Systematic Review

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Survivin c.-31G>C (rs9904341) gene transversion and urinary system cancers risk: a systematic review and a meta-analysis

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Aim: To investigate the possible association between *survivin* c.-31G>C (rs9904341) gene polymorphism and urinary system cancers by a meta-analysis approach. **Methods:** Standard electronic literature databases were searched to find eligible studies. The odds ratios (ORs) with 95% CIs were estimated to find the associations possibility. **Results:** Overall meta-analysis revealed significant associations between c.-31G>C transversion and risk of urinary tract cancers in dominant (OR: 1.34; 95% CI: 1.02–1.75; p = 0.035), recessive (OR: 1.52; 95% CI: 1.33–1.74; p < 0.001) and homozygote codominant (OR: 1.90; 95% CI: 1.37–2.62; p < 0.001) genetic models. **Conclusion:** The c.-31G>C transversion might be a risk factor for urinary system cancers. However, more articles with different ethnicities will help to obtain a more accurate conclusion.

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Keywords: bladder cancer • genetic association • genetic polymorphism • meta-analysis • prostate cancer • renal cell cancer • rs9904341 • *survivin* gene • urinary system cancer • urothelial cancer

Urinary system cancers such as prostate, kidney and bladder cancers are common forms of malignancies around the world. The incidence of these cancers is growing due to some endogenous and exogenous factors including smoking, obesity, alcohol use and infectious agents [1]. According to the Globocan 2012 statistics released by the International Agency for Research on Cancer, prostate cancer is the second most frequent malignancy in the world after lung cancer. In International Agency for Research on Cancer member countries, WHO European Region, USA and EU prostate cancer is recognized as the first ranked most frequent cancer. Indeed, bladder cancer was among the five types of cancer in the above-mentioned groups. Remarkably, kidney cancer is recorded among the five most frequent cancers in the WHO European Region [2]. Since prevention is still the best way to deal with the above-mentioned cancers, recognition of their risk factors is of great importance. There are many predisposing genetic factors which increase the risk of urinary tract cancers [3]. Polymorphisms in the genes controlling key cellular pathways are involved in the development of these cancers and are able to alter the risk of urinary tract cancers. It should be noted that programmed cell death (apoptosis) is one of the most important cellular pathways involved in cancer development and progression. Survivin protein is a key regulatory molecule in this pathway [4].

Survivin, also called *BIRC5*, is one member of the inhibitor of apoptosis proteins family. Survivin expression is commonly upregulated in several cancers [5]. The role of survivin in tumorigenesis is largely dependent on its function in apoptosis inhibition and in mitosis as a key regulator factor [6]. In typical normal cells, expression of survivin occurs throughout embryonic and fetal developmental periods. Survivin level is practically invisible in differentiated adult cells [5]. So, upregulation of this gene in most tumor cells makes it a valuable biomarker for diagnosis and treatment of cancer [7].

The *survivin* gene, located at 17q25.3, encodes a protein which contains a BIR (baculoviral IAP repeat) domain [8]. There are numerous variations in this gene and the c.-31G>C (rs9904341) is a well-known single nucleotide polymorphism (SNP) in the upstream of this gene. This SNP is positioned in the CDE/CHR repressor region of survivin and it might lead to overexpression of the gene [5]. Our literature review showed that this polymorphism is

associated with urinary system cancers, but the results of studies are inconclusive. Therefore, we aimed to evaluate the association between c.-31G>C polymorphism and urinary system cancers through a meta-analysis.

Methods

Search strategy

The current meta-analysis is in accordance with the PRISMA checklist (Supplementary Table 1) and included a relevant paper studying the association between rs9904341 gene transversion and urinary system cancers. To find all aforementioned papers, two authors (A Karimian and M Karimian) independently performed a comprehensive literature search in PubMed, ISI Web of Science, ScienceDirect and Google Scholar databases up to June 2018 by using the following keywords: 'survivin or BIRC5' and 'c.-31G>C or rs9904341', and 'polymorphism or SNP or variant or variation' and 'prostate or bladder or renal cell carcinoma or urinary tract cancer'. Moreover, the references of retrieved papers were assessed to recognize other qualified articles that were missing out on the chief search.

Inclusion & exclusion criteria

The case reports, review articles and editorials were excluded from the meta-analysis. Studies with the following criteria were considered eligible for inclusion to the meta-analysis: studies investigating the association of *survivin* c.-31G>C polymorphism with urinary system cancers such as prostate, bladder and renal cell carcinoma; studies with case-control design; and studies with sufficient data to calculate odds ratio (OR) and 95% CI.

