Research Paper

Association of Interleukin-10, Vitamin D Receptor and Cytochrome P450 1A1 Gene Polymorphisms with Renal Cell Carcinoma Risk

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The current study examined the relationship between renal cell carcinoma-related risk and gene polymorphisms in the interleukin-10, vitamin D receptor and cytochrome P450 1A1 genes. Using the preferred reporting items for systematic reviews and meta-analyses criteria, the link between gene polymorphisms and renal cell carcinoma was studied by utilizing the Web of Science, Embase, PubMed and Wanfang databases. The CC and TT genotypes along with the interleukin-10-819C/T C-allele were found to be substantially associated with renal cell carcinoma risk in the Chinese residents. Furthermore, significant relationships between the vitamin D receptor, FokI FF genotype and FokI F allele, ApaI A allele, ApaI AA and aa genotypes and renal cell carcinoma risk were observed in Asian populations. The cytochrome P450 1A1 MspI (rs4646903) polymorphism was substantially linked to an elevated risk of renal cell carcinoma in the T allele, TT genotype. However, no significant relationships were found between renal cell carcinoma risk and the single nucleotide polymorphisms interleukin-10-1082A/G, vitamin D receptor TaqI and cytochrome P450 1A1 Ile462Val (rs1544410).

Key words: Renal cell carcinoma, interleukin-10, vitamin D receptor, cytochrome P450 1A1, gene polymorphisms

With more than 270 000 new cases and 100 000 fatalities each year, Renal Cell Carcinoma (RCC) is one of the most prevalent malignancies of the urinary system and the most common kind of kidney cancer. The tolerance of traditional cancer treatments like radiation therapy and chemotherapy, the higher recurrence rate and distant metastases, the prognosis and 5 y survival rates of cancer patients are relatively poor[1]. Globally, the incidence and accompanying death rate are now on the rise. Importantly, men have around double the morbidity and death rates compared to women. Although the origin of RCC is unknown, epidemiological studies have revealed that various threatening factors, including cigarette smoking, obesity, hypertension, a family record of cancer and poor nutrition habits, are strongly associated with the disease. As a result, new diagnostic tools and prognostic biomarkers are critical for predicting RCC advancement.

Interleukin-10 (IL-10), which is an anti-inflammatory cytokine, has an overall anti-inflammatory effect. Therefore, its circulating level can be employed as a biomarker for various illnesses, including RCC. The IL-10 gene is localized to chromosome 1q and the degree of IL-10 production is impacted by three biallelic polymorphisms in the IL-10 promoter region, namely, 592C/A (rs1800872), 1082G/A (rs1800896) and 819C/T (rs1800871). Also, the IL-10 gene of humans has five exons and is located on chromosome 1q32.1[2]. Genetic polymorphisms including Fok1 (rs2228570), TaqI (rs731236), ApaI (rs7975232) and BsmI (rs1544410), restriction fragment length polymorphisms, which is related to a range of illnesses, have an impact on Vitamin D Receptor (VDR), which regulates the vitamin D's activity[3]. The Cytochrome P450 1A1 (CYP1A1) enzyme is the most efficacious in converting carcinogens of people, specifically

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aromatic polycyclic hydrocarbons into highly reactive intermediates[4]. In the CYP1A1 gene, recent research has focused mainly on two non-synonymous Single Nucleotide Polymorphisms (SNPs)-Adenine (A) to Guanine (G) transformation at codon 462 in exon 7 (Ile462Val, rs1048943) and Thymine (T) to Cytosine (C) transformation in the noncoding 39-flanking region (MspI, rs4646903)[5]. These alterations may impact gene expression and function, probably changing the balance between toxicant detoxification and metabolic activation consequently, adding to a person's vulnerability to cancer.

A previous study has found that environmental and genetic factors have a major impact on the occurrence and development of RCC. RCC risk is highly related to CYP1A1, VDR and IL-10 gene variations. As shown by Yang *et al.* the ApaI mutant AA and AC genes were significantly connected to an elevated risk of RCC in comparison with the CC genotype[6]. Also, Zhou *et al.* discovered that the VDR's ApaI A gene, ApaI AA and aa gene, BsmI B gene and Fok1 FF gene have all been linked to RCC susceptibility[7]. Despite this, Lin *et al.* and her colleagues discovered no significant relationships between RCC risk and VDR BsmI and TaqI gene polymorphisms in Asian and Caucasian populations, which may be paradoxical[3]. Based on case-control studies, a meta-analysis was done to resolve the controversial results reported and the study aims to assess the role of IL-10, VDR and CYP1A1 gene polymorphisms on the RCC risk.

MATERIALS AND METHODS

Search strategy:

Two independent researchers (Xu and Yang) reviewed the published research work in the Web of Science, Embase, PubMed and Wanfang databases before 12 Oct 2021 using the keywords sets as follows: "Interleukin-10" or "IL-10" or "CYP1A1" or "P4501A1" or "VDR" or "vitamin D receptor" and "renal cancer or "renal cell carcinoma" or RCC". Besides, the references given in chosen articles are retrieved for the purpose of finding more potential eligible studies. Two authors performed the process without any discussion.

