

Association between survivin-31C/G polymorphism and the risk of urinary system cancer: a meta-analysis

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Abstract: As an inhibitor of apoptosis protein, survivin was abundantly expressed in many human malignancies. Although many studies have demonstrated the relationship between the survivin-31C/G (rs9904341) polymorphism and urinary system cancer susceptibility, the conclusions remained controversial. In order to clarify the effects of this polymorphism on the risk of urinary system cancer, a comprehensive meta-analysis was performed. Six databases were searched to identify the eligible studies. Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated under the allelic, dominant, homozygous, heterozygous and recessive models. The data were analyzed by using the Stata 12.0. Nine case-control studies were included with a total of 2307 cases and 2722 controls. The results indicated that Survivin-31C/G (rs9904341) polymorphism was associated with increased risk of urinary system cancer (OR=1.28 95%CI=1.01-1.62, P=0.039). Stratified analysis by ethnicity (Asian and Caucasian) indicated that Survivin-31C/G variants were associated with a significantly increased risk of urinary system cancer in Asian population (OR=1.53 95%CI=1.27-1.85, P<0.001), but associated with a reduced risk of urinary tract cancer in Caucasian (OR=0.29 95%CI=0.13-0.64, P=0.002). This meta-analysis suggested that the Survivin-31C/G (rs9904341) variants increased the urinary system cancer predisposition in Asian population, and reduced the urinary system cancer predisposition in Caucasian.

Keywords: Survivin; Meta-analysis; Polymorphism; Urinary system cancer

Received 27 March 2018, Revised 12 April 2018, Accepted 15 April 2018

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1. Introduction

As we all known, the incidence of cancer has alarmingly increased over the past decades. It is a multifactorial disease that resulted from the complicated interactions between genetic and environmental factors[1]. Furthermore, there is strong evidences that various genetic variations contribute to influence the risk of cancer[2]. Emerging evidence showed that overexpression of the survivin gene was correlated in various cancers including pulmonary, hepatocellular, colorectal, cervical and bladder[3-7]. We noted that survivin-31C/G variants effect on the susceptibility of urinary system cancer.

The survivin gene is localized on human chromosome 17q25, consists of 4 exons and 3 introns, and involvement in the regulation of apoptosis and cell cycle[8,9]. Apoptosis is an important way in maintain homeostasis and preserves balance of cellular function[10,11]. Previous studies showed that the over expression of survivin gene plays an important role in the development of malignant neoplasms by reducing cancer cell apoptosis[12]. Therefore, survive in gene can be used as apotential target for diagnosis and gene therapy.

It was reported that more than 10 common single nucleotide polymorphisms (SNPs) in the promoter region of the survival genes, but the survivin-31G/C polymorphism (rs9904341) was one of the most common variants. Moreover, further examination revealed that the survivin-31G/C polymorphism (rs9904341) was associated with an increased risk of urinary system cancer. However, the

results from different groups are disputed to a degree, which might attribute to the limitations of individual studies, including the differences of sample size and ethnicity, study design or disagreements among the investigations. Therefore, we conducted a comprehensive meta-analysis to gain more reliable conclusion about associations between survivin-31G/C variants and the susceptibility of urinary system cancer risk.

2. Materials and methods

2.1. Literature search

Two investigators (Mu and Du) searched the Web of Science, PubMed, EMBASE and Google Scholar databases up to December 31, 2017 using the following terms: (“survivin” or “BIRC5 protein, human” or “EPR-1”) and (“renal” or “kidney” or “prostate” or “bladder” or “urothelial”) and (“carcinoma” or “cancer” or “tumor”) and (“single nucleotide polymorphism” or “SNP” or “genetics” or “variant” or “polymorphism”). In addition, references of the retrieved articles were manually searched as well.