Data extraction strategy

Two abovementioned authors carefully extracted the following information from all eligible studies: name of first author, publication year, the country (ethnicity), source of controls, type of cancer, genotyping methods, and allele and genotype frequencies of cases and controls. Disagreements about extracted data were solved by consensus and argument.

Statistical analysis

The Hardy–Weinberg equilibrium (HWE), base on genotype frequencies in control groups of each studies, was calculated by a Chi-squared test. The ORs with a 95% CI were estimated using random-effect or fixed-effect models based on the heterogeneity results. Random-effects model was selected if the p-value of the heterogeneity test was less than 0.1 otherwise the fixed-effects model was chosen. Cochran's Q test with inconsistency index (I^2) was applied for the calculation of heterogeneity across studies [9,10]. Meta-analysis was performed for the five following genetic models: C versus G (allelic), CC versus GG (homozygote codominant), GC versus GG (heterozygote codominant), GC + CC versus GG (dominant) and CC versus GG + GC (recessive). Also, meta-analysis was stratified for cancer type, source of controls, HWE status of control groups, sample size and ethnicity subgroups. Publication bias was evaluated by Begg's funnel plots and the Egger's test [11,12]. Finally, the sensitivity analysis was performed using removing one study at a time to determine the magnitude of the effect on the total assessment. All of these calculations were performed by the Open meta analyst (Tufts University, MA, USA; www.cebm.brown.edu/openmeta/) and Comprehensive meta analysis (Biostat, Inc., NJ, USA; www.meta-analysis.com/) software.

Results

Study characteristics

The flowchart of searching and screening procedure is displayed in Figure 1. At first, a total of 79 papers were recognized by systematic search in electronic databases. After employing selection criteria, seven eligible articles reporting the association of the c.-31G>C polymorphism with urinary system cancers risk were included into the meta-analysis [13–19]. Some information of these studies such as cancer type, source of control, ethnicity and sample size were extracted and listed in Table 1. Of these seven studies, five studies were conducted in Asian and two studies were belonged to Caucasian populations. Moreover, two studies focused on renal cell carcinoma, two on bladder cancer, two on prostate cancer and one on urothelial cancer. The genotype frequencies in the control groups of two studies were deviated from HWE. The control groups of six studies were hospital based and one remaining was population based (Table 1).

Table 1. Characteristics of included studies.

Country (Ethnicity)	Cancer type	Case/control	Allele frequencies				Genotype frequencies						HWE $P^{\dagger}$	Genotyping method	Source of control	Ref.
			Case		Control		Case			Control						
			G	C	G	C	GG	GC	CC	GG	GC	CC				
Taiwan (Asian)	Urothelial	190/210	157	223	246	174	33	91	66	80	86	44	0.024	PCR–RFLP	HB	[13]
Japan (Asian)	Bladder	235/346	199	271	334	358	50	99	86	75	184	87	0.228	PCR–RFLP	PB	[14]
China (Asian)	Renal cell	710/760	689	731	815	705	172	345	193	215	385	160	0.610	TaqMan	HB	[15]
India (Asian)	Bladder	200/200	251	149	283	117	83	85	32	98	87	15	0.471	PCR–RFLP	HB	[16]
China (Asian)	Prostate	665/710	619	711	741	679	150	319	196	205	331	174	0.079	TaqMan	HB	[17]
Portugal (Caucasian)	Renal cell	176/304	226	126	378	230	78	70	28	109	160	35	0.038	PCR–RFLP	HB	[18]
Iran (Caucasian)	Prostate	157/145	173	141	193	97	53	67	37	69	55	21	0.075	PCR–RFLP	HB	[19]

†Hardy–Weinberg equilibrium in the control group (groups with p-value < 0.05 did not satisfy the Hardy–Weinberg equilibrium).
HB: Hospital based; HWE: Hardy–Weinberg equilibrium; PB: Population based; PCR-RFLP: Polymerase chain reaction-restriction fragment length polymorphism.