Inclusion criteria: Inclusion criteria were the following-The IL-10, VDR and CYP1A1 gene polymorphisms and RCC were investigated in case-control studies; at least 2 groups for comparison of control group *vs.* case group and the study satisfies the conditions for the Hardy-Weinberg Equilibrium (HWE).

Exclusion criteria: Exclusion criteria included review articles and editorials, case reports, no reporting of IL-10, VDR or CYP1A1 gene polymorphism or RCC prognosis and no inquiry detailed genotype data of IL-10, VDR and CYP1A1 in RCC.

Data extraction:

From each eligible study, two independent researchers collected the following information. First author's surname, origin, year of publication, location, number of cases, control basis of the matched group and controls for IL-10, VDR and CYP1A1 genotype. The discussion was used to address the existing disparities between the two sets of data.

The validated Newcastle-Ottawa Scale (NOS) for non-randomized research was employed to evaluate the study quality. Research might earn one star in each of the selection and exposure categories, as well as two stars in the comparability category. In our meta-analysis, only high-quality studies with scores greater than 5 were included.

Statistical investigation:

Based on the five genetic comparison models, the strength of the link between the RCC susceptibility and three gene polymorphisms was assessed using pooled Odds Ratios (ORs) with 95 % Confidence Intervals (CIs). The models include the recessive, allele, homozygous, dominant and heterozygous models. The outcomes of dichotomous data were shown using ORs as well as 95 % CIs were generated. To determine the statistical value of the pooled ORs, a test was used. The heterogeneity of the selected research was evaluated using I^2. In this investigation, the fixed-effect model (a Mantel-Haenszel approach) was used, since p values of 0.05 and I^2>50 % were regarded to indicate considerable heterogeneity. Otherwise, a DerSimonian and Laird approach was used, which is also known as the random-effect model. To determine the cause of considerable heterogeneity, subgroup analyses were carried out. When there were more than two included publications to assess, we conducted a subgroup analysis. Stratification studies were undertaken to identify possible sources of variability among factors such as ethnicity, age groups, sample size, genotyping technologies and

control types. Additionally, a sensitivity analysis was done to examine the impact of every study on the whole findings and avoid the possibility that the existence of separate studies may cause the pooled findings to be reversed. Egger's linear regression test, funnel plots and Begg's rank correlation test were employed to identify publication bias in the present studies. A statistically significant value of $p<0.05$ was included. For all statistical studies, STATA 16.0 was employed.

RESULTS AND DISCUSSION

During the search, 838 studies were found in the PubMed (n=163), Embase (n=252), Web of Science (337) and Wanfang (n=86) databases. Following the removal of 380 duplicate articles, further publications were deleted by checking the title and abstract. The total of reviews, conference papers, meta-analyses, letters and abstracts from conferences, editorials, brief surveys and notes were 431. Furthermore, the total of publications involving animals or *in vitro* studies is 30.

We rejected 14 papers after reading the complete text of these studies for the following reasons, other genes or SNPs of renal illness were researched; the study was not pertinent to the gene; other illnesses were included, but there was no data available for the study. In addition, four studies were discovered through other means. Finally, for this meta-analysis, 17 studies were kept. The flowchart representing the process of selecting and searching the literature is shown in fig. 1. Furthermore, 3 studies have discovered a correlation for both the incidence of RCC and IL-10 gene polymorphism (Table 1). There into, 2 studies assessed IL-10-819C/T gene polymorphism and 3 studies[8-10] analyzed IL-10-1082A/G gene polymorphism[8,9]. In addition, 7 studies[6,11-16] illustrated the connection between VDR gene polymorphism and the susceptibility to RCC in Table 2. Among these, 5 studies focused on VDR FokI rs2228570 gene polymorphism, 3 studies[6,11-13,16] on VDR ApaI rs7975232, 5 studies[6,11-14] on BsmI rs1544410 and 5 studies[6,11,13-15] on VDR TaqI rs731236. Simultaneously, 5 studies[17-21] retrieved the association between CYP1A1 gene polymorphism with RCC in Table 3. Among these, 4 studies[17-19,21] mainly focused on MspI (rs4646903) gene polymorphism and Ile462Val (rs1544410) gene polymorphism, respectively[17,19-21].

