EUROPEAN JOURNAL OF CANCER 46 (2010) 3332–3338

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FGFR4 transmembrane domain polymorphism and cancer risk: A meta-analysis including 8555 subjects

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ARTICLE INFO

Article history:
Received 8 March 2010
Accepted 14 June 2010
Available online 16 July 2010

Keywords:
FGFR4
Carcinoma
Genetic polymorphism
Susceptibility
Meta-analysis

ABSTRACT

Fibroblast growth factor receptor 4 (FGFR4), belonging to the receptor tyrosine kinase family, is involved in cancer initiation and progression. The *FGFR4* Gly388Arg polymorphism in the transmembrane domain of the receptor was shown to contribute to genetic susceptibility to cancer but the results were inconsistent. We performed a meta-analysis using 12 eligible case-control studies with a total of 4892 patients and 3663 controls to summarise the data on the association between the *FGFR4* Gly388Arg polymorphism and cancer risks. The overall odds ratio (OR) with a 95% confidence interval (CI) showed statistical association between the *FGFR4* Gly388Arg polymorphism and cancer risks under homozygote comparison, allele contrast and the recessive genetic model. In the subgroup analysis by ethnicity, statistically significantly increased cancer risks were found among Asians for homozygote comparison (OR = 1.43, 95% CI = 1.13–1.80, $P_{heterogeneity} = 0.24$), allele contrast (OR = 1.16, 95% CI = 1.04–1.29, $P_{heterogeneity} = 0.25$) and the recessive genetic model (OR = 1.47, 95% CI = 1.19–1.81, $P_{heterogeneity} = 0.15$). In the subgroup analysis for different tumour types, Arg^{388} allele had an effect of increasing the risks of breast (homozygote comparison OR = 1.57, 95% CI = 1.04–2.37, $P_{heterogeneity} = 0.83$ and the recessive model OR = 1.51, 95% CI = 1.02–2.24, $P_{heterogeneity} = 0.80$) and prostate cancer (Gly/Arg versus Gly/Gly: OR = 1.16, 95% CI = 1.02–1.32, $P_{heterogeneity} = 0.74$; Arg versus Gly: OR = 1.17, 95% CI = 1.07–1.29, $P_{heterogeneity} = 0.18$ and the dominant model: OR = 1.20, 95% CI = 1.06–1.35, $P_{heterogeneity} = 0.89$). Our meta-analysis suggests that the *FGFR4* Gly388Arg polymorphism most likely contributes to susceptibility to cancer, especially in Asians. Besides, the Arg^{388} allele might be associated with increased risks of breast and prostate cancer.

1. Introduction

Tumours are caused by a series of molecular changes within the complex regulatory machineries of cells. Dysregulated cell growth due to gene amplification or overexpression of the pivotal factors is one of the decisive events of malignant progression.[1] During recent years, mounting evidence has shown that specific protein tyrosine kinases (PTKs) are critically involved in diverse and important biological processes in the pathogenesis of human tumors[2] and a variety of receptor tyrosine kinases (RTKs) has emerged as major potential targets in cancer therapy.

Fibroblast growth factor receptors (FGFRs), belonging to RTK family, consist of four closely related genes (*FGFR1-4*) with a similar protein structure and are thought to be involved in critical cellular processes including cell cycle

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0959-8049/$ - see front matter
doi:10.1016/j.ejca.2010.06.017

regulation, migration, metabolism, survival and cellular proliferation and differentiation.[3] Activation of the extracellular domain of FGFRs leads to intracellular multiple signal transduction pathways including phospholipase Cγ (PLCγ), phosphatidylinositol 3-kinase (PI3K), mitogen-activated protein kinases (MAPK) and signal transducers and activators of transcription (STATs), which have been shown to be upregulated in many types of cancers and there are strong evidences linking each of these pathways to cancer initiation and progression.[3,4] FGFR4, in response to more than 20 known ligands, appears to activate MAPK weakly and yet it can promote proliferation.[5] When transfected into COS-7 cells, FGFR4 is the only FGFR that can promote membrane ruffling which is associated with changes in the actin cytoskeleton related to increased motility.[6] Therefore, FGFR4 activation may be more important in altering motility or other properties when compared with similar stimulation of other FGFRs. High expression of FGFR4 has been observed in breast cancer,[7] prostate cancer,[8] hepatocellular carcinoma,[9] pancreatic cancer,[10] renal cell carcinoma[11] and cutaneous melanoma[12] and represents a potential target for therapeutic intervention.