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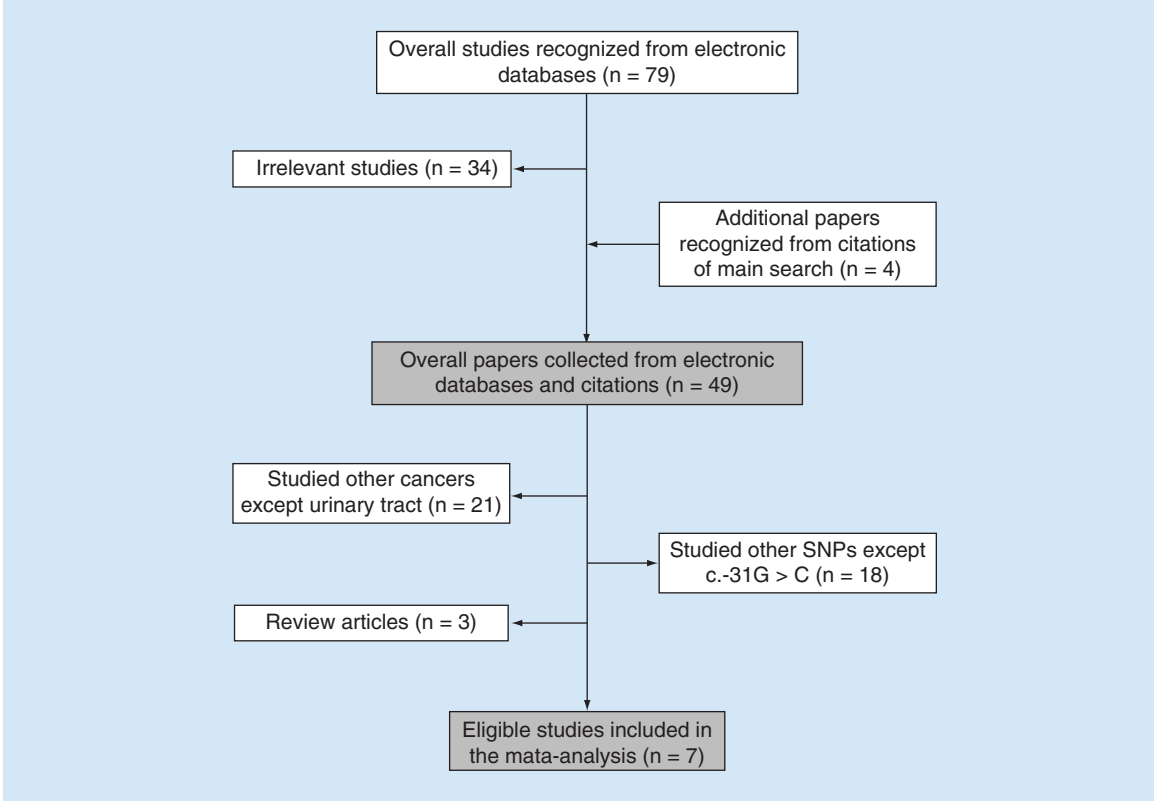

Figure 1. Results of the search strategy and the reasons for exclusion.
SNPs: Single-nucleotide polymorphisms.

Association of c.-31G>C with urinary cancers risk

The chief results of the meta-analysis are detailed in Table 2. Overall, we observed significant associations between c.-31G>C transversion and risk of urinary tract cancer in homozygote codominant (Figure 2A), dominant (Figure 2B) and recessive (Figure 2C) genetic models. When the analysis was stratified by cancer type, we observed an increased risk for bladder cancer, renal cell carcinoma and prostate cancer. Also, significant associations were observed for hospital based studies. Stratified analysis by HWE status of control groups showed that there were significant associations for studies with $P_{HWE} > 0.05$ and $P_{HWE} < 0.05$. After analysis of ethnicity subgroups, we observed that there were significant associations for Caucasians and Asians. Moreover, after stratified analysis by sample sizes of studies, we observed significant associations for studies with less than 1000 and more than 1000 participants (Table 2).

Heterogeneity, publication bias & sensitivity analysis

Significant heterogeneities were found in overall analysis (C vs G: $P_{heterogeneity} < 0.001$, $I^2 = 96\%$; CC vs GG: $P_{heterogeneity} = 0.002$; $I^2 = 71\%$; GC vs GG: $P_{heterogeneity} < 0.001$, $I^2 = 75\%$; GC + CC vs GG: $P_{heterogeneity} < 0.001$, $I^2 = 76\%$). Therefore, we applied a random-effects model with wider CIs to estimate the association results. Our data revealed that true heterogeneities remain after stratified analyses by source of control, HWE status, ethnicity and sample size. However, when the stratification was done based on the cancer type, heterogeneities significantly disappeared (Table 3). Both Begg's funnel plot and Egger's test were used to assess the publication bias. The results of Egger's tests are summarized in Table 3. In overall meta-analysis, there is only a significant publication bias in the genetic model (p = 0.014). Also, qualitative results of publication bias showed a symmetrical distribution for the mentioned analysis in allelic (Figure 3A), homozygote codominant (Figure 3B), heterozygote codominant (Figure 3C) and dominant (Figure 3D) genetic models. Also, publication biases were observed for receive model after stratification by the source of control (p = 0.027), HWE status of the control group (p = 0.006), and ethnicity (p = 0.010). To detect the impact of the single dataset on the pooled ORs, we excluded an individual study from

Table 2. Association results in the meta-analysis.