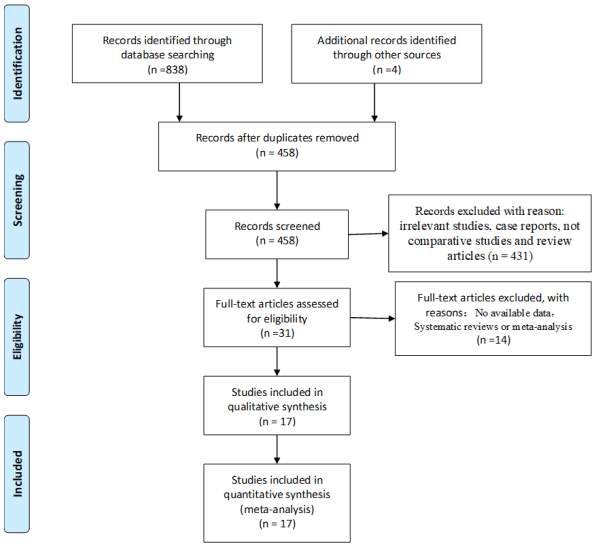

Fig. 1: Flow chart of study search and selection

TABLE 1: EFFECTS OF IL-10 GENE POLYMORPHISM ON RCC RISK

Gene sites	Author	Year	Ethnicity	Country	Source of control	Case				Control			
						AA	AG	GG	Total	AA	AG	GG	Total
IL-10-1082A/G	Chang	2016	Asian	China	PB	71	16	5	92	414	107	29	550
	Romero	2009	Granada	Spain	PB	42	62	22	126	58	87	30	175
						CC	CT	TT	Total	CC	CT	TT	Total
IL-10-819C/T	Chang	2016	Asian	China	PB	62	26	4	92	310	209	61	580
	Romero	2009	Granada	Spain	PB	81	37	9	127	98	63	14	175

Note: PB: Population-Based study

TABLE 2: SUMMARY OF THE EFFECTS OF VDR GENE POLYMORPHISM ON RCC RISK

Gene sites	Author	Year	Ethnicity	Country	Source of Control	Case				Control			
						FF	Ff	ff	Total	FF	Ff	ff	Total
FokI	Tian	2021	Asian	China	PB	191	143	32	366	432	263	40	735
	Yang	2016	Asian	China	PB	61	171	70	302	64	159	79	302
	Southard	2012	Caucasian	Finland	PB	22	66	64	152	48	144	113	305
	Arjumand	2011	Asian	Indian	PB	40	94	62	196	38	98	114	250
	Karami	2008	Caucasian	United States	HB	149	376	286	811	199	492	338	1029
						AA	Aa	aa	Total	AA	Aa	aa	Total
ApaI	Tian	2021	Asian	China	PB	182	149	35	366	475	226	34	735
	Yang	2016	Asian	China	PB	35	153	114	302	18	135	149	302
	Obara	2007	Asian	China	PB	23	52	60	135	11	71	68	150
						TT	Tt	tt	Total	TT	Tt	tt	Total
TaqI	Tian	2021	Asian	China	PB	200	139	27	366	460	241	34	735
	Yang	2016	Asian	China	PB	0	41	261	302	0	30	272	302
	Karami	2008	Caucasian	United States	HB	97	361	320	778	137	438	402	977
	Obara	2007	Asian	China	PB	0	31	104	135	1	37	112	150
	Ikuyama	2002	Asian	Japan	HB	1	19	82	102	8	70	126	204
						BB	Bb	bb	Total	BB	Bb	bb	Total
BsmI	Tian	2021	Asian	China	PB	211	130	25	366	466	236	33	735
	Yang	2016	Asian	China	PB	0	47	255	302	0	37	265	302
	Arjumand	2011	Asian	Indian	PB	50	88	58	196	83	130	37	250
	Karami	2008	Caucasian	United States	HB	81	370	324	775	112	474	407	993
	Obara	2007	Asian	Japan	PB	0	33	102	135	1	41	108	150

Note: PB: Population-Based study and HB: Hospital-Based study

TABLE 3: SUMMARY OF THE EFFECTS OF CYPA1 GENE POLYMORPHISM ON RCC RISK

Restriction sites	Author	Year	Ethnicity	Country	Case				Control			
					Wt/Wt (TT)	Wt/Vt (CT)	Vt/Vt (CC)	Total	Wt/Wt (TT)	Wt/Vt (CT)	Vt/Vt (CC)	Total
MspI (rs4646903)	Wang	2012	Asian	China	89	87	31	207	113	91	32	236
	Chen	2011	Asian	China	80	83	18	181	237	94	19	350
	Wang	2008	Asian	China	62	64	17	143	96	40	17	153
	Longuemaux	1999	Caucasian	France	114	52	5	171	156	50	4	210
					Ile/Ile (AA)	Ile/Val (GA)	Val/Val (GG)	Total	Ile/Ile (AA)	Ile/Val (GA)	Val/Val (GG)	Total
Ile462Val (rs1544410)	Ahmad	2013	Asian	India	53	98	45	196	112	106	32	250
	Wang	2012	Asian	China	106	80	21	207	116	90	30	236
	Chen	2011	Asian	China	77	63	41	181	174	122	54	350
	Wang	2008	Asian	China	69	66	23	158	56	48	35	139

