 polymorphisms to cancer susceptibility and provide wider information in this important regulator of cancers (Rev 1-2).

Methods

Literature search and inclusion criteria

We performed a literature research for all eligible articles regarding the association between FGFR4 polymorphisms on multiple electronic databases including Web of Science, PubMed, Scopus, and Google Scholar databases through using the following terms: ‘FGFR4 OR CD334’ AND ‘polymorphism OR, SNP, OR variation OR mutation’ AND ‘cancer OR carcinoma OR neoplasm OR tumor’ up to 10 May 2020. Besides, we also screened references of the included studies. Figure 1 shows the process of studies selection. Relevant studies included the meta-analysis if they met the following inclusion criteria: (1) original case–control studies addressing the correlation between FGFR4 polymorphisms; (2) studies containing sufficient genotype data in both cases and controls; (3) the largest sample sizes were selected when repeatedly published articles by the same team. The exclusion criteria were: (1) conference abstract, case reports, reviews, duplication data; (2) insufficient genotype data provided.

Data extraction

Two investigators independently screened the literature and extracted data from eligible studies according to exclusion and inclusion criteria. The following data were collected from each study including the first author’s name, publication year, country, ethnicity of participants, cancer type, genotyping methods, the sample size, and the genotype and allele frequencies of cases and controls (Table 1).

Quality assessment

Two investigators evaluated the quality of each study using the quality assessment criteria [52]. Quality scores of studies ranged from 0 (lowest) to 15 (highest). Studies with scores \( \leq 9 \) were considered as low quality, while those with scores \( > 9 \) were considered as high quality.

Statistical analysis

Meta-analysis was carried out using STATA 14.0 software (Stata Corporation, College Station, TX, U.S.A.). The Hardy–Weinberg equilibrium (HWE) of control genotypes was determined by the chi-square test.