2.2. Inclusion and exclusion criteria

The selected studies had to match the following inclusion criteria: (1) case-control or cohort study; (2) investigation of survivin-31G/C polymorph is mand urinary cancer risk; (3) sufficient genotype distributions of cases and controls were provided to calculate the odds ratio (OR) and 95% confidence interval (95%CI); (4) full-text publications; (5)

published in English or Chinese were included in our meta-analysis; (6) genotype distributions of the controls were in Hardy–Weinberg equilibrium (HWE). Moreover, abstracts, unpublished findings, reports without control population or genotype frequency data,

duplication of previous publications, case reports, reviews, or meta-analysis, animal studies, and irrelevant papers were all excluded. A flow diagram of the study selection process is presented in Figure 1.

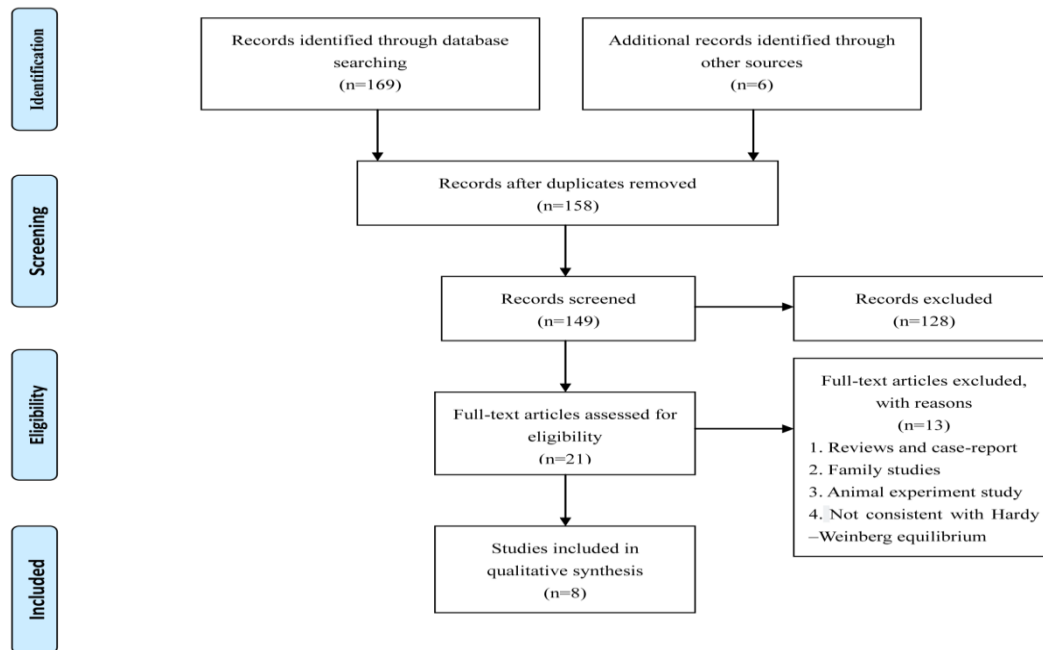


Figure 1. Flow diagram for the process of selecting literatures.

2.3. Data extraction

Two investigators (KF Mu and T He) independently extracted the information from all the eligible studies, and any disagreements were resolved by discussion between them. The following characteristics were collected from selected studies: first author, year of publication, country, ethnicity, sample sizes of cases and controls, genotype numbers, age, gender, genotyping methods, and HWE.

2.4. Statistical analysis

The association between survivin-31G/C polymorphism and urinary system cancer susceptibility was assessed from selected studies using odds ratios (ORs) and 95% confidence intervals. In this meta-analysis, five genetic models, such as allelic (G vs. C), dominant (GG+GC vs. CC), homozygous (GG vs. CC), heterozygous (GC vs. GG) and recessive (GG vs. GC+CC) models, were analyzed for survivin-31G/C polymorphism. Heterogeneity was evaluated by I^2 -statistics[13,14], and I^2 value >50% indicated that significant heterogeneity (no heterogeneity: $I^2 < 25\%$; moderate heterogeneity: $I^2 = 25\text{--}50\%$) exist[15]. If significant heterogeneity existed, the random-effect model was used; otherwise the fixed-model was adopted[16]. The potential publication bias was checked by visual inspection of a funnel plot and p -value of Begg's test. The asymmetric

plot and p -value of Begg's test below 0.05 were considered a significant publication bias[17]. To assess the stability of the results, sensitivity analysis was conducted by omitting each individual study in turn from the all selected studies and reanalyzed remainder. All statistical tests were carried out using the Stata 12.0 (Stata Corp, College Station, Texas 77845, USA).