Association between RCC susceptibility and IL-10 gene polymorphism was explained here. The A allele and genotype of IL10-1082A/G were not linked with the incidence of RCC in the Chinese and Grenada populations (A allele: OR=1.14, 95 % CI: (0.92-1.43), p=0.233; AA genotype: OR=1.22, 95 % CI: (0.90-1.65), p=0.196; GG genotype: OR=0.91, 95 % CI: 0.60-1.37, p=0.639) as shown in fig. 2. The IL-10-819C/T C allele and CC genotypes, on the other hand, had shown significant correlation of RCC susceptibility (C allele: OR=1.76, 95 % CI: 1.19; 2.61, p=0.005; CC genotype: OR=1.80, 95 % CI: 1.13; 2.87, p=0.013) in the Chinese residents was shown in fig. 3.

Association between VDR gene polymorphism and RCC susceptibility was explained here. The VDR FokI allele and genotype were not relevant to an elevated risk of RCC (f *vs.* F: OR=1.10, 95 % CI: (0.91-1.32), p=0.326; ff *vs.* FF+Ff: OR=1.05, 95 % CI: (0.89-1.24), p=0.575; FF *vs.* Ff+ff: OR=0.88, 95 % CI: (0.68-1.14), p=0.328) was shown fig. 4. As depicted, the F allele and FF genotype remain linked to a higher risk of developing RCC, instead of ff genotype in the Asian population. Additionally, neither the ff nor FF genotypes nor the VDR FokI f allele was linked to an elevated risk of developing RCC in Caucasians. Asians were more likely to develop RCC if they had the VDR ApaI A allele, AA or aa genotype (A *vs.* a: OR=2.57, 95 % CI: (1.81-3.65), p=0.000; AA *vs.* Aa+aa: OR=2.22, 95 % CI: (1.58-3.11), p=0.000; aa *vs.* AA+Aa: OR=0.65, 95 % CI: (0.49-0.88), p=0.004) (fig. 5). The correlation between RCC susceptibility and the VDR TaqI gene wasn't statistically significant, T allele: OR=0.97, 95 % CI: (0.71-1.31), p=0.817; tt genotype: OR=1.00, 95 % CI: (0.57-1.77), p=0.996; TT genotype: OR=1.03, 95 % CI: (0.73-1.45), p=0.87 (fig. 6). In general populations, there are no known significant relationships between the VDR BsmI B allele, BB genotype, or bb genotype with RCC risk, B allele: OR=0.95, 95 % CI: (0.75-1.20), p=0.649; BB genotype: OR=0.96, 95 % CI: (0.65; 1.41), p=0.824; bb genotype: OR=1.12, 95 % CI: (0.82-1.53), p=0.498 (fig. 7). There is no link between the VDR BsmI gene polymorphism and RCC risk in Asians or Caucasians, according to research that was stratified by ethnicity.

Link amongst CYPA1 gene polymorphism and RCC susceptibility was explained here. The high risk of RCC is closely associated with the MspI polymorphism, when the genotype is TT (T genotype: OR=0.56, 95 % CI: (0.38; 0.81), p=0.009; T allele: OR=0.65, 95 % CI: (0.49; 0.87), p=0.003) (fig. 8). For all genetic models, the correlation of the Ile462Val polymorphism and RCC risk was not significant, A allele: OR=0.88, 95 % CI: (0.60; 1.69), p=0.503; AA genotype: OR=0.80, 95 % CI: (0.54; 1.21), p=0.824; aa genotype: OR=1.01, p=0.800 (fig. 9). However, we identified a substantial link between CYPA1 gene polymorphism and a low risk of RCC among Indians with the AA genotype, A allele and aa genotype, A genotype: OR=0.46, 95 % CI: (0.31; 0.68), p=0.000; aa genotype: OR=0.20, 95 % CI: (1.23; 3.34), p=0.005.