The strength of the association between FGFR4 polymorphisms and cancer susceptibility was evaluated by pooled odds ratios (ORs) and their 95% confidence intervals (CIs) in five (heterozygous, homozygous, dominant, recessive, and allele) genetic models. The significance of the pooled OR was assessed by the Z-test, and \( P < 0.05 \) was considered to be statistically significant. The between-study heterogeneity was evaluated by the Q statistic. When the PQ < 0.1,
| First author | Year | Country | Ethnicity | Type of cancer | Source of control | Genotyping method | Case/control | Case | Control | HWE Score | Score |
|--------------|------|---------|-----------|----------------|------------------|-------------------|--------------|-------|---------|-----------|-------|
| Ansell       | 2009 | Sweden  | Caucasian | HNSCC          | PB               | PCR-RFLP          | 110/192      | 61    | 49      | -         | -     |
| Bange        | 2002 | Russia  | Caucasian | Breast        | PB               | PCR-RFLP          | 81/123       | 55    | 60      | 8         | 170   |
| Bange        | 2002 | Germany | Caucasian | Breast        | PB               | PCR-RFLP          | 84/123       | 55    | 60      | 8         | 170   |
| Bange        | 2002 | Italy   | Caucasian | Colon cancer  | PB               | PCR-RFLP          | 82/123       | 55    | 60      | 8         | 170   |
| Batschauer   | 2011 | Brazil  | Caucasian | Breast        | PB               | PCR-RFLP          | 88/85        | 47    | 35      | 3         | 129   |
| Chen         | 2018 | Taiwan  | Asian     | Cervical cancer | HB     | TaqMan            | 226/335      | 96    | 165     | 74        | 357   |
| Chou         | 2017 | Taiwan  | Asian     | OSCC           | PB               | TaqMan            | 955/1191     | 334   | 596     | 261       | 1264  |
| Fang         | 2013 | China   | Asian     | NSCLC          | HB               | Sequencing        | 629/729      | 193   | 331     | 105        | 717   |
| FitzGerald   | 2009 | U.S.A.  | Caucasian | Prostate      | PB               | SNPlex            | 1254/1251    | 587   | 544     | 123        | 1718  |
| FitzGerald   | 2009 | U.S.A.  | African   | Prostate      | PB               | SNPlex            | 146/80       | 104   | 39      | 3         | 247   |
| Gao          | 2014 | China   | Asian     | NHL            | NA               | PCR-RFLP          | 421/486      | 117   | 189     | 115        | 423   |
| Heinze       | 2012 | Austria | Caucasian | Colon cancer  | PB               | TaqMan            | 85/1660      | 42    | 33      | 10        | 117   |
| Ho           | 2009 | Singapore | Asian     | HCC           | PB               | Sequencing        | 58/88        | 30    | 38      | 20        | 98    |
| Ho           | 2010 | U.K.    | Caucasian | Prostate      | PB               | TaqMan            | 397/291      | 183   | 182     | 32        | 548   |
| Hosseini     | 2017 | Iran    | Asian     | Breast cancer  | PB               | PCR-RFLP          | 126/160      | 87    | 33      | 6         | 207   |
| Jiang        | 2015 | China   | Asian     | Breast cancer  | NA               | Snapshot          | 747/716      | 205   | 404     | 138       | 814   |
| Li           | 2017 | China   | Asian     | Cervical cancer | HB  | PCR-RFLP          | 162/162      | 35    | 79      | 48        | 149   |
| Ma           | 2008 | Japan   | Asian     | Prostate      | HB               | PCR-RFLP          | 492/179      | 163   | 196     | 133       | 522   |
| Mawrin       | 2006 | Germany | Caucasian | Glioma        | PB               | PCR-RFLP          | 94/25        | 10    | 13      | 2         | 33    |
| Morimoto     | 2003 | Japan   | Asian     | Sarcomas      | NA               | PCR-RFLP          | 143/102      | 54    | 72      | 17        | 180   |
| Naide        | 2009 | Malaysia | Asian     | Breast        | HB               | PCR-RFLP          | 387/252      | 179   | 172     | 36        | 530   |
| Nan          | 2009 | U.S.A.  | Caucasian | Skin cancer   | PB               | Sequencing        | 768/833      | 365   | 325     | 78        | 1055  |
| Shen         | 2013 | China   | Asian     | Gastric cancer | PB               | Sequencing        | 304/982      | 118   | 124     | 62        | 360   |
| Sheu         | 2015 | China   | Asian     | HCC           | HB               | TaqMan            | 289/595      | 82    | 150     | 57        | 314   |
| Spinola      | 2005 | Italy   | Caucasian | Lung          | HB               | Pyrosequencing    | 274/401      | 148   | 104     | 22        | 400   |
| Spinola      | 2005 | Italy   | Caucasian | Breast       | HB               | Pyrosequencing    | 142/220      | 67    | 55      | 20        | 189   |
| Spinola      | 2005 | Italy   | Caucasian | CRC          | HB               | Pyrosequencing    | 179/220      | 98    | 63      | 18        | 259   |
| Tanuma       | 2010 | Japan   | Asian     | OSCC          | HB               | PCR-SSCP          | 150/100      | 69    | 53      | 28        | 191   |
| Tsay         | 2020 | Taiwan  | Asian     | Cervical cancer | HB  | TaqMan            | 428/856      | 114   | 222     | 92        | 450   |
| Ture         | 2015 | Turkey  | Asian     | Lung cancer   | HB               | PCR-RFLP          | 124/100      | 66    | 47      | 11        | 179   |
| Wang         | 2004 | U.S.A.  | Caucasian | Prostate      | PB               | PCR-RFLP          | 284/97       | 125   | 117     | 42        | 367   |
| Wang         | 2004 | U.S.A.  | African   | Prostate      | PB               | PCR-RFLP          | 45/94        | 37    | 6       | 2         | 80    |
Table 1 Characteristics of the studies eligible for meta-analysis (Continued)