3. Results

3.1. Characteristics of selected studies

Finally, 9 case-control studies with 2307 cases and 2722 controls were identified in this meta-analysis (one of the articles contained two case-control studies). Of those studies, four studies were performed in China [18-21], two in Serbia[22,23], one in Japan[24], one in India[25]. In terms of the ethnicity, 6 studies were carried out in Asian population[18-21,24,25], two other studies focused on Caucasian population[22,23]. By the source of the tumor, four studies focused on bladder cancer(BC)[19,20,24,25], one studies focused on renal cell cancer(RCC)[18], one studies focused on Willms tumor (WT)[23], two studies on urothelial cancer (UC)[20,22], one studies focused on prostate cancer(PC)[21]. Primary characteristics, the genotype distributions of survivin-31C/G polymorphism in the eligible studies were listed in Table 1.

Table 1. Basic characteristics of the 10 selected studies included

First author	Year	Country	Ethnicity	Cancer type	No. of case/control	Case			Control			Genotyping Method
						GG	GC	CC	GG	GC	CC	
Qin	2012	China	Asian	RCC	710/760	172	345	193	215	385	160	PCR-RFLP
Jaiswal	2011	India	Asian	BC	200/200	83	85	32	98	87	15	PCR-RFLP
Kawata	2010	Japan	Asian	BC	235/346	50	99	86	75	184	87	PCR-RFLP
Ye	2012	China	Asian	BC	115/166	21	53	41	46	78	42	PCR-RFLP
Bogdanovic	2017	Serbia	Caucasian	UC	92/82	54	31	7	26	45	11	PCR-RFLP
Lin	2017	China	Asian	UC	185/188	43	112	30	48	99	41	PCR-RFLP
Lin	2017	China	Asian	BC	46/188	9	25	12	48	99	41	PCR-RFLP
Chen	2013	China	Asian	PC	665/710	150	319	196	205	331	174	PCR-RFLP
Radojevic	2012	Serbia	Caucasian	WC	59/82	36	19	4	26	45	11	PCR-RFLP

HWE: Hardy-Weinberg equilibrium; PCR: polymerase chain reaction; RFLP: restricted fragment length polymorphism; RCC: renal cell cancer; UC: urothelial cancer; BC: bladder cancer; PC: prostate cancer WC: Wilms tumor

3.2. Association of Survivin-31C/G Polymorphism with urinary system cancer susceptibility

The relationship between survivin-31C/G polymorphism and urinary system cancer susceptibility was analyzed in 9 independent studies. In the overall analysis, the results indicated that Survivin-31C/G variants were associated with an increased risk of urinary system cancer (G vs. C: OR=1.06, 95%CI=0.88-1.29, P=0.524; GG+GC vs. CC: OR=1.28, 95%CI=1.01-1.62, P=0.039; GG vs. CC: OR=1.28, 95%CI=0.93-1.77, P=0.127, GC vs. CC: OR=0.78, 95%CI=0.63-0.97, P=0.023; GG vs. GC+CC: OR=1.00, 95%CI=0.74-1.35, P=0.982; Figure 2 and Table 2). Stratified analysis based on ethnicity suggested that Survivin-31C/G variants were associated with increase the risk of urinary system cancer in Asian population, but associated with a reduced risk of urinary tract cancer in Caucasian. (Asian: G vs. C: OR=1.24, 95%CI=1.14-1.35, P<0.001; GG+GC vs. CC:

OR=1.39, 95%CI=1.12-1.71, P=0.002; GG vs. CC: OR=1.53, 95%CI=1.27-1.85, P<0.001, GC vs. CC: OR=0.76, 95%CI=0.69-0.96, P=0.024; GG vs. GC+CC: OR=1.28, 95%CI=1.13-1.47, P<0.001; Caucasian: G vs. C: OR=0.45, 95%CI=0.32-0.64, P<0.001; GG+GC vs. CC: OR=0.51, 95%CI=0.23-1.09, P<0.001; GG vs. CC: OR=0.29, 95%CI=0.13-0.64, P<0.001, GC vs. CC: OR=1.11, 95%CI=0.50-2.50, 0.794; GG vs. GC+CC: OR=0.31, 95%CI= 0.20-0.50, P<0.001; Figure 3 and Table 2). Furthermore, in the subgroup analysis by Cancer types (RCC, BC, UC, PC and WT), we found that Survivin-31C/G variants were associated with a increased risk on BC (G vs. C: OR=1.35, 95%CI=1.16-1.57, P<0.001; GG+GC vs. CC: OR=1.72, 95%CI=1.34-2.21, P<0.001; GG vs. CC: OR=1.81, 95%CI=1.32-2.48, P<0.001, GC vs. CC: OR=0.59, 95%CI=0.45-0.78, P<0.001; GG vs. GC+CC: OR=1.28, 95%CI=1.01-1.63, P=0.045; Figure 4 and Table 2).

Table 2. Meta-analysis results of the relationship between survivin-31C/G polymorphism and urinary system cancer risk

Items	N	G vs. C			GG+GC vs. CC			GG vs. CC			GC vs. CC			GG vs. GC+CC		
		OR(95%CI)	I ²	p	OR(95%CI)	I ²	p	OR(95%CI)	I ²	p	OR(95%CI)	I ²	p	OR(95%CI)	I ²	p
Total	9	1.06(0.88-1.29)	78.30%	0.524	1.28(1.01-1.62)	55.3%	0.039	1.28(0.93-1.77)	64.9%	0.127	0.78(0.63-0.97)	40.3%	0.023	1.00(0.74-1.35)	77.70%	0.982
Ethnicity																
Asian	7	1.24(1.14-1.35)	0.00%	<0.001	1.39(1.12-1.71)	47.7%	0.002	1.53(1.27-1.85)	13.3%	<0.001	0.76(0.69-0.96)	52.4%	0.024	1.28(1.13-1.47)	0.00%	<0.001
Caucasian	2	0.45(0.32-0.64)	0.00%	<0.001	0.51(0.23-1.09)	0.00%	0.081	0.29(0.13-0.64)	0.00%	0.002	1.11(0.50-2.50)	0.00%	0.794	0.31(0.20-0.50)	0.00%	<0.001
Stroke subtypes																
UC	2	0.68(0.35-1.33)	84.1%	0.261	0.66(0.41-1.04)	83.1%	0.073	0.55(0.21-1.41)	59.2%	0.215	1.43(0.89-2.32)	0.00%	0.143	0.62(0.18-2.09)	89.7%	0.440
BC	4	1.35(1.16-1.57)	0.00%	<0.001	1.72(1.34-2.21)	0.00%	<0.001	1.81(1.32-2.48)	0.00%	<0.001	0.59(0.45-0.78)	0.00%	<0.001	1.28(1.01-1.63)	0.00%	0.045