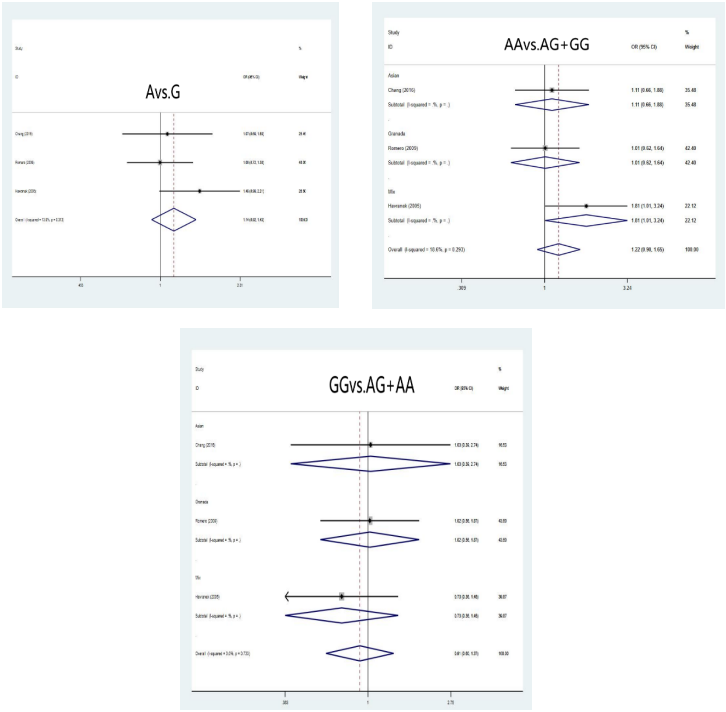

Fig. 2: Association of methylenetetrahydrofolate reductase IL-10-1082A/G gene polymorphism with RCC susceptibility

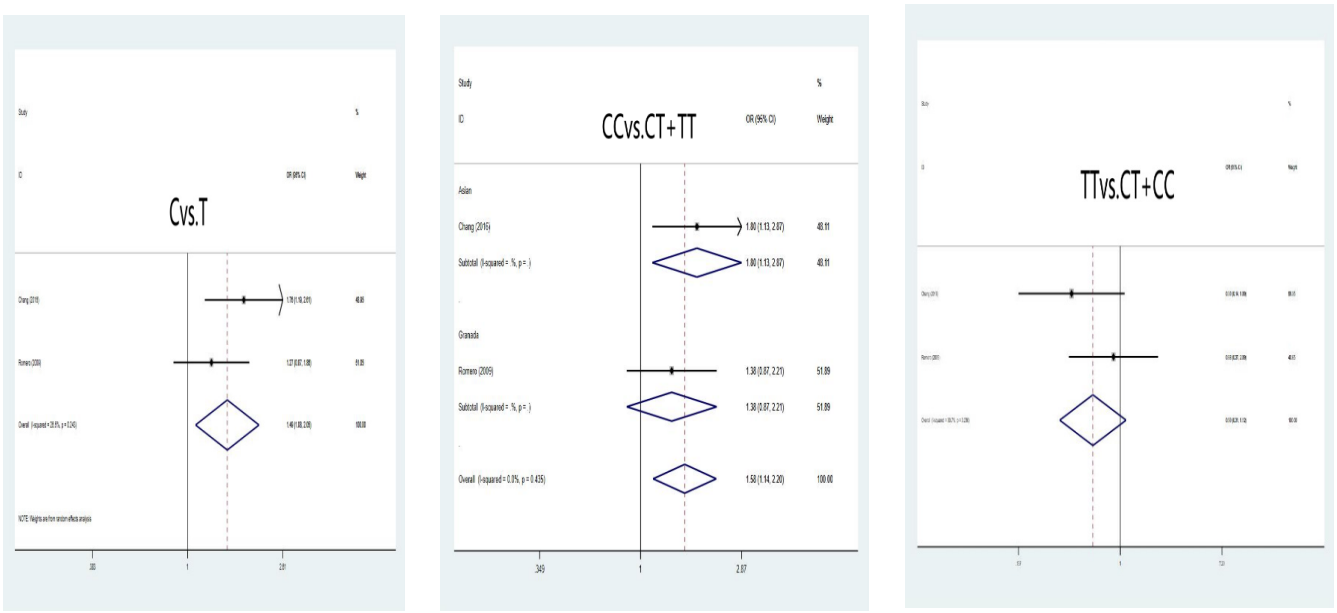

Fig. 3: Association of methylenetetrahydrofolate reductase IL-10-819C/T gene polymorphism with RCC susceptibility