| First author | Year | Country | Ethnicity | Type of cancer | Source of control | Genotyping method | Case/control | Cases | Controls | HWE Score |
|--------------|------|---------|-----------|----------------|------------------|------------------|--------------|-------|----------|-----------|
| Whittle      | 2016 | U.S.A.  | Caucasian | Neuroblastoma  | NA               | PCR-RFLP         | 126/114      | 45    | 69       | 12        | 159       | 93    | 50    | 60    | 4       | 160       | 68    | 0.006  | 9       |
| Wimmer       | 2019 | Germany | Caucasian | HNSCC         | PB               | PCR-RFLP         | 284/123      | 188   | 84       | 12        | 460       | 108   | 55    | 60    | 8       | 170       | 76    | 0.114  | 9       |
| Yang         | 2012 | China   | Asian     | HCC           | HB               | TaqMan           | 711/740      | 216   | 351      | 144       | 783       | 639   | 247   | 361   | 132      | 855       | 625   | 0.996  | 10      |
| Gly388Arg    |      |         |           |               |                  |                 | GG AG AA G A |       |          |           |       |       |      |       |          |       |        |        |
| rs351855G    |      |         |           |               |                  |                 | GG AG AA G A |       |          |           |       |       |      |       |          |       |        |        |
| Whittle      | 2016 | U.S.A.  | Caucasian | Neuroblastoma  | NA               | PCR-RFLP         | 126/114      | 61    | 105      | 61        | 227       | 227   | 91    | 168   | 76      | 350       | 320   | 0.927  | 9       |
| Wimmer       | 2019 | Germany | Caucasian | HNSCC         | PB               | PCR-RFLP         | 284/123      | 213   | 514      | 228       | 940       | 970   | 742   | 447   | 65      | 1931      | 577   | 0.827  | 15      |
| Yang         | 2012 | China   | Asian     | HCC           | HB               | TaqMan           | 711/740      | 132   | 15       | 0         | 279       | 15    | 70    | 10    | 0       | 150       | 50    | 0.551  | 13      |
| Val10Ile     |      |         |           |               |                  |                 | GG AG AA G A |       |          |           |       |       |      |       |          |       |        |        |
| rs1966265    |      |         |           |               |                  |                 | GG AG AA G A |       |          |           |       |       |      |       |          |       |        |        |
| Chen         | 2018 | Taiwan  | Asian     | Uterine Cervical | HB               | TaqMan           | 227/335      | 61    | 105      | 61        | 227       | 227   | 91    | 168   | 76      | 350       | 320   | 0.927  | 9       |
| Chou         | 2017 | Taiwan  | Asian     | OSCC          | PB               | TaqMan           | 955/1191     | 213   | 514      | 228       | 940       | 970   | 742   | 447   | 65      | 1931      | 577   | 0.827  | 15      |
| Sheu         | 2015 | China   | Asian     | HCC           | HB               | TaqMan           | 289/595      | 132   | 15       | 0         | 279       | 15    | 70    | 10    | 0       | 150       | 50    | 0.551  | 13      |
| Val10Ile     |      |         |           |               |                  |                 | GG AG AA G A |       |          |           |       |       |      |       |          |       |        |        |
| rs7708357    |      |         |           |               |                  |                 | GG AG AA G A |       |          |           |       |       |      |       |          |       |        |        |
| Chen         | 2018 | Taiwan  | Asian     | Uterine cervical | HB               | TaqMan           | 227/335      | 321   | 13       | 1         | 655       | 15    | 0.038 | 9       |
| Chou         | 2017 | Taiwan  | Asian     | OSCC          | PB               | TaqMan           | 955/1191     | 1167  | 23       | 1         | 2357      | 25    | 0.015 | 11      |
| Sheu         | 2015 | China   | Asian     | HCC           | HB               | TaqMan           | 289/595      | 577   | 18       | 0         | 1172      | 18    | 0.708 | 8       |
| Val10Ile     |      |         |           |               |                  |                 | GG AG AA G A |       |          |           |       |       |      |       |          |       |        |        |
| rs2011077    |      |         |           |               |                  |                 | GG AG AA G A |       |          |           |       |       |      |       |          |       |        |        |
| Chen         | 2018 | Taiwan  | Asian     | UT-cervical   | HB               | TaqMan           | 227/335      | 94    | 163      | 78        | 351       | 319   | 0.652 | 9       |
| Chou         | 2017 | Taiwan  | Asian     | OSCC          | PB               | TaqMan           | 955/1191     | 288   | 577      | 326       | 1153      | 1229  | 0.299 | 11      |
Table 1 Characteristics of the studies eligible for meta-analysis (Continued)

| First author | Year | Country | Ethnicity | Type of cancer | Source of control | Genotyping method | Case/control | Cases | Controls | HWE | Score |
|--------------|------|---------|-----------|----------------|------------------|-------------------|--------------|-------|----------|-----|-------|
| Ma           | 2008 | Japan   | Asian     | Prostate       | HB               | PCR-RFLP          | 492/179      | 94    | 283      |     | 0.075 |
| Sheu         | 2015 | China   | Asian     | HCC            | HB               | TaqMan            | 289/595      | 66    | 159      |     | 0.968 |
| Tsay         | 2020 | Taiwan  | Asian     | Cervical cancer| HB               | TaqMan            | 428/856      | 94    | 224      |     | 0.495 |
| FitzGerald   | 2009 | U.S.A.  | Caucasian | Prostate       | PB               | SNPlex            | 1238/1245    | 703   | 448      |     | 0.013 |
| Nan          | 2009 | U.S.A.  | Caucasian | Skin cancer    | PB               | TaqMan            | 762/830      | 451   | 273      |     | 0.026 |
indicating the presence of heterogeneity, the random-effects model was selected, otherwise, the fixed-effects model was chosen.

Publication bias was inspected by using Begg’s funnel plots and the asymmetric plots implied potential publication bias. Egger’s test was used to measure the degree of asymmetry. A $P < 0.05$ indicated significant publication bias.

Sensitivity analyses was done to evaluate whether a single study influenced the overall pooled results by omitting each study in turn.