Variables	*n*	C vs G		CC vs GG		GC vs GG		GC + CC vs GG		CC vs GG + GC	
		OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Total	7	1.16 (0.75–1.79)	0.503	1.90 (1.37–2.62)	<0.001	1.17 (0.88–1.56)	0.273	1.34 (1.02–1.75)	0.035	1.52 (1.33–1.74)	<0.001
Cancer type											
–Bladder	2	1.33 (1.11–1.60)	0.002	1.77 (1.21–2.59)	0.004	0.97 (0.72–1.3)	0.853	1.18 (0.89–1.57)	0.248	1.86 (1.36–2.54)	<0.001
–Renal cell	2	1.12 (0.78–1.60)	0.529	1.42 (1.10–1.84)	0.008	0.85 (0.47–1.53)	0.579	0.95 (0.55–1.65)	0.856	1.41 (1.13–1.75)	0.002
–Prostate	2	0.81 (0.21–3.12)	0.757	1.65 (1.26–2.15)	<0.001	1.37 (1.09–1.73)	0.008	1.47 (1.18–1.82)	<0.001	1.60 (0.93–2.73)	0.087
Source of control											
–Hospital based	6	1.14 (0.69–1.90)	0.606	2.00 (1.37–2.90)	<0.001	1.24 (0.91–1.69)	0.167	1.40 (1.03–1.90)	0.031	1.56 (1.29–1.89)	<0.001
HWE											
–Yes	5	1.09 (0.63–1.89)	0.755	1.62 (1.36–1.93)	<0.001	1.18 (1.0141.36)	0.032	1.31 (1.14–1.51)	<0.001	1.49 (1.29–1.72)	< 0.001
–No	2	1.36 (0.63–2.92)	0.438	2.38 (0.55–10.34)	0.249	1.24 (0.31–5.07)	0.762	1.42 (0.35–5.77)	0.620	1.76 (1.25–2.48)	0.001
Ethnicity											
–Asian	5	1.14 (0.65–2.01)	0.650	2.02 (1.37–3.00)	<0.001	1.26 (0.95–1.66)	0.112	1.43 (1.10–1.86)	0.008	1.49 (1.30–1.72)	<0.001
–Caucasian	2	1.21 (0.69–2.12)	0.505	1.54 (1.01–2.36)	0.045	0.97 (0.38–2.47)	0.953	1.11 (0.45–2.76)	0.827	1.79 (1.21–2.65)	0.004
Sample size											
– <1000	5	1.40 (1.08–1.81)	0.011	2.16 (1.27–3.66)	0.004	1.17 (0.72–1.89)	0.533	1.37 (0.86–2.18)	0.190	1.87 (1.51–2.32)	<0.001
– >1000	2	0.74 (0.23–2.33)	0.601	1.52 (1.24–1.87)	<0.001	1.21 (1.01–1.45)	0.038	1.31 (1.11–1.55)	0.002	1.34 (1.13–1.59)	<0.001

Significant differences between the case and control groups are bolded.
HWE: Hardy–Weinberg equilibrium; OR: Odds ratio.

