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Review Article

-31G>C polymorphism in the functional promoter of survivin increased the risk of gastrointestinal cancer: evidence based on an update meta-analysis

Bairen Yang, Jun Huang, Weichang Guo

Department of General Surgery, The First People's Hospital of Yibin, Yibin 64400, Sichuan, China

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Abstract: Background and aim: The association between surviving -31G>C polymorphism and gastrointestinal cancer risk are still inconclusive. The aim of this study is to pool previous studies to get a more precise assessment of the association between this SNP and gastrointestinal cancer risk. Methods: Case-control studies were searched among databases. The strength of the association between survivin -31G/C polymorphism and gastric or colorectal cancer risk was estimated by pooling odds ratios (OR) and 95% confidence intervals (CI) under five genetic models. Results: Eight qualified studies were included for this met-analysis. The association between survivin -31G/C polymorphism and the risk of gastrointestinal cancers was significant under all of the five models (allele model: OR=1.45, 95% CI: 1.23-1.71, P<0.00001; dominant model: OR=1.51, 95% CI: 1.21-1.89, P=0.0003; recessive model: OR=1.67, 95% CI: 1.34-2.09, P<0.00001; homozygous model: OR=1.94, 95% CI: 1.43-2.64, P<0.0001; heterozygous model: OR=1.55, 95% CI: 1.34-1.81, P<0.00001). However, single allele variant was insufficient to significantly increase gastric cancer risk, but was sufficient for colorectal cancer. Conclusion: This study provided strong evidence about the association between survivin -31G/C polymorphism and the risk of gastrointestinal cancers in both Asian and Caucasian. To further verify these findings, more large well-designed epidemiological studies are required.

Keywords: Survivin, -31G/C polymorphism, rs9904341, gastrointestinal cancer, meta-analysis

Introduction

Gastric and colorectal cancers ranked the 2nd and 4th most common cause of cancer death across the world in 2011 [1]. These two gastrointestinal cancers are generally viewed as multifactorial disease, which is closely related to complex interactions between environmental and genetic factors [2]. However, the detailed mechanism of carcinogenesis remains largely unknown. Genetic variations, which interrupt the normal cellular process is one of the most important factors of cancer risks [3]. Apoptosis, as an important cellular process in maintaining homeostasis, plays a critical role in tumor development and progression [4].

Survivin, which is also called baculoviral inhibitor of apoptosis repeat-containing 5 (BIRC5), is an inhibitor of apoptosis protein (IAP). Survivin mainly regulates apoptosis and in cell cycle control and is upregulated in almost all human tumors [5, 6]. The human survivin gene is located on chromosome 17q2, with 4 exons and 3 introns [7]. Although over 10 single nucleotide polymorphisms (SNPs) were identified in the promoter gene of Survivin, the -31G/C polymorphism (rs9904341) is the most common one that located at the cell cycle-dependent element and cell cycle homology region (CDE/CHR) repressor binding site [8]. Due to its important position, this SNP may alter cell cycle-dependent transcription and increase survivin expression at both mRNA and protein levels [9]. Overexpression of survivin was already considered as an important diagnostic and prognostic marker for gastric and colorectal cancer [10, 11]. Because the profound influence of -31G/C

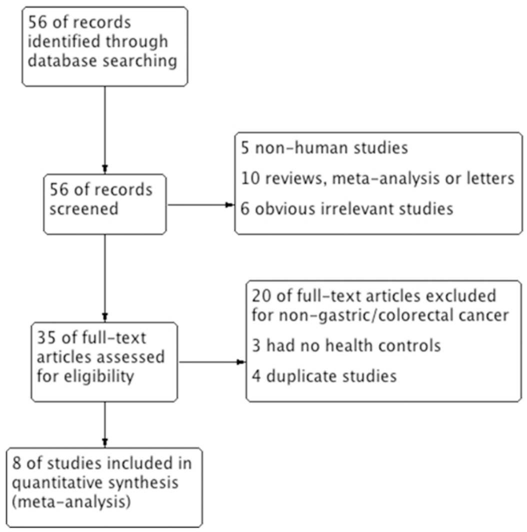

Figure 1. The searching and screening process.

polymorphism on survivin expression, this SNP may also modulate susceptibility to gastrointestinal cancer.

Recently, many studies explored the association between surviving -31G>C polymorphism and gastrointestinal cancer risk and reported conflicting results. Due to relatively small sample size of individual studies, their conclusions are not statistically conclusive. The aim of this study is to pool previous studies to get a more precise assessment of the association between the survivin -31G/C polymorphism and gastrointestinal cancer risk.