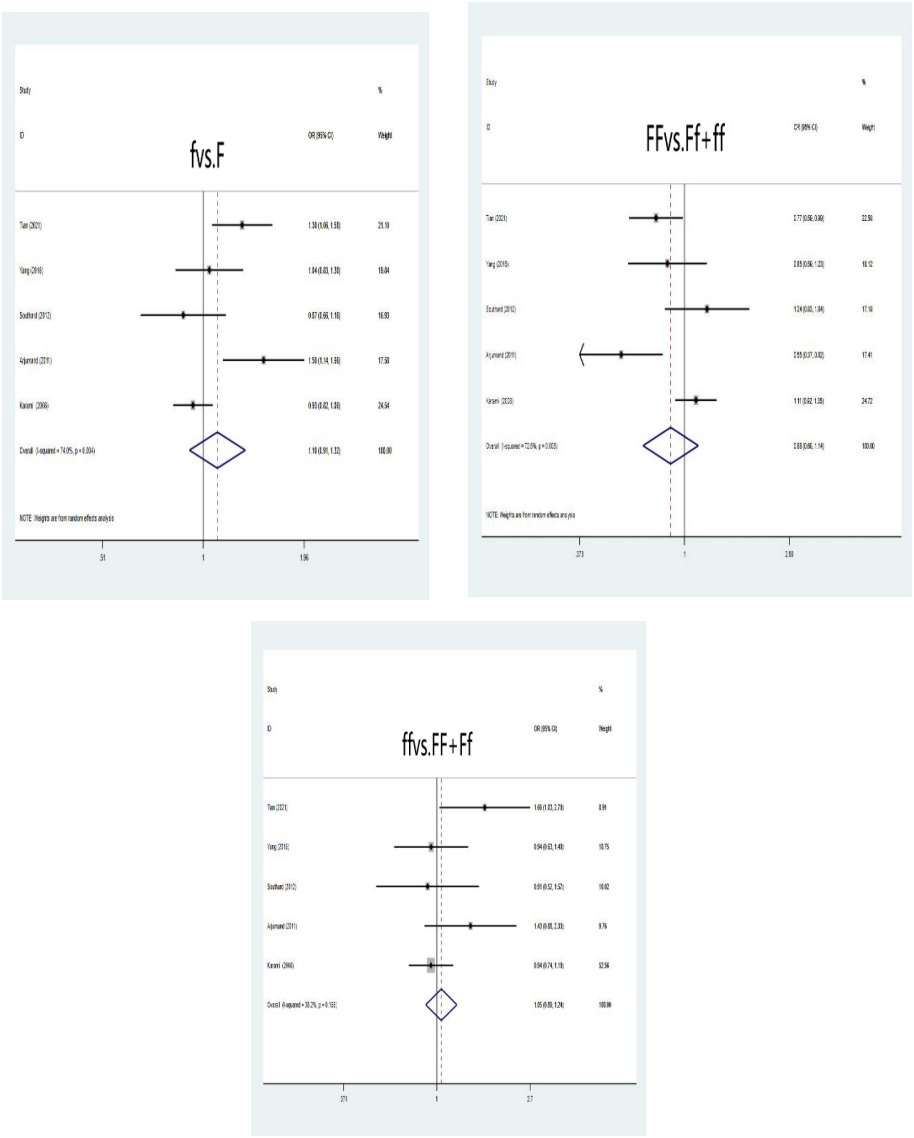

Fig. 4: Association of VDR Fok1 gene polymorphism with RCC susceptibility

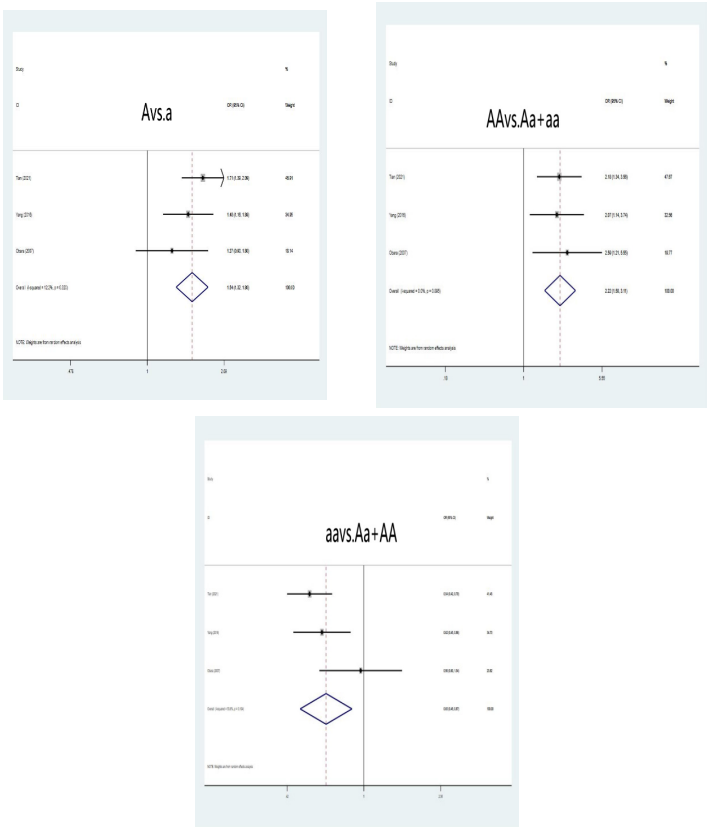

Fig. 5: Association of VDR Apa1 gene polymorphism with RCC susceptibility

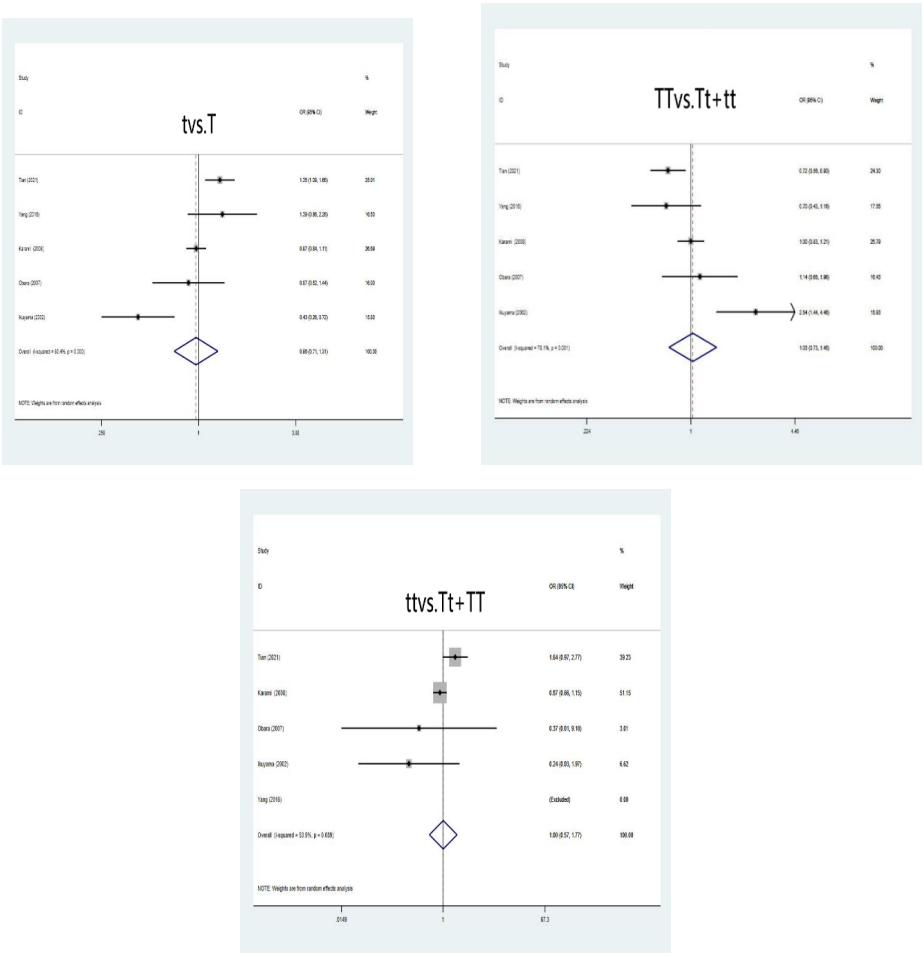