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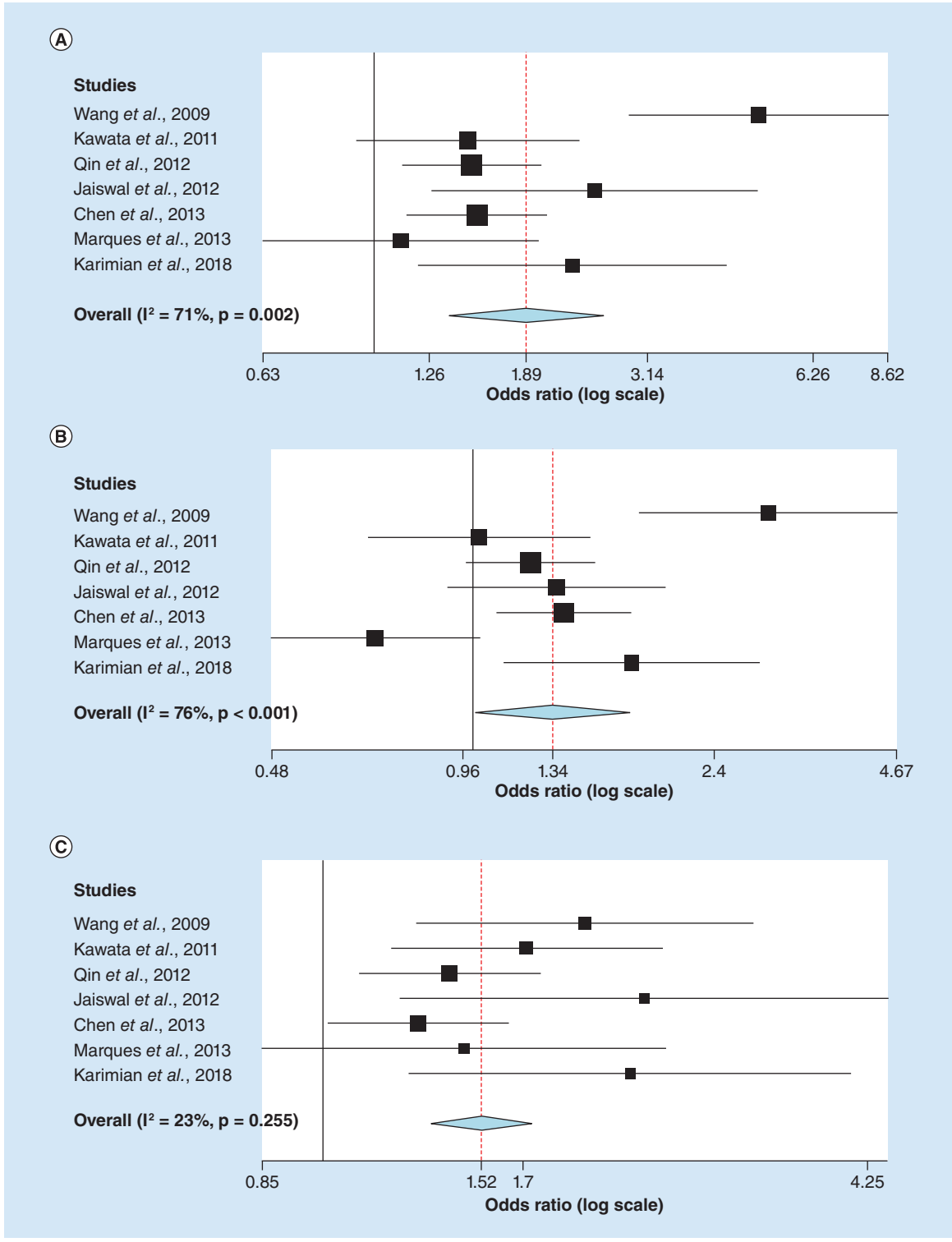

Figure 2. Forest plot for the association of c.-31G>C polymorphism of *survivin* gene with urinary system cancers in overall analysis. Significant association was observed in homozygote codominant **(A)**, dominant **(B)** and recessive **(C)** genetic models.

Table 3. Results of heterogeneity and publication bias in the meta-analysis.

Variables	C vs G			CC vs GG			GC vs GG			GC + CC vs GG			CC vs GG + GC		
	Ph	I^2	*Pe*	*Ph*	I^2	*Pe*	*Ph*	I^2	*Pe*	*Ph*	I^2	*Pe*	*Ph*	I^2	*Pe*
Total	<0.001	96%	0.493	0.002	71%	0.290	<0.001	75%	0.835	<0.001	76%	0.649	0.255	23%	0.014
Cancer type															
–Bladder	0.526	0%	–	0.207	37%	–	0.245	26%	–	0.332	0%	–	0.408	0%	–
–Renal cell	0.020	81%	–	0.363	0%	–	0.012	84%	–	0.013	84%	–	0.899	0%	–
–Prostate	<0.001	98%	–	0.269	18%	–	0.522	0%	–	0.359	0%	–	0.081	67%	–
Source of control															
–Hospital based	<0.001	97%	0.563	0.001	75%	0.304	<0.001	77%	0.663	<0.001	79%	0.553	0.202	31%	0.027
HWE															
–Yes	<0.001	97%	0.693	0.520	0%	0.060	0.274	22%	0.890	0.457	0%	0.763	0.189	35%	0.006
–No	<0.001	93%	–	<0.001	93%	–	<0.001	95%	–	<0.001	95%	–	0.364	0%	–
Ethnicity															
–Asian	<0.001	97%	0.831	0.001	78%	0.197	0.012	69%	0.680	0.012	69%	0.459	0.206	32%	0.010
–Caucasian	0.009	85%	–	0.103	62%	–	0.004	88%	–	0.002	89%	–	0.276	16%	–
Sample size															
– <1000	0.002	76%	0.533	0.002	76%	0.734	<0.001	83%	0.058	<0.001	84%	0.041	0.729	0%	0.411
– >1000	<0.001	99%	–	0.921	0%	–	0.377	0%	–	0.479	0%	–	0.628	0%	–

Ph, *P*heterogeneity ($p < 0.1$ was considered as a significant difference). *Pe*, *P*egger ($p < 0.05$ was considered as a significant difference).
HWE: Hardy–Weinberg equilibrium.