In the 266 single nucleotide polymorphisms (http://www.ncbi.nlm.nih.gov/SNP/index.html), a common single nucleotide polymorphism (SNP) rs351855 located in exon 9 of the *FGFR4* gene, which resulted in an amino acid change (Gly388Arg) in the transmembrane domain of the receptor,[13] has been reported to associate with the development of several types of cancer, such as those that occur in the breast,[13–17] prostate,[18–22] head and neck,[23–27] lung,[28–30] liver,[9,31] colon,[13,14] skin,[12,32] bladder[33] and soft tissue.[34] However, the observed associations of these studies were inconsistent and a single study may be too underpowered to detect a possible small effect of the polymorphism on cancer, especially when the sample size is relatively small. Hence, we performed a meta-analysis of all eligible studies to derive a more precise estimation of the association of *FGFR4* Gly388Arg SNP with cancer risks.

2. Materials and methods

2.1. Publication search

We carried out a search in Medline, Embase and Chinese National Knowledge Infrastructure (CNKI) databases, covering all the papers published between 1991 and 2010, with a combination of the following keywords: 'fibroblast growth factor receptor 4/FGFR4', 'polymorphism' and 'cancer' (last search was updated on 10 January 2010). We evaluated potentially relevant publications by examining their titles and abstracts and all the studies matching the eligible criteria were retrieved. Besides the database search, the bibliographies of the selected papers and reviews were also checked for potentially relevant publications that might be missed in the initial search.

2.2. Inclusion criteria

Studies included in the current meta-analysis had to meet all the following criteria: (a) evaluation of the *FGFR4* Gly388Arg polymorphism and cancer risks, (b) use of a case-control

Table 1 – Main characteristics of all the studies included in the meta-analysis.

Author (year)	Country	Ethnicity	Cancer type	Genotyping method	No. (cases/controls)	Case (%)			Control (%)		
						Gly/Gly	Gly/Arg	Arg/Arg	Gly/Gly	Gly/Arg	Arg/Arg
Bange 2002	Italy	European	Breast	PCR–RFLP	145/123	67(46.2)	62(42.8)	16(11.0)	55(44.7)	60(48.9)	8(6.5)
		European	Colon	PCR–RFLP	82/123	37(45.1)	38(46.3)	7(8.5)	55(44.7)	60(48.9)	8(6.5)
Morimoto 2003	Japan	Asian	Soft tissue	PCR–RFLP	143/102	54(37.8)	72(50.3)	179(11.9)	39(38.2)	50(49.0)	13(12.7)
Wang 2004	United States of America	European	Prostate	RT-PCR	284/97	125(44.0)	117(41.2)	42(14.8)	53(54.6)	40(41.2)	4(4.1)
		African-American	Prostate	RT-PCR	45/94	37(82.8)	6(13.3)	2(4.4)	76(80.9)	18(19.1)	0(0)
Spinola 2005	Italy	European	Breast	RT-PCR	142/220	67(47.2)	55(38.7)	20(14.1)	112(50.9)	83(37.7)	25(11.4)
		European	Colorectal	RT-PCR	179/220	98(54.7)	63(35.2)	18(10.1)	112(50.9)	83(37.7)	25(11.4)
Monica 2005	Italy	European	Lung	RT-PCR	274/401	148(54.0)	104(38.0)	22(8.0)	193(48.1)	168(41.9)	40(10)
Yang 2008	China	Asian	Hepatic	Taqman	715/385	217(30.3)	353(49.4)	145(20.1)	123(32.0)	195(50.6)	67(17.4)
Ma 2008	Japan	Asian	Prostate	PCR–RFLP	492/179	163(33.1)	196(39.8)	133(27.0)	67(37.4)	87(48.6)	25(14.0)
Han 2009	Germany	Asian	Hepatic	RT-PCR	57/88	27(47.4)	17(29.8)	14(24.6)	30(34.1)	38(43.2)	20(22.7)
FitzGerald 2009	USA	European	Prostate	RT-PCR	1254/1251	587(46.8)	544(43.4)	123(9.8)	631(50.4)	496(39.6)	124(9.9)
		African-American	Prostate	RT-PCR	146/80	104(71.2)	39(26.7)	3(2.05)	60(75.0)	18(22.5)	2(2.5)
Naidu 2009	Malaysia	Asian	Breast	PCR–RFLP	387/252	179(46.3)	172(44.4)	36(9.3)	132(52.4)	105(41.6)	15(6.0)
Tanuma 2010	Japan	Asian	Oral	PCR–SSCP	150/100	69(46.0)	53(38.7)	28(15.3)	42(42.0)	48(48.0)	10(10.0)
Ho 2010	United Kingdom	European	Prostate	Taqman	397/291	183(46.1)	182(45.8)	32(8.1)	150(51.5)	117(40.2)	24(8.2)