**Results**

**Study characteristics**

A total of 57 case–control studies from 30 published articles [13–42] that met the inclusion criteria were included in our meta-analyses. Of these 57 studies, the FGFR4 rs351855 in 35 studies, rs1966265 in 8 studies, rs7708357 in 6 studies, rs2011077 in 5 studies, and rs376618 in 3 studies were analyzed, respectively. The characteristics and relevant data of the included studies are presented in Table 1.

**Meta-analysis results**

The findings did not support an association between FGFR4 rs351855 polymorphism and overall cancer susceptibility in heterozygous (OR = 0.97, 95% CI = 0.87–1.07, $P = 0.514$, AG vs GG), homozygous (OR = 1.14, 95% CI = 0.95–1.37, $P = 0.166$, AG vs GG), dominant (OR = 0.98, 95% CI = 0.87–1.10, $P = 0.686$, AG+AA vs GG), recessive (OR = 1.15, 95% CI = 0.98–1.33, $P = 0.79$, AA vs AG+GG), and allele (OR = 1.02, 95% CI = 0.93–1.12, $P = 0.663$, A vs G) genetic models (Figure 2 and Table 2). Stratified analysis was achieved by ethnicity and cancer type (Table 3 and Figure 3). The results indicated that rs351855 variant significantly increased the risk of prostate cancer in heterozygous (OR = 1.16, 95% CI = 1.02–1.32, $P = 0.025$, AG vs GG), dominant (OR = 1.20, 95% CI = 1.06–1.35, $P = 0.004$, AG+AA vs GG), and allele (OR = 1.22, 95% CI = 1.06–1.41, $P = 0.005$, A vs G) genetic models.
Figure 2. Forest plot for the association of the FGFR4 rs351855 polymorphism with overall cancer susceptibility in codominant (AG+AA vs GG)

| Study          | OR (95% CI) | Weight |
|----------------|-------------|--------|
| Ansell (2009)  | 0.59 (0.37, 0.94) | 2.59   |
| Bange (2002)   | 1.09 (0.59, 2.02)  | 1.98   |
| Bange (2002)   | 0.85 (0.49, 1.48)  | 2.22   |
| Bange (2002)   | 0.98 (0.56, 1.73)  | 2.20   |
| Batschauer (2011)| 0.92 (0.48, 1.75) | 1.89   |
| Chen (2018)    | 0.91 (0.63, 1.32)  | 3.11   |
| Chou (2017)    | 1.26 (1.04, 1.54)  | 4.03   |
| Fang (2013)    | 0.65 (0.51, 0.83)  | 3.79   |
| FitzGerald (2009)| 1.16 (0.99, 1.35) | 4.21   |
| FitzGerald (2009)| 1.21 (1.05, 1.25) | 1.97   |
| Gao (2014)     | 1.41 (1.06, 1.87)  | 3.58   |
| Heinzel (2012) | 0.96 (0.62, 1.48)  | 2.77   |
| Ho (2009)      | 0.59 (0.30, 1.17)  | 1.77   |
| Ho (2010)      | 1.24 (0.92, 1.68)  | 3.47   |
| Hosseini (2017)| 0.23 (0.14, 0.38)  | 2.46   |
| Jiang (2015)   | 1.60 (1.28, 2.00)  | 3.91   |
| Li (2017)      | 1.62 (0.98, 2.67)  | 2.46   |
| Ma (2008)      | 1.21 (0.85, 1.72)  | 3.18   |
| Mawrin (2006)  | 0.94 (0.38, 2.31)  | 1.21   |
| Minamoto (2003)| 1.02 (0.60, 1.72)  | 2.36   |
| Naidu (2009)   | 1.28 (0.93, 1.76)  | 3.39   |
| Nan (2009)     | 1.05 (0.86, 1.28)  | 4.03   |
| Shen (2013)    | 0.80 (0.59, 1.09)  | 3.42   |
| Sheu (2015)    | 0.92 (0.67, 1.26)  | 3.41   |
| Spinola (1) (2005)| 0.79 (0.58, 1.07)| 3.44   |
| Spinola (2) (2005)| 1.16 (0.76, 1.77)| 2.83   |
| Spinola (2) (2005)| 0.86 (0.58, 1.27)| 2.97   |
| Tanuma (2010)  | 0.85 (0.51, 1.42)  | 2.41   |
| Tsay (2020)    | 1.09 (0.84, 1.41)  | 3.70   |
| Ture (2015)    | 0.81 (0.58, 1.17)  | 2.34   |
| Wang (2004)    | 1.53 (0.96, 2.44)  | 2.63   |
| Wang (2004)    | 0.91 (0.36, 2.29)  | 1.17   |
| Whittle (2016) | 1.41 (0.84, 2.36)  | 2.38   |
| Wimmer (2019)  | 0.41 (0.27, 0.64)  | 2.79   |
| Yang (2012)    | 1.15 (0.92, 1.45)  | 3.91   |
| Overall (I-squared = 72.2%, p = 0.000) | 0.96 (0.87, 1.01) | 100.00 |