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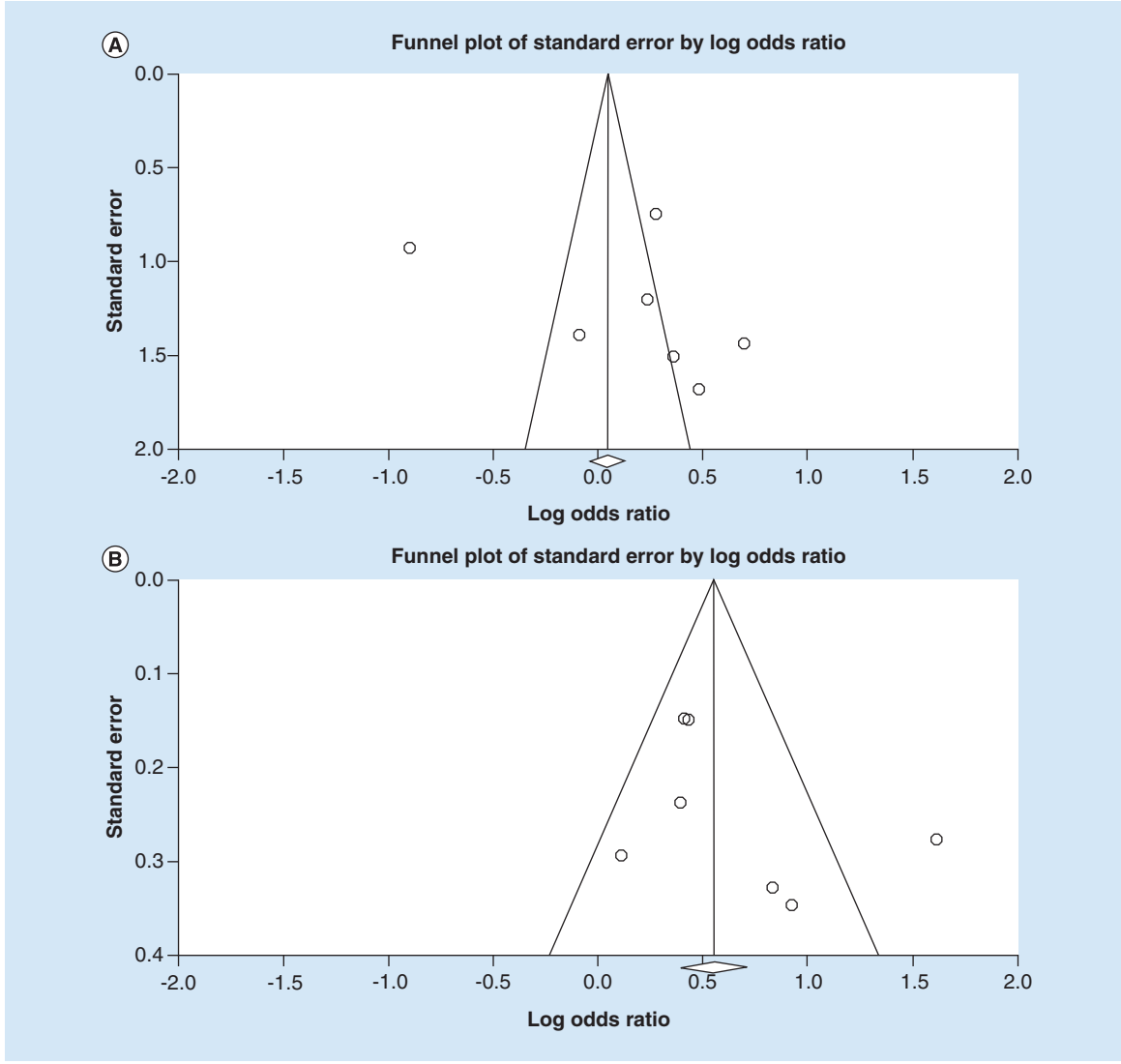

Figure 3. Funnel plot for association of c.-31G>C polymorphism of *survivin* gene with urinary system cancers in overall analysis. An symmetrical distribution was found in allelic **(A)**, homozygote codominant **(B)**, heterozygote codominant **(C)** and dominant **(D)** genetic models.

the meta-analysis each time and then recalculated ORs. Our results showed that the respective pooled ORs was not substantially chanced (data not shown), suggesting that the meta-analysis were statistically robust.