design, (c) sufficient published data for estimating an odds ratio (OR) with a 95% confidence interval (CI).

2.3. Data extraction

Data were independently abstracted in duplicate by two investigators (Xu and Li) using a standard protocol and data-collection form according to the inclusion criteria listed above. Characteristics abstracted from the studies included the name of first author, publication date, country origin, ethnicity, cancer type, characteristics of controls, genotyping methods, total number of cases and controlsand numbers of cases and controls with *FGFR4* Gly388Arg genotypes, respectively. Different ethnicity descents were categorised as European, Asian and African-American.

2.4. Statistical methods

Crude ORs with 95% CIs were used to assess the strength of the association between the *FGFR4* Gly388Arg polymorphism and cancer risks. The significance of the pooled OR was determined by the *Z*-test and $P < 0.05$ was considered as statistically significant. We first estimated cancer risks associated with *FGFR4* Gly388Arg by Gly/Arg and Arg/Arg genotypes comparing with the wild-type homozygote (Gly/Gly) and then evaluated allele contrast (Arg versus Gly) and finally estimated the risks associated with (Gly/Arg + Arg/Arg) versus Gly/Gly and Arg/Arg versus (Gly/Arg + Gly/Gly), assuming the dominant and recessive effects of the variant Arg allele, respectively. Stratification analyses were also performed by cancer types and ethnicity descents. Then we examined whether the *FGFR4* Gly388Arg polymorphism was associated with the risk of these cancers in the subgroups.

Heterogeneity assumption was checked by the chi-square-based *Q*-test.[35] A *P*-value >0.10 for the *Q*-test indicates a lack of heterogeneity among the studies, then the pooled OR estimate of each study was calculated by the fixed-effects model (the Mantel–Haenszel method).[36] Otherwise, the random-effects model (the DerSimonian and Laird method)[37] was used. Hardy–Weinberg equilibrium (HWE) in the control group was assessed via Fisher's exact test and a *P*-value <0.05 was considered significant. Publication bias was assessed by visual inspection of funnel plots in which the standard error of log (OR) of each study was plotted against its log (OR). An asymmetric plot suggests a possible publication bias. Funnel plot asymmetry was assessed by the method of Egger's linear regression test, a linear regression approach to measure funnel plot asymmetry on the natural logarithm scale of the OR. The significance of the intercept was determined by the *t*-test ($P < 0.05$ was considered representative of statistically significant publication bias).[38] All of the statistical analyses were performed with STATA 9.2 (StataCorp, College Station, TX), using two-sided *P*-values.