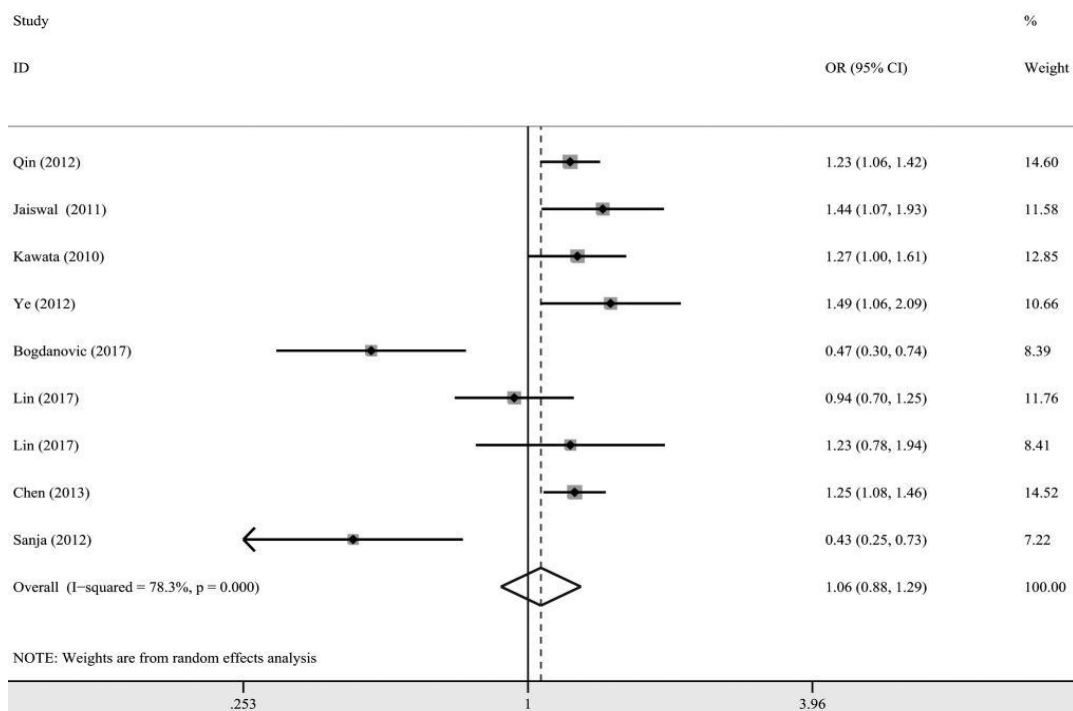


Figure 2. Forest plot of the association between survivin-31G/C polymorphism and urinary system cancer susceptibility in the overall population