Methods

Search strategy

Relevant literatures published between Jan 2000 and Apr 2014 about the association between survivin -31G/C polymorphism and the risk of gastrointestinal cancer were searched among PubMed, Web of Science and Medline by using the following search terms and strategy: ("survivin" OR "BIRC5") AND ("-31G/C" OR "rs9904341" OR "polymorphism" or "SNP") AND ("gastrointestinal" OR "gastric" OR "colorectal" OR "'stomach" OR "intestinal") AND ("cancer" OR "tumor" OR "neoplasm"). No language restriction was applied for searching. Reference list of studies included and other relevant meta-analyses or review were manually searched to find other potentially qualified studies.

Criteria for inclusion and exclusion

Studies meeting the following criteria simultaneously were included for this meta-analysis: (1) case-control study; (2) the study explored the association between survivin -31G/C polymorphism and gastric or colorectal cancer risks; (3) cancer of the patients was confirmed by pathological or histological examinations; (4) detailed data of genotype frequency could be extracted from original studies; (5) the genotype distribution of the controls were as expected by Hardy-Weinberg equilibrium (HWE). Studies were included regardless of publication status, date of publication and language. Studies were excluded if they meet any of the following criteria: (1) not a cohort or a case-control study; (b) incomplete data; (d) case report, letters, reviews or editorial articles.

Data extraction

Two authors independently extracted data from original studies. Disagreement was resolved by referring to original studies in group discussion. The basic information extracted included first author, year of publication, country, ethnicity, cancer type, numbers of subjects, source controls, genotyping methods, genotype frequency of case and control respectively and *p* value of Hardy-Weinberg equilibrium (HWE) in controls.

Quality assessment of studies included

The quality of included studies was assessed with the modified Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) quality score system. This system involves forty assessment items to appraise a trial's quality by giving score from 0 to 40. Therefore, the quality of a study could be defined according to the score range: low quality (0-19), moderate quality (20-29), and high quality (30-40).

Statistical analysis

Cochrane Review Manager (version 5.2, Cochrane Collaboration, Copenhagen, Denmark) was used for data integration and analysis. The strength of the association between survivin -31G/C polymorphism and gastric or colorectal cancer risk was estimated by pooling odds ratios (OR) and 95% confidence intervals (CI) under five genetic models, including allele mo-

Table 1. Characteristics of studies included **Table 1** Characteristics of studies included

Study	Country	Ethnicity	Cancer	Source of control	No. Participants		SNP	Genotype method	Quality score
					Case	Control			
Yang 2009	China	Asian	GC	HB	220	220	rs9904341 (-31G/C)	PCR-RFLP	28
Liarmakopoulos 2013	Greece	Caucasian	GC	HB	88	480	rs9904341 (-31G/C)	PCR-RFLP	28
Cheng 2008	China	Asian	GC	PB	96	67	rs9904341 (-31G/C)	PCR-RFLP	26
Borges 2011	Brazil	Caucasian	GC	HB	47	57	rs9904341 (-31G/C)	PCR-SSCP	26
Li 2013	China	Asian	CRC	PB	275	270	rs9904341 (-31G/C)	PCR-RFLP	26
Huang 2010	China	Asian	CRC	HB	702	711	rs9904341 (-31G/C)	PCR-RFLP	22
Gazouli 2009	Greece	Caucasian	CRC	HB	312	362	rs9904341 (-31G/C)	PCR-RFLP	26
Antonacopoulou 2011	Greece	Caucasian	CRC	HB	163	132	rs9904341 (-31G/C)	Taqman	28

GC = gastric cancer; CRC = colorectal cancer; HB = hospital-based; PB = population-based; PCR-RELP = polymerase chain reaction-restriction fragment length polymorphism; PCR-SSCP = polymerase chain reaction-single strand conformation polymorphism; SNP = single nucleotide polymorphism.