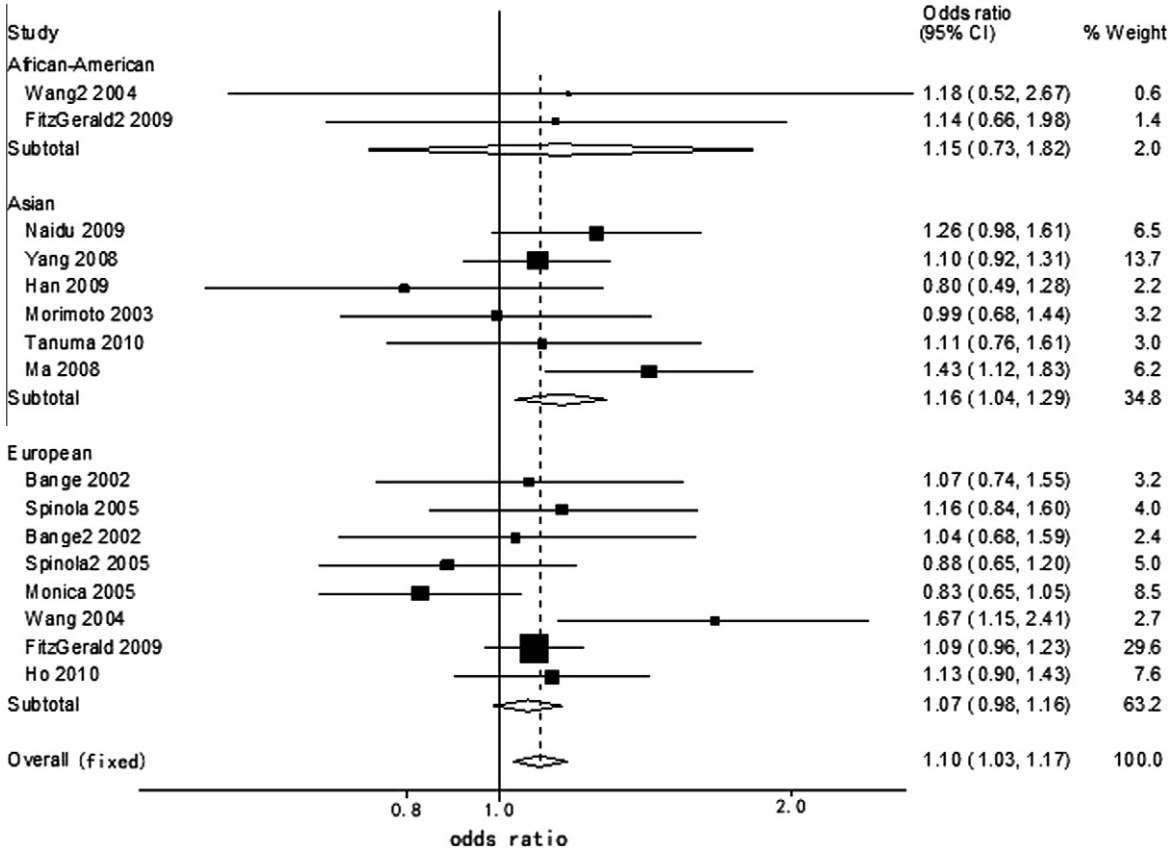

Fig. 1 – Forest plot of cancer risk associated with *FGFR4* Gly388Arg polymorphism under allele contrast (Arg versus Gly) in different ethnicity. The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the study-specific weight (inverse of the variance). The diamond represents the pooled OR and 95% CI.

3. Results

3.1. Study characteristics

There were 24 eligible studies as a result of the search and screening. During the extraction of data, 12 articles[12,15,16,18,23–26,28,29,31,32] were excluded, because they did not provide *FGFR4* polymorphism allele frequencies needed for OR calculation or their contents mainly associated with cancer prognosis and therapy, leaving 12 eligible articles[9,13,14,17,19–22,27,30,31,34] including 16 data sets based on the search criteria. Among the 12 eligible studies, four articles[13,14,19,21] which studied either two groups of populations or two types of cancers, were then viewed as two independent studies and brought into the current meta-analysis, respectively. The characteristics of selected studies are summarised in Table 1. All of the 4892 cases with different cancer types and 3663 healthy controls described Gly388Arg genotypes. There were eight subjects[13,14,19,21,22,30] of Europeans, six subjects of Asians[9,17,20,27,31,34] and two subjects[19,21] of African-Americans. The controls of all the studies mainly came from a healthy population and matched for sex and age. The distribution of genotypes in the controls was in agreement with Hardy–Weinberg equilibrium.