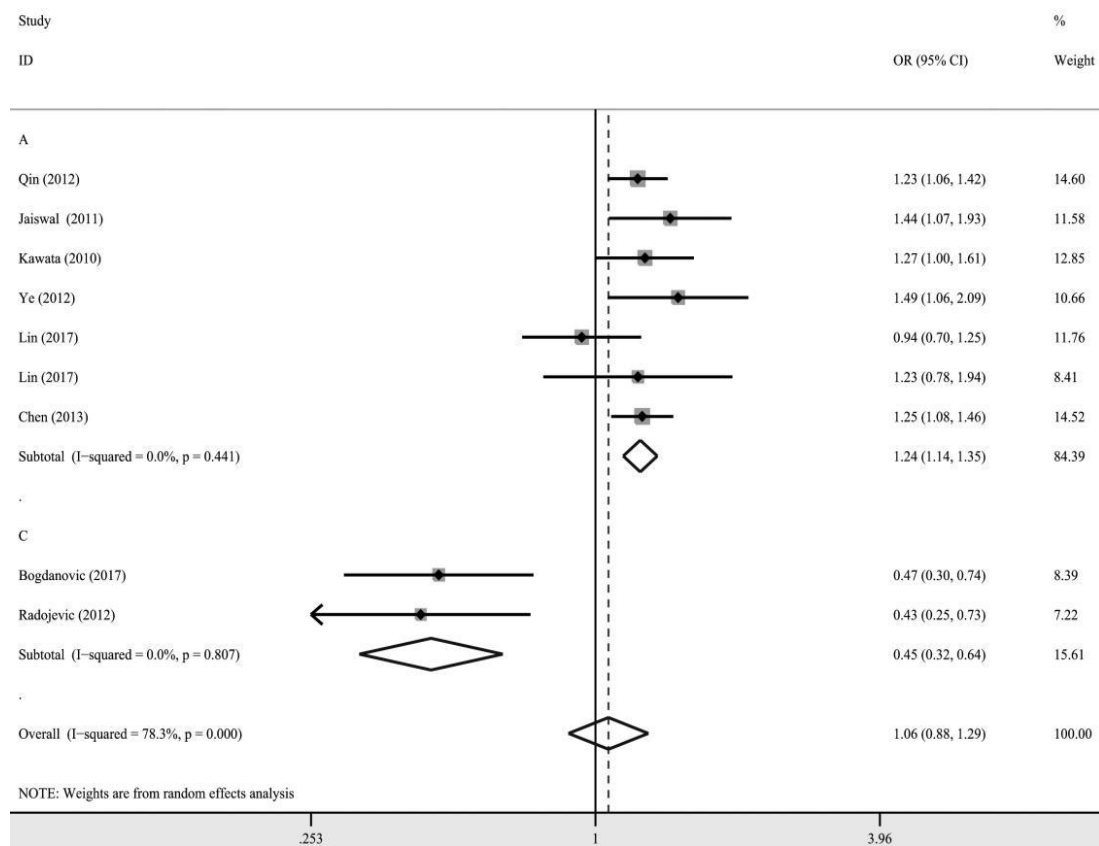


Figure 3. Forest plot for the association of survivin-31G/C polymorphism with urinary system cancer susceptibility in the subgroup analysis by ethnicity (G vs. C).

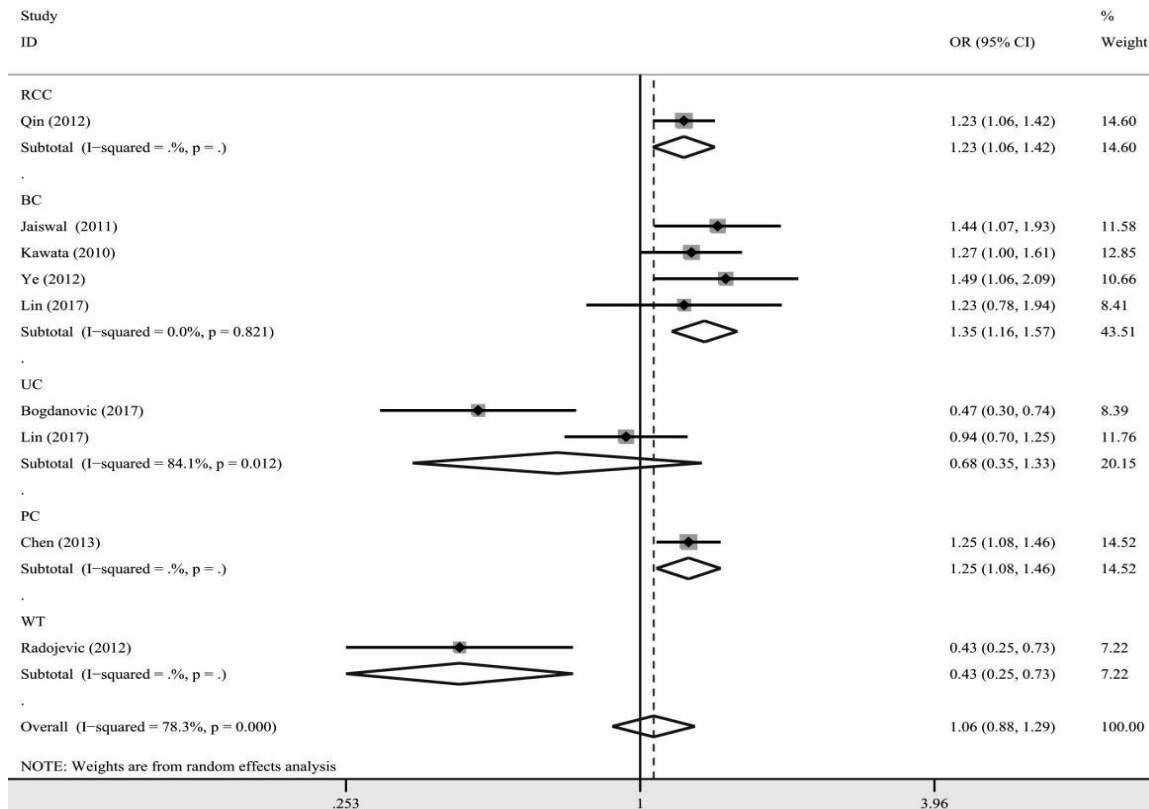


Figure 4. Forest plot for the association of survivin-31G/C polymorphism with urinary system cancer susceptibility in the subgroup analysis by tumor types (G vs. C).