Table 2. The genotype distribution of survivin -31G/C polymorphism

Study	Ethnicity	Cancer	SNP	Case			Control			P.HWE
				GG	GC	CC	GG	GC	CC	
Yang 2009	Asian	GC	rs9904341 (-31G/C)	46	110	64	47	122	51	0.1
Liarmakopoulos 2013	Caucasian	GC	rs9904341 (-31G/C)	18	44	26	163	216	101	0.06
Cheng 2008	Asian	GC	rs9904341 (-31G/C)	20	38	38	31	28	8	0.67
Borges 2011	Caucasian	GC	rs9904341 (-31G/C)	20	18	9	21	28	8	0.78
Li 2013	Asian	CRC	rs9904341 (-31G/C)	42	123	110	55	138	77	0.63
Huang 2010	Asian	CRC	rs9904341 (-31G/C)	144	302	256	180	345	186	0.43
Gazouli 2009	Caucasian	CRC	rs9904341 (-31G/C)	68	131	113	123	163	76	0.11
Antonacopoulou 2011	Caucasian	CRC	rs9904341 (-31G/C)	63	84	16	66	50	16	0.18

GC = gastric cancer; CRC = colorectal cancer; HWE = Hardy-Weinberg equilibrium.

del (C vs. G), homozygote model (CC vs. GG), heterozygote model (CC vs. GC), dominant model (CC+GC vs. GG) and recessive model (CC vs. GC+GG), respectively. Statistical heterogeneity among studies were quantified by Chi square-based Q test and I^2 [12]. χ^2 tests P<0.1 or I^2 >50% indicates significant heterogeneity [12]. If no significant heterogeneity was observed, the fixed effects model (Mantel-Haenszel method) was used to make estimate. If significant heterogeneity observed, the random effects model (DerSimonian Laird method) was used. To explore the source of heterogeneity, subgroup analysis was performed by cancer types and ethnicity. Sensitivity was conducted by omitting each study in turn to check the robustness of the findings. Publication bias was assessed by visual check the funnel plots. Symmetrical or nearly symmetrical distribution of the plots suggests low risk of publication bias. The statistical significance of the pooled OR was examined by Z test, in which P<0.05 was considered as significant difference.

Results

The characteristics of studies included

Through searching and screening with preset criteria, a total of eight studies were included in this meta-analysis. The general process of searching and screening is given in **Figure 1**. The basic characteristics of the eight included studies were summarized in **Table 1**. The eight case-control studies [13-20] include 1,903 cases and 2,299 healthy controls. Four studies [13, 15-17] assessed the association between survivin -31G/C polymorphism and gastric cancer risk and the remaining four [14, 18-20] assessed the association with colorectal cancer risk. Four studies [13, 16, 18, 19] were based on Asian population, while the remaining four are based on Caucasians [14, 15, 17, 20]. Except Antonacopoulou's et al study [20] used TaqMan method for genotyping, other seven all used PCR-RFLP. Quality score of the studies ranged from 22 to 28, suggesting a moderate quality. The genotype distribution of survivin