3.2. Meta-analysis results

The allele frequencies were calculated for controls from the corresponding genotype distributions. The Arg^{388} allele had a higher representation among the controls of Asian descent

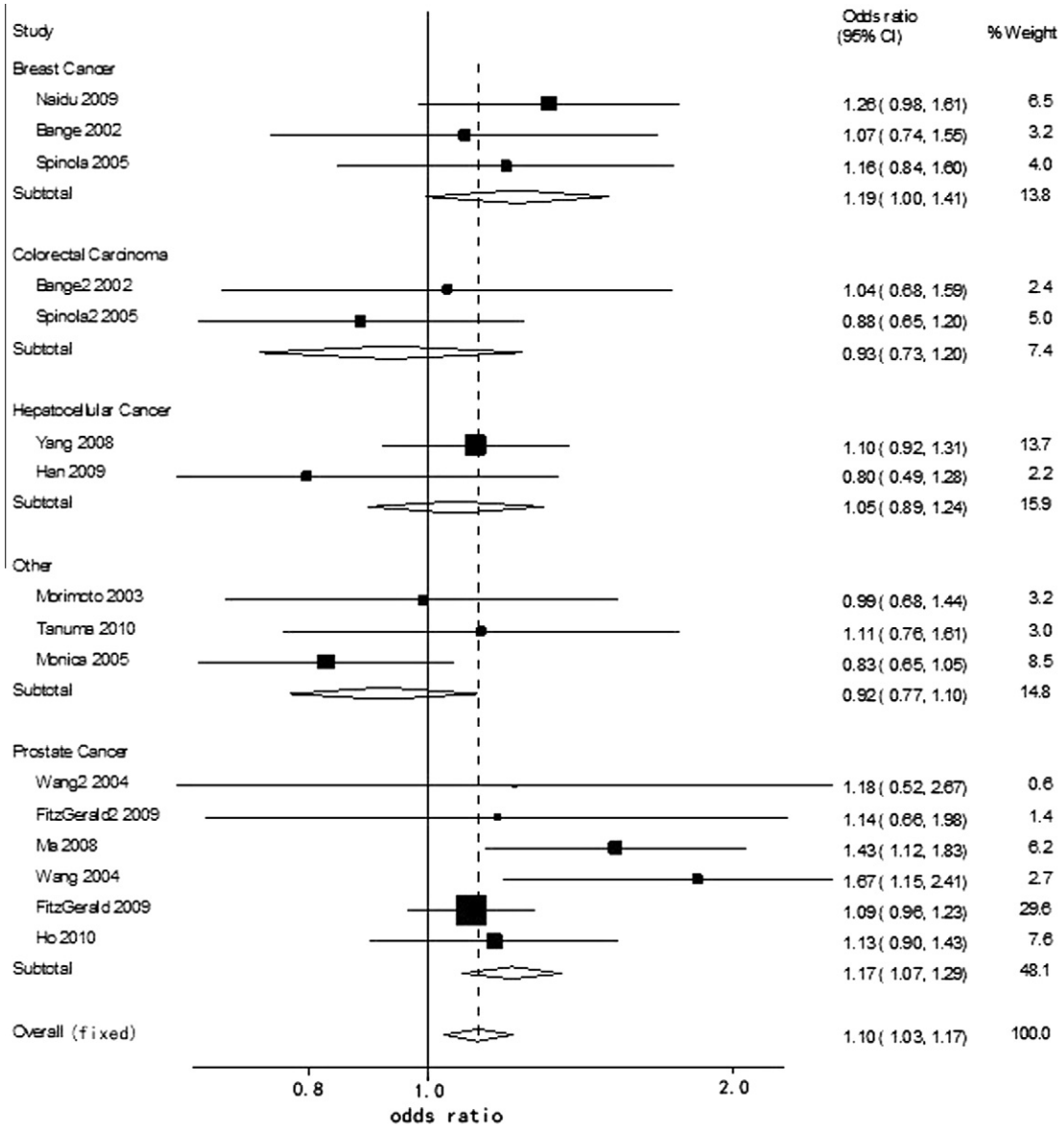

Fig. 2 – Forest plot of cancer risk associated with *FGFR4* Gly388Arg polymorphism under allele contrast (Arg versus Gly) in different types of cancers. The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the study-specific weight (inverse of the variance). The diamond represents the pooled OR and 95% CI.

(37.2%, 95% CI = 33.8–40.6) than in controls of European descent (29.5%, 95% CI = 27.3–31.7) and African-American descent (11.7%, 95% CI = 8.71–14.6).