3.3. Sensitivity analysis and publication bias

By omitting any single study each time, the results suggested that no materially alterations in pooled OR and 95% CI under the allelic model, which indicated the stability of our meta-analysis (Figure 5). In addition, the funnel plots and P value for Begg’s test were executed to weigh the presence of publication

bias in this meta-analysis of Survivin-31C/G polymorphism. Symmetrical funnel plots and P value for Begg’s test (G vs. C:P=0.348; GG+GC vs. CC: P=0.602; GG vs. CC: P=0.251; GC vs. CC: P=0.602 and GG vs. GC+CC: P=0.466) indicated that no publication bias existed in this meta-analysis (Figure 6).

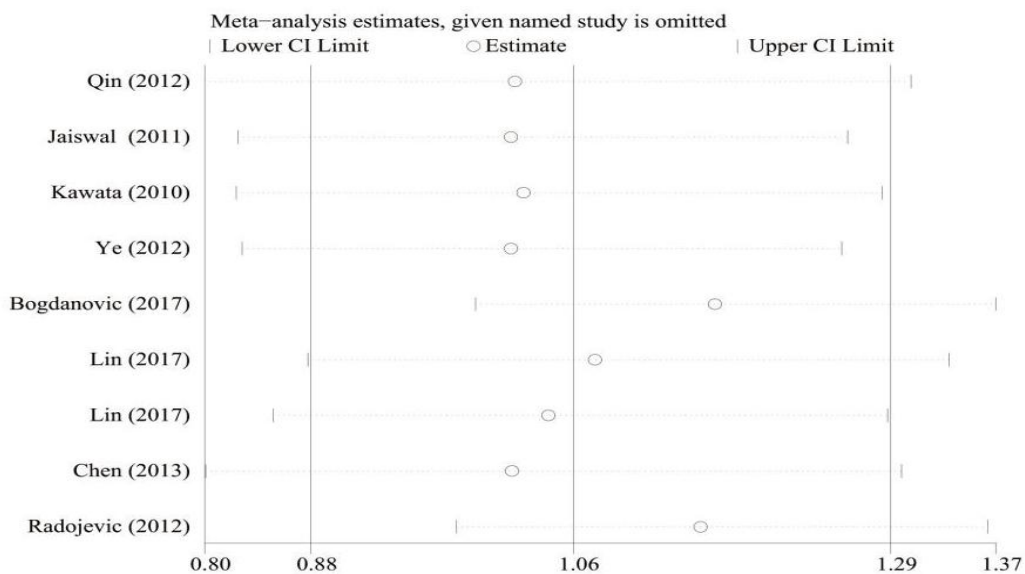


Figure 5. Sensitivity analysis of the summary OR coefficients under the allelic model (G vs. C)