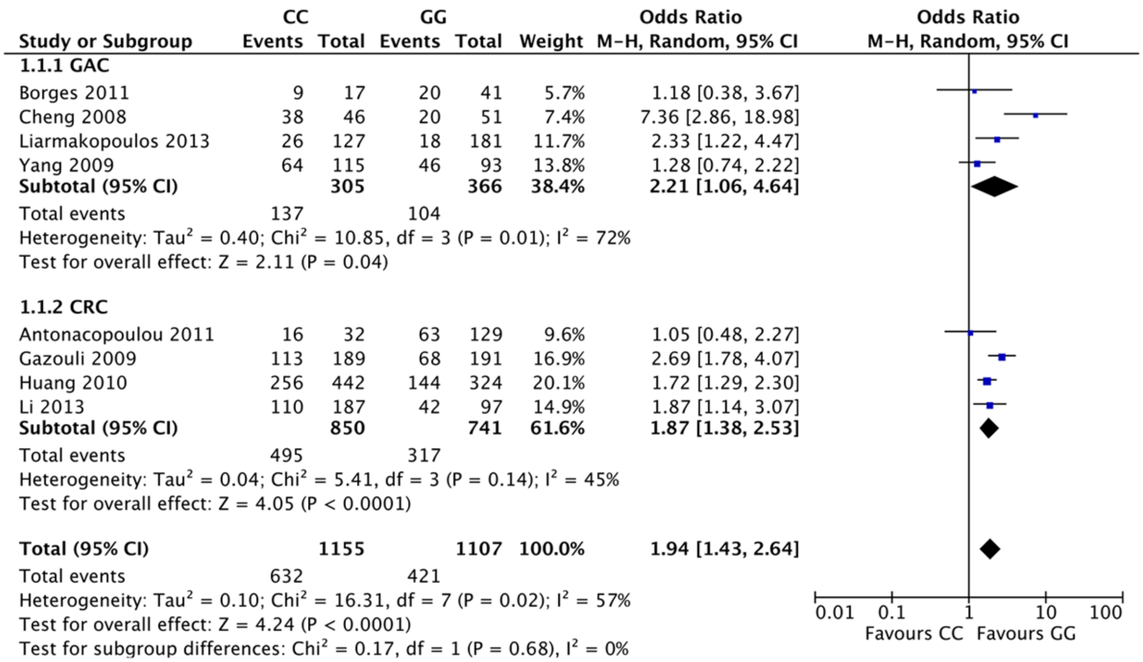

Figure 2. Survivin -31G/C polymorphism and gastrointestinal cancer risks under homozygous model, subgroup by cancer type.

-31G/C polymorphism is presented in **Table 2**. All of the studies had genotype distribution in controls in agreement with Hardy-Weinberg equilibrium (HWE) expectation.

Survivin -31G/C polymorphism and gastrointestinal cancer risks

The overall frequency of C allele of the eight studies was 55.5% in cases and 46.5% in control. Through pooling the OR of the eight studies, it was observed that homozygous CC variant was associated with significantly increased risk of gastrointestinal cancers compared with homozygous GG genotype (OR: 1.94, 95% CI 1.43-2.64, P<0.0001). Subgroup analysis showed consistent risk increasing effect in both gastric cancer (GC) (CC vs. GG: 2.21, 95% CI 1.06-4.64, P=0.04) and colorectal cancer (CRC) group (CC vs. GG: 1.87, 95% CI 1.38-2.53, P<0.0001) (**Figure 2**). The association between survivin -31G/C polymorphism and the risk of gastrointestinal cancers under all genetic models were summarized in **Table 3**. The association was significant under all of the five models (allele model: OR=1.45, 95% CI: 1.23-1.71, P<0.00001; dominant model: OR=1.51, 95% CI: 1.21-1.89, P=0.0003; recessive model: OR=1.67, 95% CI: 1.34-2.09, P<0.00001; homozygous model: OR=1.94, 95% CI: 1.43-2.64, P<0.0001; heterozygous model: OR=1.55, 95% CI: 1.34-1.81, P<0.00001) (**Table 3**). However, except analysis under heterozygous model, the remaining groups all had significant heterogeneity (P<0.1).

Stratified analysis of survivin -31G/C polymorphism and gastrointestinal cancer risks

In the stratified analysis by cancer types, significant associations were observed between survivin -31G/C polymorphism and gastric cancer risk under recessive (OR=1.85, 95% CI: 1.12-3.04, P=0.02), homozygous (OR=2.21, 95% CI: 1.06-4.64, P=0.01) and heterozygous models (OR=1.55, 95% CI: 1.14-2.10, P=0.005). The association under allele model and dominant model was not significant, suggesting the homozygous CC genotype had stronger association with gastric cancer than heterozygous GC genotype and single allele variant had no significant risk increasing effect. In colorectal cancer, the risk increasing effect of this SNP was evident under all of the five models (allele model: OR=1.44, 95% CI: 1.26-1.64, P<0.00001; dominant model: OR=1.48, 95% CI: 1.25-1.76, P<0.0001; recessive model: OR=1.64, 95% CI: 1.27-2.12, P=0.0002; homozygous

Table 3. Overall and stratified analyses of association between survivin -31G/C polymorphism and gastrointestinal cancer risk