The overall OR with its 95% CI showed statistical association between the *FGFR4* Gly388Arg polymorphism and the risks for cancers (Arg/Arg versus Gly/Gly: OR = 1.24, 95% CI = 1.07–1.43, $P_{heterogeneity}$ = 0.10; Arg versus Gly: OR = 1.10, 95% CI = 1.03–1.18, $P_{heterogeneity}$ = 0.17 and the recessive model: OR = 1.27, 95% CI = 1.04–1.56, $P_{heterogeneity}$ = 0.05). In the subgroup analysis by ethnicity, statistically and significantly increased cancer risks were found among Asians for Arg/Arg versus Gly/Gly (OR = 1.43, 95% CI = 1.13–1.80, $P_{heterogeneity}$ = 0.24), allele contrast (OR = 1.16, 95% CI = 1.04–1.29, $P_{heterogeneity}$ = 0.25, Fig. 1) and the recessive model (OR = 1.47, 95% CI = 1.19–1.81, $P_{heterogeneity}$ = 0.15). In the subgroup analysis for different tumour types, Arg^{388} allele had an effect of increasing the risk of breast (Arg/Arg versus Gly/Gly: OR = 1.57, 95% CI = 1.04–2.37, $P_{heterogeneity}$ = 0.83 and the recessive model: OR = 1.51, 95% CI = 1.02–2.24, $P_{heterogeneity}$ = 0.80) and prostate cancer (Gly/Arg versus Gly/Gly: OR = 1.16, 95% CI = 1.02–1.32, $P_{heterogeneity}$ = 0.74; Arg versus Gly: OR = 1.17, 95% CI = 1.07–1.29, $P_{heterogeneity}$ = 0.18, Fig. 2; the dominant model: OR = 1.20, 95% CI = 1.06–1.35, $P_{heterogeneity}$ = 0.89). The data are shown in Table 2.

3.3. *Bias diagnostics*

Begg's funnel plot and Egger's test were performed to assess the publication bias of the literature. The shapes of the funnel plot for the comparison of the Arg allele and the Gly allele seemed approximately symmetrical and Egger's test did not show any evidence of publication bias (*t* = 0.02, df = 15, *P* = 0.98).

4. Discussion

The human fibroblast growth factor (*FGF*) gene family consists of at least 23 different genes encoding related polypeptides.[3] These gene polymorphisms leading to alterations in the coding sequence of the encoded protein have been reported to impact upon the initiation and/or progression in a variety of human malignancies. For example, translocation and fusion of the *FGFR1* and *FGFR3* gene play important roles in development of leukaemia and multiple myeloma[4]; *FGFR2* and *FGFR3* somatic mutations have been detected in human bladder, cervical and colorectal carcinomas.[39] *FGFR4* Gly388Arg polymorphism, a general hot spot in RTKs for disease-related sequence variations have also been shown to associate with some types of cancer development and progression.[9,12,13,15,19–25,27,29,30,34] In the current meta-analysis, we also found a significant relationship between *FGFR4* Gly388Arg polymorphism and the risks of cancers, especially, an increased susceptibility was found in the subgroups of Asians, to breast and prostate cancers.

One important property of the gene polymorphisms is that their incidence can vary substantially between different racial or ethnic populations.[19] In this meta-analysis, we found a highly significant difference in the prevalence of the *EGFR4* Arg^{388} allele among controls of Asians (37.2%), Europeans (29.5%) and African-Americans (11.7%). In the

Table 2 – Main results of pooled ORs and stratification analysis of the *FGFR4* Gly388Arg polymorphism on cancer risk in the meta-analysis.