Fig. 6: Association of VDR Taq1 gene polymorphism with RCC susceptibility

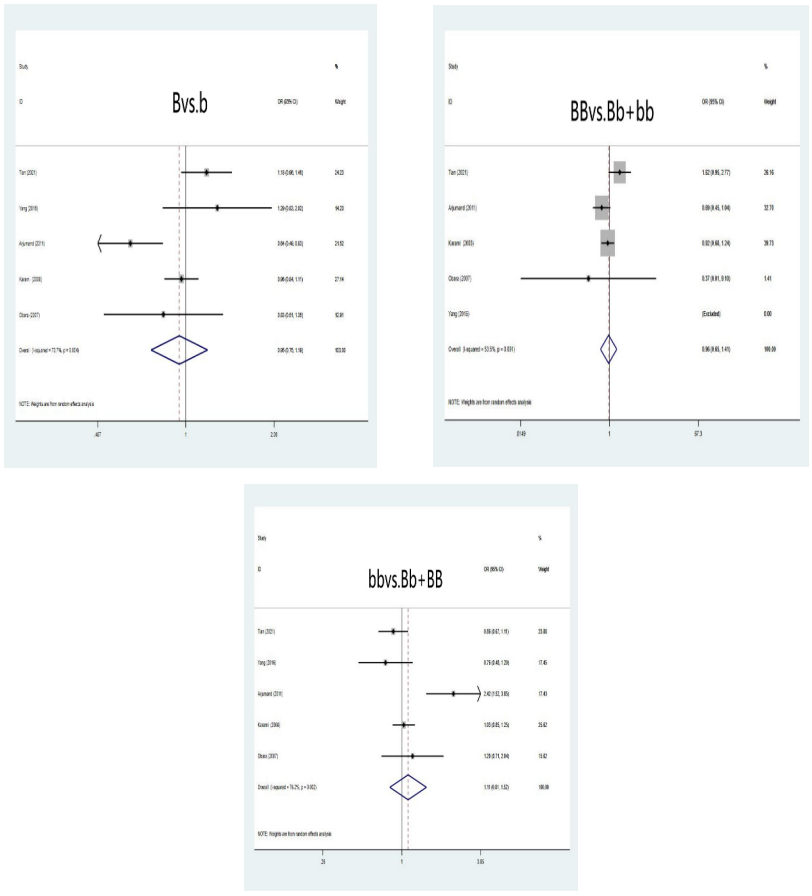

Fig. 7: Association of VDR Bsm1 gene polymorphism with RCC susceptibility

Fig. 8: Association of MspI (rs4646903) gene polymorphism with RCC susceptibility