NOTE: Weights are from random effects analysis

Figure 3. Forest plot for the association of the FGFR4 rs351855 polymorphism with prostate cancer susceptibility (A vs G)

| Study          | OR (95% CI) | Weight |
|----------------|-------------|--------|
| FitzGerald (2009) | 1.09 (0.66, 1.76) | 38.37 |
| FitzGerald (2009) | 1.14 (0.66, 1.98) | 5.81   |
| Ho (2010)      | 1.13 (0.90, 1.43) | 21.45  |
| Ma (2008)      | 1.43 (1.12, 1.83) | 20.14  |
| Wang (2004)    | 1.67 (1.15, 2.41) | 11.43  |
| Wang (2004)    | 1.18 (0.52, 2.67) | 2.80   |
| Overall (I-squared = 33.8%, p = 0.183) | 1.22 (1.06, 1.41) | 100.00 |

NOTE: Weights are from random effects analysis
Table 2: The pooled ORs and 95% CIs for the association between FGFR4 polymorphisms and cancer susceptibility

| n     | Genetic model | Association test | Heterogeneity test | Egger’s test | Begg’s test |
|-------|---------------|------------------|-------------------|--------------|-------------|
|       |               | OR (95% CI) | Z    | P  | χ² | I² (%) | P  |               |             |
| Overall |               |             |      |    |    |      |    |              |              |
| rs351855 G>A | 35 | AG vs GG | 0.97 (0.87–1.07) | 0.65 | 0.514 | 82.87 | 60.2 | <0.0001 | 0.012 | 0.084 |
| AA vs GG | 1.14 (0.95–1.37) | 1.39 | 0.166 | 116.25 | 71.6 | <0.0001 | 0.966 | 0.975 |
| AG+AA vs GG | 0.98 (0.87–1.10) | 0.40 | 0.686 | 122.33 | 72.2 | <0.0001 | 0.061 | 0.129 |
| AA vs AG+GG | 1.15 (0.98–1.33) | 1.76 | 0.79 | 94.88 | 65.2 | <0.0001 | 0.476 | 0.306 |
| A vs G | 1.02 (0.93–1.12) | 0.47 | 0.639 | 150.59 | 78.1 | <0.0001 | 0.416 | 0.293 |
| rs1966265 C>T | 8 | CT vs CC | 1.01 (0.89–1.14) | 0.14 | 0.891 | 11.12 | 37.1 | 0.133 | 0.739 | 1.000 |
| TT vs CC | 0.94 (0.77–1.16) | 0.56 | 0.574 | 14.60 | 58.9 | 0.024 | 0.373 | 0.176 |
| CT+TT vs CC | 0.98 (0.87–1.11) | 0.31 | 0.759 | 11.52 | 39.2 | <0.0001 | 0.810 | 0.805 |
| TT vs CT+CC | 0.87 (0.78–0.97) | 2.61 | 0.009 | 14.07 | 57.3 | 0.029 | 0.094 | 0.051 |
| T vs C | 0.95 (0.87–1.04) | 1.03 | 0.303 | 14.24 | 50.8 | 0.047 | 0.722 | 0.805 |
| rs7708357 G>A | 6 | AG vs GG | 1.17 (0.95–1.44) | 1.45 | 0.146 | 5.61 | 10.9 | 0.346 | 0.221 | 0.039 |
| AA vs GG | 1.10 (0.87–1.40) | 0.83 | 0.406 | 3.61 | 0.00 | 0.607 | 0.143 | 1.000 |
| AG+AA vs GG | 1.17 (1.02–1.36) | 2.19 | 0.028 | 4.72 | 0.00 | 0.451 | 0.467 | 0.091 |
| AA vs AG+GG | 0.98 (0.79–1.21) | 0.20 | 0.840 | 3.77 | 0.00 | 0.593 | 0.097 | 0.624 |
| A vs G | 1.08 (0.99–1.20) | 1.51 | 0.132 | 4.22 | 0.00 | 0.518 | 0.964 | 0.348 |
| rs2011077 C>T | 5 | CT vs CC | 1.03 (0.79–1.33) | 0.21 | 0.831 | 11.30 | 64.6 | 0.023 | 0.054 | 0.014 |
| TT vs CC | 0.79 (0.49–1.25) | 1.02 | 0.309 | 28.54 | 86.0 | <0.0001 | 0.228 | 0.327 |
| CT+TT vs CC | 0.94 (0.69–1.28) | 0.39 | 0.695 | 17.85 | 77.6 | 0.001 | 0.091 | 0.050 |
| TT vs CT+CC | 0.79 (0.56–1.13) | 1.27 | 0.203 | 28.84 | 86.1 | <0.0001 | 0.681 | 1.000 |
| T vs C | 0.89 (0.70–1.13) | 0.97 | 0.332 | 33.89 | 88.2 | <0.0001 | 0.380 | 0.327 |
| rs376618 A>G | 3 | AG vs AA | 0.95 (0.85–1.09) | 0.56 | 0.753 | 1.76 | 0.0 | 0.414 | 0.761 | 0.602 |
| GG vs AA | 1.04 (0.81–1.33) | 0.29 | 0.771 | 4.12 | 51.5 | 0.012 | 0.067 | 0.117 |
| AG+GG vs AA | 0.97 (0.76–1.20) | 0.45 | 0.654 | 1.27 | 0.00 | 0.531 | 0.858 | 0.602 |
| GG vs AG+AA | 1.19 (0.74–1.93) | 0.71 | 0.476 | 5.04 | 60.3 | 0.080 | 0.014 | 0.117 |
| G vs A | 0.99 (0.90–1.09) | 0.20 | 0.841 | 2.21 | 9.5 | 0.331 | 0.383 | 0.602 |