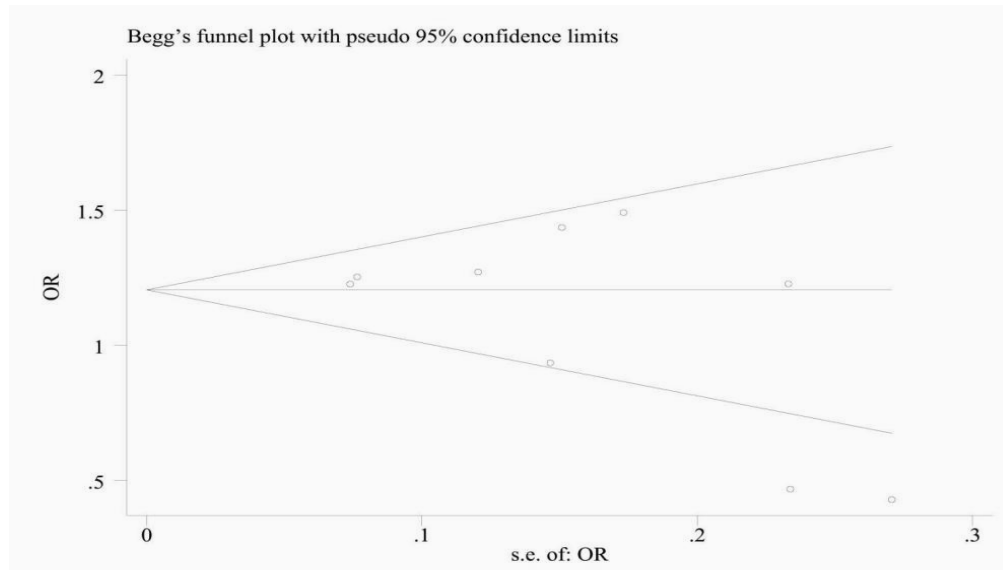


Figure 6. Begg's funnel plot for publication bias in selected studies on the survivin-31G/C polymorphism (G vs. C).

4. Discussion

Survivin, an inhibitor of apoptosis protein, play an important role in modulating processes such as cell proliferation, cell cycle checkpoints, cell stress response, activation of various cell signaling pathways and cytokine[26]. So far, about 199 single nucleotide polymorphisms (SNPs) have been found in the human survival gene[27]. Among them, the -31G/C polymorphism (rs9904341) is most widely studied, and is believed to be associated with malignant neoplasm. Recently, multiple studies have revealed the association between the survivin-31C/G polymorphism and variety of urological malignancy. However, due to the limitation of sample size, most of the studies are hard to draw a convincing conclusion. Our meta-analysis attempted to investigate the association between survivin-31G/C polymorphism and the risk of urological malignancy, involving about 2307 cases and 2722 controls. Our meta-analysis indicated that the survivin-31G/C variants were overall associated with urinary system cancer susceptibility.

In addition, moderate heterogeneity appeared in all five models (Table 2). In the stratified analysis based on ethnicity (Asian and Caucasian), no heterogeneity ($I^2=0$) was detected in both two subgroups under the all five models (Table 2). The results demonstrated that survivin-31G/C variants contributed to increase the risk of urinary system cancer in Asian population, and reduced the urinary system cancer predisposition in Caucasian. We also performed a subgroup analysis by tumor types. Due to the limited number of cases in the study, we only selected the type of disease with two more control studies for analysis (BC and UC). No heterogeneity was detected in BC group under all five models. However, greater heterogeneity existed in UC

group under the allelic, homozygous, dominant, and recessive models (Table 2). We noted that one studies focused on UC involved in Caucasian; the other studies were conducted in Asia population. As mentioned above, survivin-31G/C variants contributed to increase the risk of urinary system cancer in Asian population, and decrease the risk of urinary system cancer in Caucasian. No heterogeneity ($I^2=0$) was detected in both Asian and Caucasian population under the all five models (Table 2). In a word, our meta-analysis represented that the survivin-31G/C variants increased the urinary system cancer predisposition in Asian population, and reduced the urinary system cancer predisposition in Caucasian.

It should be emphasized that there are some limitations in this meta-analysis. Firstly, only published studies were included in our meta-analysis, the publication bias may exist. Secondly, only two studies focused on the Caucasian population, the results may be suspect. Finally, the role of gene-gene and gene-environment interactions were not considered which may play an important role in modulation of cancer risk. Besides, the number of published studies was not sufficient enough for a comprehensive analysis, especially for any particular cancer type.

5. Conclusion

In summary, this meta-analysis suggested that survivin-31G/C variants increased the urinary system cancer predisposition in Asian population, and reduced the urinary system cancer predisposition in Caucasian. Considering the limitations mentioned above, well-designed studies with larger sample sizes and more ethnicities are necessary to validate those associations.

Acknowledgments

We would like to acknowledge the all authors for their helpful comments on this paper. This work was supported by the Natural Science Foundation of Shandong province (No.ZR2014HM059).

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