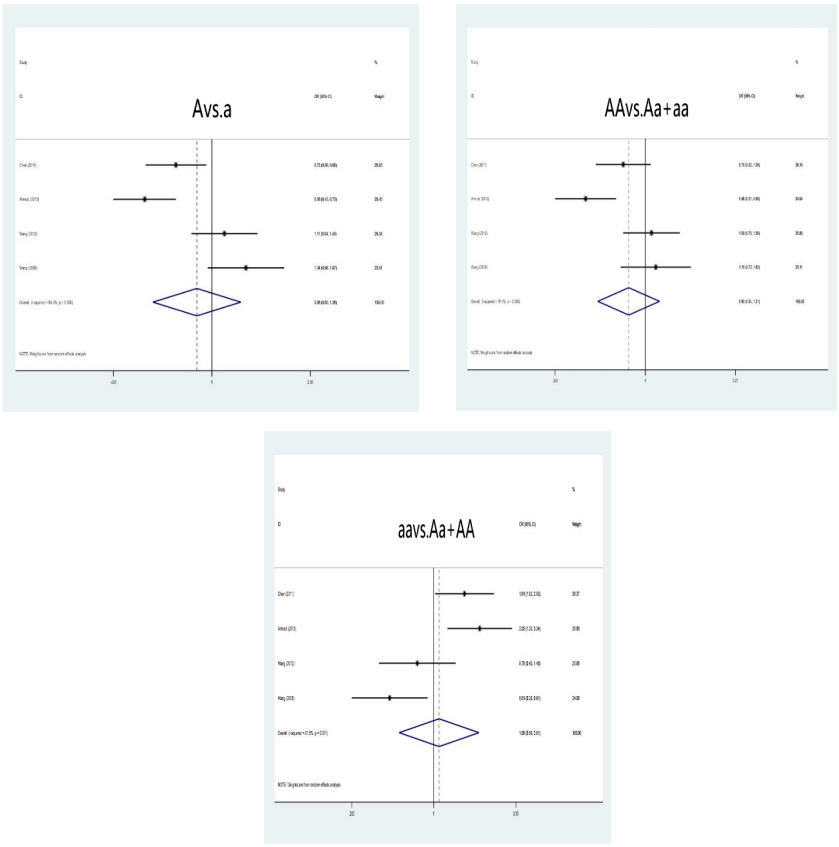

Fig. 9: Association of Ile462Val (rs1544410) gene polymorphism with RCC susceptibility

IL-10 is an anti-inflammatory cytokine that regulates cellular homeostasis. The IL-10-819C/T C allele, along with the CC and TT genotypes, had shown a significant correlation with the incidence of RCC in the Chinese population.

A phase I enzyme called CYP1A1 can impact the metabolism of environmental contaminants as well as modify cancer susceptibility. It is required for polycyclic aromatic hydrocarbon phase I metabolism and hormone metabolism. CYP1A1 dysfunction can cause Deoxyribonucleic Acid (DNA), lipid and protein damage, which can lead to carcinogenesis[7].

VDR is found on the long arm of chromosome 12q12-q14 and has been associated with cancer risk through a variety of single nucleotide polymorphisms. Each mutation is called after the target sequence that was originally used to characterize it. The VDR BsmI and TaqI polymorphisms, in general, are unrelated to the risk of developing RCC. According to a meta-analysis conducted by Zhou *et al.* three genotypes (ApaI AA, Fok1 FF and BsmI BB) and the Fok1 f allele are all linked to the risk of RCC in Asians[7]. There was more reliability than Zhou *et al.* since it contained more research in our analysis. Nunes *et al.* revealed that the rs228570 VDR gene polymorphism, particularly the protective f allele, showed a significant correlation with arterial hypertension[22]. Furthermore, vitamin D can also influence cell proliferation, differentiation and death in a variety of organs and protects against some forms of cancer. Moreover, the relevance between the haplotype blocks of those genes and RCC must be studied. For starters, some subgroup studies used a tiny sample size, which might not be illustrative of the entire population. Second, a rigorous study in the control group contradicted HWE. In addition, just a few electronic databases were examined. More study is needed to understand the pathways that connect VDR, IL-10 and cell cancer. As a result, our findings should be taken into account and additional case-control studies are needed to corroborate our findings.

In the present study, the gene-gene and gene-environment interactions are not described such as participant's average food consumption, macronutrient nutritional content and use of vitamin D supplements, especially vitamin D or energy. Even though cancer is a complex interaction between inherited and environmental factors, the authors did not even look into these nutritional elements. Finally, it may not provide any more information on its impact on cell cancer.

Author's contributions:

Ning Xu made the substantial contributions to the conception and design of the work; Ning Xu, Maoquan Yang searched selected materials and extracted data; Ning Xu wrote this manuscript; Xiangling Li, Jie Liu, Suzen Li and Zihao Zhu revised the paper carefully and also contributed to the statistical analyses. All authors have read and approved the final manuscript.

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Conflict of interests:

The authors declared no conflict of interest.

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