	N	Arg/Arg versus Gly/Gly OR (95% CI) P_h	Gly/Arg versus Gly/Gly OR (95% CI) P_h	Arg versus Gly OR (95% CI) P_h	Dominant model OR (95% CI) P_h	Recessive model OR (95% CI) P_h
Total	16	1.24(1.07, 1.43)0.10	1.05(0.96, 1.15)0.37	1.10(1.03, 1.18)0.17	1.09(0.99, 1.19)0.44	1.27(1.04, 1.56)0.05
Cancer types						
Prostate cancer	6	1.60(0.99, 2.61)0.02	1.16(1.02, 1.32)0.74	1.17(1.07, 1.29)0.18	1.20(1.06, 1.35)0.89	1.58(0.92, 2.65)0.01
Breast cancer	3	1.57(1.04, 2.37)0.83	1.09(0.86, 1.38)0.51	1.19(0.99, 1.41)0.77	1.16(0.93, 1.46)0.58	1.51(1.02, 2.24)0.80
Colorectal carcinoma	2	0.93(0.53, 1.64)0.48	0.89(0.63, 1.26)0.82	0.93(0.73, 1.20)0.54	0.90(0.65, 1.24)0.69	0.98(0.57, 1.69)0.49
Hepatocellular cancer	2	1.14(0.82, 1.60)0.34	0.78(0.40, 1.56)0.08	1.05(0.89,1.24)0.22	0.99(0.78, 1.28)0.11	1.19(0.88, 1.60)0.80
Others	3	0.95(0.64, 1.42)0.23	0.82(0.64, 1.05)0.54	0.92(0.77, 1.10)0.40	0.85(0.67, 1.07)0.71	1.06(0.73, 1.54)0.74
Ethnicity						
European	8	1.12(0.93, 1.35)0.15	1.08(0.97, 1.21)0.36	1.07(0.98, 1.16)0.10	1.09(0.98, 1.21)0.22	1.08(0.90, 1.29)0.19
Asian	6	1.43(1.13, 1.80)0.24	1.01(0.83, 1.15)0.26	1.16(1.04, 1.29)0.25	1.08(0.93, 1.26)0.38	1.47(1.19, 1.81)0.15
African-American	2	1.94(0.45, 8.31)0.17	1.04(0.61, 1.78)0.32	1.15(0.73, 1.82)0.95	1.11(0.67, 1.85)0.62	1.91(0.45, 8.10)0.18

N indicates number of studies involved; P_h: *P*-value of Q-test for heterogeneity test.

subgroup analysis by ethnicity, we found that the association between Arg variant genotypes and increased risks of cancer was significant only in Asians but not in Europeans or African-Americans, suggesting genetic diversity among different ethnicities.

In another subgroup analysis by cancer types, we found that *FGFR4* Gly388Arg polymorphism led to an increased incidence of breast and prostate cancer. Some studies reported that breast or prostate cancer might progress from a steroid-dependent to a steroid-independent phenotype, rendering it unresponsive to hormonal therapies. An attractive hypothesis to explain the progression of steroid-independence was that these tumours acquired the ability to constitutively express some autocrine growth factors which were previously induced by the steroid hormone itself. Many evidences in some cancer models indicated that particular FGFs might act as autocrine growth factors capable of conferring steroid-independence.[40] However, the biochemical mechanism of Arg^{388} allele increasing the risks of breast and prostate cancer was unclear. The results of two independent studies[13,18] were unable to show increased tyrosine kinase activity in breast and prostate cancer cells attributable to the *FGFR4* Gly388Arg polymorphism, respectively. It was possible that the effect of the Arg^{388} polymorphism might be attributable to other changes, such as alterations of ligand affinity or changes in the interaction with the components of intracellular signal transduction pathways.

In interpreting the results, the main limitations of the study should be considered. Firstly, lack of the original data of the reviewed studies limited our further evaluation of potential interactions, because the interactions between gene-to-gene, gene-to-environment and even different polymorphic loci of the same gene may modulate cancer risk. Secondly, because some relevant published and unpublished studies which were likely to have null results were not included, a possible bias, especially the outcome-reporting bias, could not be ruled out, although the result for publication bias was not statistically significant.

In summary, this meta-analysis supports that the *FGFR4* Gly388Arg polymorphism most likely contributes to susceptibility to cancer, especially in Asians. Besides, the Arg^{388} allele might be associated with increased risks of breast and prostate cancer. However, larger well-designed studies with subjects of the same ethnic background and tissue-specific biochemical and biological characterisation are warranted to validate these findings. Moreover, gene–gene and gene–environment interactions should also be considered in the future analysis.

Conflict of interest statement

None declared.

Acknowledgement

This work was supported by a grant from the National Natural Science Foundation of China (No. 30971320).

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