For FGFR4 rs1966265 polymorphism, the findings revealed that this variant significantly reduced the risk of cancer susceptibility in recessive (OR = 0.87, 95% CI = 0.78–0.97, P = 0.009, TT vs CT+CC) model (Table 2 and Figure 4). The rs7708357 variant of FGFR4 significantly increased the risk of cancer development in dominant (OR = 1.17, 95% CI = 1.02–1.36, P = 0.028, AG+AA GG) genetic model (Table 2 and Figure 5).

The rs2011077 and rs376618 variants were not associated with overall cancer risk in any genetic models tested (Table 2).

**Heterogeneity and publication bias**

As shown in Table 2, heterogeneity among the studies was observed in all genetic comparisons for rs351855 and rs2011077. For rs1966265, heterogeneity was not found in heterozygous and dominant genetic models. While, heterogeneity was not detected in all genetic models for rs7708357 and rs376618.

The potential publication bias was evaluated using Begg’s funnel plot and Egger’s test. The shape of funnel plots was symmetrical and the Egger’s test supported no existence of publication bias in all comparison except rs351855 polymorphism in heterozygous and rs376618 polymorphism in recessive genetic model (Table 2 and Figure 6).

**Sensitivity analysis**

We performed sensitivity analysis to assess the effect of a specific publication on the overall estimate. For rs351855, the pooled ORs showed no significant change appeared when each study was neglected, one at a time, in heterozygous, dominant, and allele genetic models (Figure 7). For rs1966265, sensitivity analysis indicated no changes of results in heterozygous, homozygous, dominant, recessive, and allele genetic models. For rs7708357, no alterations of results were detected in homozygous, recessive, and allele genetic models. Thus, the final pooled results are both stable and reliable.
**Table 3** Stratified analysis of rs351855 polymorphisms by ethnicity and cancer type