Discussion

Some epidemiological studies have investigated the association of *survivin* c.-31G>C polymorphism with the urinary tract cancers risk, but the results of these studies are inconclusive and sometimes they might be inconsistent. This may arise from the limitations of single studies. Meta-analysis has been widely used in epidemiological studies; mostly for the evaluation of gene polymorphisms for cancer susceptibility. It could make better statistical potency, subsequently obtaining a more accurate conclusion [20]. Therefore, we used a meta-analysis to find out the association of c.-31G>C transversion with the urinary cancers risk. The data from our meta-analysis showed that there is a significant association between c.-31G>C polymorphism and risk of urinary cancers in several genetic models with a true heterogeneity. Also, stratified meta-analysis showed that significant associations remain significant. Of course, the significant heterogeneities disappear after stratifying by cancer type; therefore, it may be source of heterogeneities. In the meta-analysis, we did not observe main publication biases and also sensitivity analysis showed our meta-analysis is reliable and robust.

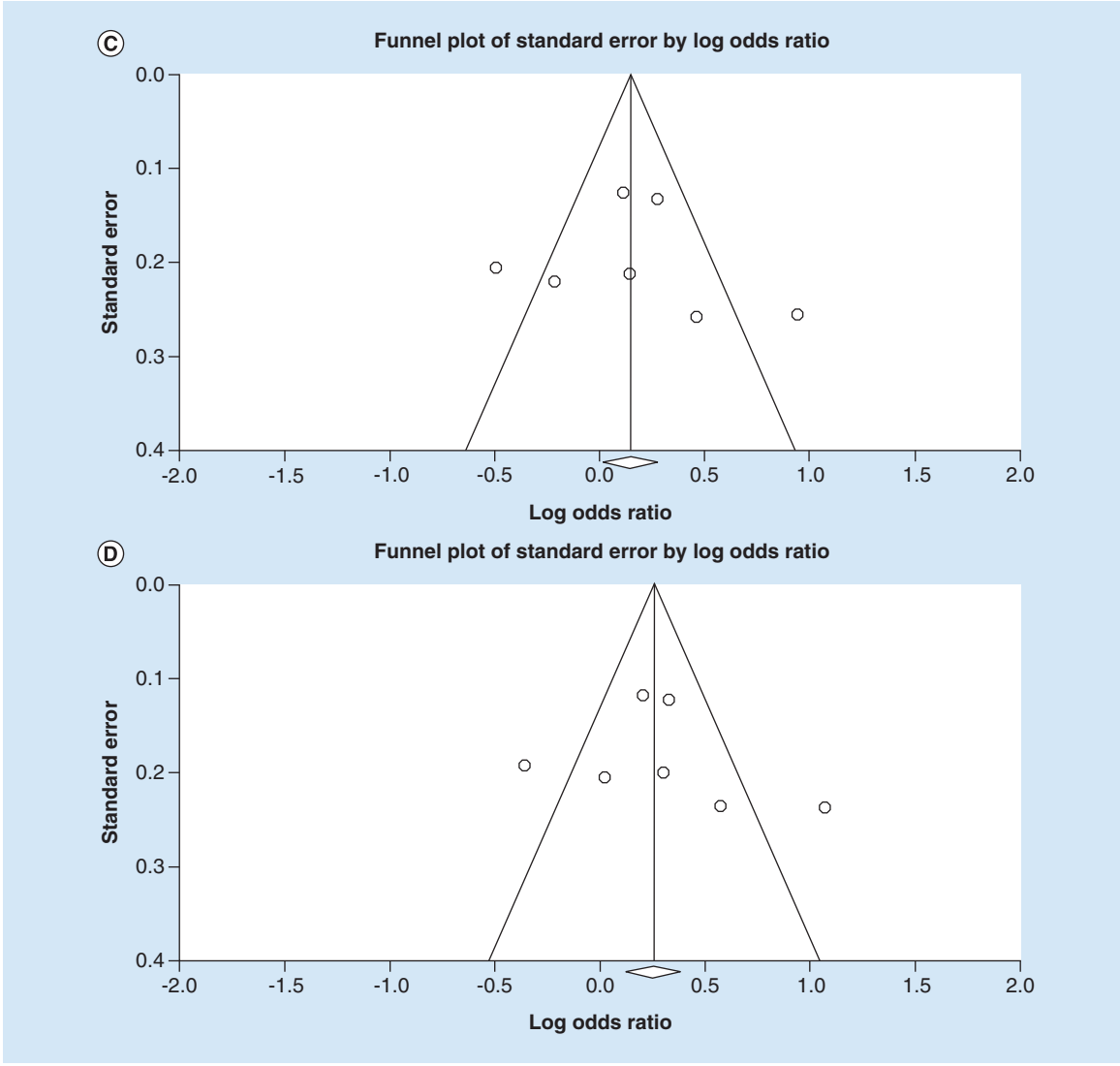

Figure 3. Funnel plot for association of c.-31G>C polymorphism of *survivin* gene with urinary system cancers in overall analysis (cont.). An symmetrical distribution was found in allelic **(A)**, homozygote codominant **(B)**, heterozygote codominant **(C)** and dominant **(D)** genetic models.

Our study showing the association of c.-31G>C polymorphism with risk of urinary system cancers is biologically reasonable. It is largely approved that changes in the expression profile of antiapoptotic and proapoptotic proteins [21,22] could result in cancer's resistance to apoptosis. Survivin, an antiapoptotic molecule, has a main role in the pathway of apoptosis and also in cell proliferation. Evidence is expanding that survivin was strikingly upregulated in several human cancers cells, consisting with the deregulated apoptosis in tumor cells [17,23]. Genetic variations including SNPs could alter the mRNA structure, gene expression pattern and protein function [24–26]. The exact mechanism explaining the association of rs9904341 with risk of urinary system cancers is still unclear. Some reports proposed that key genetic variations could change the expression of *survivin* gene. Upregulation of survivin made by mentioned key SNPs may reduce apoptotic capacity and increase tumor development [27]. The c.-31G>C SNP can interrupt the CDE/CHR repressor element and then increase the *survivin* overexpression. *In vitro* examination also showed that c.-31G allele is less active transcriptionally rather than c.-31C allele so, c.-31CC genotype will have overexpression of *survivin* gene [28]. Nikiteas *et al.* discovered that *survivin* mRNA expression of -31CC homozygous phenotype were around 1.6-times greater than GG and GC phenotypes [29]. Xu *et al.* also established that the incidence of variation including rs9904341 SNP was associated with up-regulation of survivin

in some cell lines [30]. Regarding these explanations, we expected that surviving possibility contributed to increasing the urinary system cancers risk, and our study established this suggestion.

Some latest papers displayed that using *in silico* tools could be a beneficial attitude to comprehend and deduce the polymorphism influences more precisely [31,32]. In our previous study, we employed *in silico* software to predict the impacts of c.-31G>C polymorphism in function of *survivin* gene [19]. We found that the mentioned SNP cause to change in regulation of *survivin* transcription. We reported that it may change interactions of transcription factors with the promoter region and it may influence *survivin* gene expression. Also, we found that, c.-31G>C polymorphism happens in a CpG island and any change in this region may influence methylation profile of the promoter [19]. CpG Islands methylation has been broadly defined as a mechanism related with regulation of gene expression [33] particularly in prostate malignancy [34].

There are some limitations in this study which should be considered. We did not access to original data such as age, BMI, Gleason score, etc. to adjust the results in the meta-analysis. Also, there were no paper investigating the association of c.-31G>C polymorphism with urinary system cancers in African and Latino population. Furthermore, we did not include the non-English articles that it may result in language bias.

Conclusion & future perspective

The *survivin* c.-31G>C mutation could increase the risk of urinary system cancer. However, a meta-analysis with more articles and different ethnicities will help to obtain a more accurate conclusion. Regard to the rate and increase of urinary system cancers worldwide, prevention of these cancers could be the best way to deal with them. Therefore, recognizing the risk factors of urinary system cancers has a high value. Many risk factors for the diseases have been identified that the role of genetic factors is noteworthy. In the meantime, c.-31G>C polymorphism as a genetic risk factor could be a helpful molecular biomarker for screening of susceptible individuals to mentioned cancers.

Executive summary

- Polymorphisms in *survivin* may alter the risk of cancer susceptibility.
- Association of *survivin* c.-31G>C gene polymorphism with urinary system cancers was investigated by a meta-analysis.
- Significant associations between c.-31G>C polymorphism and risk of urinary tract cancers were found in overall and stratified meta-analysis.
- The *survivin* c.-31G>C polymorphism may be a genetic risk factor for urinary system cancer.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/full/10.2217/pme-2018-0053

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Author contributions

M Karimian and A Karimian tried to electronic search. M Karimian and T Mazoochi performed statistical analysis. H Ehteram and A Karimian prepared the initial draft of manuscript. All of authors read and confirm the final version of the paper.

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- **These references contain some interest because they provide useful content about function and structure of survivin.**

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