|                  | n   | Genetic model       | Association test | Heterogeneity test | Egger's test | Begg's test |
|------------------|-----|---------------------|------------------|--------------------|--------------|-------------|
|                  |     |                     | OR (95% CI)      | Z                  | $\chi^2$ (%) | P           |             |
|                  |     |                     | Z                | P                  |              |             |             |
|                  |     |                     | $I^2$ (%)        |                    |              |             |             |
| Caucasian        | 15  | AG vs GG            | 0.97 (0.84–1.12) | 0.42               | 0.672        | 26.56       | 47.3        | 0.002       | 0.162       | 0.586       |
|                  |     | AA vs GG            | 1.11 (0.95–1.29) | 1.30               | 0.193        | 19.36       | 27.7        | 0.152       | 0.331       | 0.216       |
|                  |     | AG+AA vs GG         | 0.96 (0.83–1.12) | 0.47               | 0.636        | 35.15       | 57.3        | 0.002       | 0.257       | 0.471       |
|                  |     | AA vs AG+GG         | 1.09 (0.94–1.26) | 1.09               | 0.278        | 16.49       | 15.1        | 0.284       | 0.118       | 0.125       |
|                  |     | A vs G              | 1.03 (0.92–1.15) | 0.43               | 0.666        | 30.34       | 53.9        | 0.007       | 0.789       | 0.458       |
| Asian            | 17  | AG vs GG            | 0.96 (0.82–1.12) | 0.56               | 0.572        | 55.29       | 71.1        | 0.000       | 0.023       | 0.039       |
|                  |     | AA vs GG            | 1.1 (0.84–1.44)  | 0.72               | 0.470        | 94.65       | 83.1        | 0.000       | 0.636       | 0.510       |
|                  |     | AG+AA vs GG         | 0.98 (0.81–1.17) | 0.27               | 0.786        | 86.32       | 81.5        | 0.000       | 0.092       | 0.070       |
|                  |     | AA vs AG+GG         | 1.13 (0.91–1.40) | 1.12               | 0.262        | 76.08       | 79.0        | 0.000       | 0.832       | 0.458       |
|                  |     | A vs G              | 1.01 (0.87–1.16) | 0.11               | 0.913        | 119.83      | 86.6        | 0.000       | 0.352       | 0.217       |
| Breast cancer    | 7   | AG vs GG            | 0.94 (0.66–1.33) | 0.35               | 0.729        | 26.00       | 76.9        | 0.000       | 0.050       | 0.099       |
|                  |     | AA vs GG            | 1.03 (0.48–2.22) | 0.08               | 0.939        | 44.25       | 86.4        | 0.000       | 0.358       | 0.186       |
|                  |     | AG+AA vs GG         | 0.91 (0.58–1.44) | 0.40               | 0.691        | 50.88       | 88.2        | 0.000       | 0.135       | 0.099       |
|                  |     | AA vs AG+GG         | 1.05 (0.56–1.96) | 0.16               | 0.877        | 31.50       | 81.0        | 0.000       | 0.540       | 0.176       |
|                  |     | A vs G              | 0.92 (0.61–1.38) | 0.40               | 0.690        | 71.30       | 91.6        | 0.000       | 0.233       | 0.072       |
| Prostate cancer  | 6   | AG vs GG            | 1.16 (1.02–1.32) | 2.25               | 0.025        | 2.91        | 0.0        | 0.714       | 0.422       | 0.188       |
|                  |     | AA vs GG            | 1.60 (0.98–2.61) | 1.90               | 0.058        | 13.39       | 62.7        | 0.020       | 0.378       | 0.462       |
|                  |     | AG+AA vs GG         | 1.20 (1.06–1.35) | 2.89               | 0.004        | 1.87        | 0.0        | 0.892       | 0.639       | 0.851       |
|                  |     | AA vs AG+GG         | 1.56 (0.92–2.65) | 1.63               | 0.103        | 17.29       | 71.1        | 0.004       | 0.452       | 0.624       |
|                  |     | A vs G              | 1.22 (1.06–1.41) | 2.81               | 0.005        | 7.55        | 33.8        | 0.183       | 0.279       | 0.260       |
| Gastrointestinal cancer | 7 | AG vs GG            | 0.92 (0.80–1.08) | 1.17               | 0.243        | 6.73        | 10.9       | 0.346       | 0.071       | 0.090       |
|                  |     | AA vs GG            | 1.06 (0.88–1.28) | 0.63               | 0.528        | 3.72        | 0.0        | 0.715       | 0.581       | 0.881       |
|                  |     | AG+AA vs GG         | 0.95 (0.84–1.09) | 0.70               | 0.487        | 6.14        | 2.2        | 0.408       | 0.093       | 0.652       |
|                  |     | AA vs AG+GG         | 1.10 (0.94–1.30) | 1.17               | 0.241        | 2.34        | 0.0        | 0.886       | 0.824       | 0.762       |
|                  |     | A vs G              | 1.01 (0.92–1.10) | 0.16               | 0.873        | 4.97        | 0.0        | 0.627       | 0.172       | 0.230       |

Bold values denote statistical significance at the $P < 0.05$ level.

**Figure 4.** Forest plot for the association between FGFR4 rs1966265 and overall cancer risk in recessive (TT vs CT+CC) models

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Discussion

FGFs and their receptors (FGFRs) regulate numerous cellular processes including the regulation of cell proliferation, differentiation, migration, and metabolism [12]. Deregulation of FGFRs signaling have been found to play an important role in cancer development and progression as well as resistance to anticancer [53–55]. Overexpression of FGFR4 predict metastasis and poor survival outcome in various cancers [56–58]. Blocking FGFR4 significantly suppresses the cancer and indicates that FGFR4 is a potential target for the cancer treatment [59]. Polymorphisms in the FGFR4 rs351855 (Gly388Arg) polymorphism, is positioned in the transmembrane domain of the EGFR4. It has been found that Arg\textsuperscript{388} allele causes increased receptor stability and prolonged receptor activation [60].
Several reports have examined the relationship between FGFR4 gene polymorphisms and diverse cancer types [13–20,22–42]. However, the findings were inconsistent. Therefore, this updated meta-analysis including more eligible studies was performed to evaluate the impact of FGFR4 polymorphisms on cancer susceptibility. For FGFR4 rs351855 polymorphism, the findings from 34 studies including 10407 cases and 12382 controls did not support an association between this polymorphism and overall cancer susceptibility. Stratified analyses showed that this SNP significantly increased the risk of prostate cancer (n=6) in heterozygous, homozygous, dominant, and allele genetic models. The variant was not related to breast cancer as well as gastrointestinal cancer. Furthermore, the variant was not correlated with ethnicity. A meta-analysis performed by Xiong et al. [51] from 27 studies indicated a significant association between FGFR4 rs351855 polymorphism and overall cancer risk in recessive genetic model. Stratified analysis showed that rs351855 SNP significantly increased the risk of prostate cancer. A meta-analysis performed by Shu et al. [61] on 14 studies investigated the association between FGFR4 rs351855 polymorphism and various cancer risks indicated a significant association between this SNP and risk of overall cancer in all heterozygous, homozygous, dominant, recessive, and allele tested genetic models.

FGFR4 rs1966265 changes chemotherapy response in breast cancer [62], higher risk of oral squamous cell carcinoma susceptibility [31], initiation of cervical cancer (Taiwanese women) [19], and higher risk of breast cancer in Chinese women of Heilongjiang province [16]. FGFR4 rs2011077 TC+CC polymorphism is associated with higher tumor stage, tumor size, and grading in urothelial cell carcinoma [21]. FGFR4 rs2011077 with the GG genotype also increased the risk of prostate cancer in Japanese population [26].

To the best of our knowledge, for the first time, we performed pooled analysis to inspect the impact of rs1966265, rs7708357, rs2011077, and rs376618 polymorphisms and overall cancer risk.

For FGFR4 rs1966265 polymorphism, the findings revealed that this variant significantly reduced the risk of cancer susceptibility in recessive (OR = 0.87, 95% CI = 0.78–0.97, P = 0.009, TT vs CT+CC) model (Table 2 and Figure 3). Regarding rs7708357 polymorphism, the finding indicated that the rs1966265 variant significantly increased the risk of overall cancer in dominant (OR = 1.17, 95% CI = 1.02–1.36, P = 0.028, AG+AA GG) genetic model (Table 2 and Figure 4). While, the rs2011077 and rs376618 polymorphisms were not associated with cancer risk in any genetic models tested (Table 2).

Some limitations of this meta-analysis should be taken into account. First, the sample sizes of this meta-analysis were not large especially for rs1966265 (n=7 studies), rs7708357 (n=5 studies), rs2011077 (n=4 studies), and rs376618 (n=3 studies) polymorphisms as well as in stratified analyses, which may lead to reduced statistical power. Second, the strength of the association were measured by unadjusted ORs for confounding factors due to the lack

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Figure 7. Sensitivity analysis on the association between the rs351855 polymorphism and susceptibility of overall cancer in allele genetic model (A vs G)
of demographic and environmental factors, which might have affected the results. Third, publication bias may be unavoidable since we were only able to acquire data from published articles. Finally, the meta-analysis was associated with a significant heterogeneity in some polymorphisms.

The current investigation provided a source for basic medical scientist and clinician to understand the importance of FGFR4 in different types of cancers and use the results as potential biomarkers for susceptibility to cancers. It also provided a collection of previous investigation on this gene to help epidemiologist scientists for their future investigations (Rev 1-4).

In summary, this meta-analysis revealed that FGFR4 rs351855 (Gly388Arg) polymorphism might be a marker for susceptibility to prostate cancer. The rs1966265 polymorphism significantly decreased and rs1966265 polymorphism significantly increased the risk of overall cancer. No significant associations were found for the FGFR4 rs2011077 and rs376618 polymorphisms. However, these findings need to be further confirmed through large samples and different ethnic populations.

Competing Interests
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Author Contribution
Abdolkarim Moazeni-Roodi did the analysis, participated in revision and updating the manuscript. Sahel Sarabandi and Shima Karami did the literature review and helped in data analysis. Mohammad Hashemi prepared the final draft of manuscript and supervised the analysis. Saeid Ghavami prepared the final edit of manuscript, supervised the whole project and led the revision after passing away of Professor Mohammad Hashemi.

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Abbreviations
CD334, cluster of differentiation 334; CI, confidence interval; EGFR , epidermal growth factor receptor; EMT , epithelial-to-mesenchymal transition; FGF, fibroblast growth factor; FGFR, FGF receptor; HNSCC , head and neck squamous cell carcinoma; MAPK , mitogen-activated protein kinase; OR, odds ratio; PI3K , Phosphoinositide 3-kinases; PLCγ, phospholipase C gamma; RTK, receptor tyrosine kinases; SNP , single nucleotide polymorphism; STAT, signal transducer and activator of transcription.

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