Subgroups	No. Studies	Cases/ controls	C vs. G (Allele model)			CC+GC vs. GG (Dominant model)			CC vs. GG+GC (Recessive model)			CC vs. GG (Homozygous model)			CC vs. GC † (Heterozygous model)		
			OR (95% CI)	P	P-H	OR (95% CI)	P	P-H	OR (95% CI)	P	P-H	OR (95% CI)	P	P-H	OR (95% CI)	P	P-H
Overall	8	1,903/ 2,299	1.45 (1.23, 1.71)	<0.00001	0.008	1.51 (1.21, 1.89)	0.0003	0.06	1.67 (1.34, 2.09)	<0.00001	0.07	1.94 (1.43, 2.64)	<0.0001	0.02	1.55 (1.34, 1.81)	<0.00001	0.15
Cancer																	
Gastric	4	451/ 824	1.51 (0.99, 2.30)	0.06	0.002	1.52 (0.85, 2.73)	0.16	0.01	1.85 (1.12, 3.04)	0.02	0.07	2.21 (1.06, 4.64)	0.04	0.01	1.55 (1.14, 2.10)	0.005	0.27
Colorectal	4	1,452/ 1,475	1.44 (1.26, 1.64)	<0.00001	0.23	1.48 (1.25, 1.76)	<0.0001	0.46	1.64 (1.27, 2.12)	0.0002	0.11	1.87 (1.38, 2.53)	<0.0001	0.14	1.56 (1.31, 1.85)	<0.00001	0.08
Ethnicity																	
Asian	4	1,293/ 1,268	1.49 (1.15, 1.94)	0.003	0.005	1.46 (1.03, 2.06)	0.03	0.05	1.75 (1.29, 2.37)	0.0003	0.07	2.03 (1.27, 3.26)	0.003	0.02	1.60 (1.34, 1.93)	<0.00001	0.35
Caucasian	4	610/ 1,031	1.45 (1.16, 1.80)	0.0009	0.16	1.63 (1.21, 2.19)	0.001	0.23	1.53 (1.00, 2.32)	0.05	0.11	1.89 (1.19, 3.01)	0.007	0.14	1.45 (1.10, 1.90)	0.008	0.07

OR = odds ratios; 95% CI = 95% confidence interval; P-H = *P* value of heterogeneity; † = estimates for random effects model.

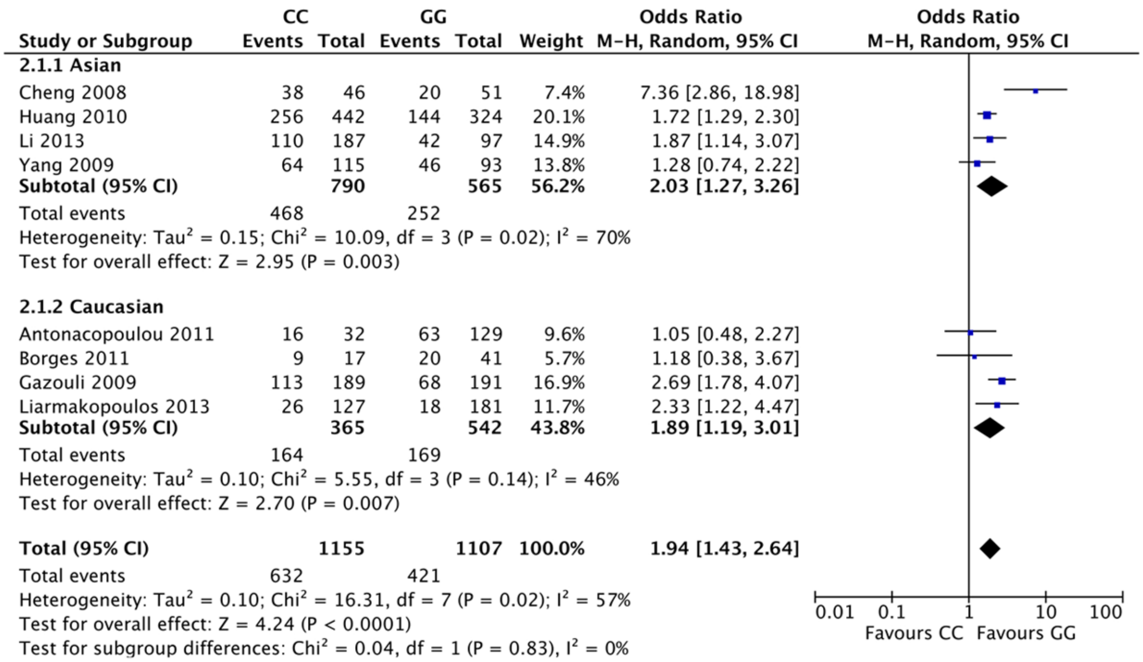

Figure 3. Subgroup survivin -31G/C polymorphism and gastrointestinal cancer risks under homozygous model, subgroup by ethnicity.

model: OR=1.87, 95% CI: 1.38-2.53, P<0.0001; heterozygous model: OR=1.56, 95% CI: 1.31-1.85, P<0.00001). Significant heterogeneity was only observed in homozygous model (P=0.08). The risk increasing effect of survivin -31G/C polymorphism was highly consistent in colorectal cancer and both homozygous (CC) and heterozygous (GC). Single allele change could significantly increase colorectal cancer susceptibility.

In the stratified analysis by ethnicity, significant associations were observed between survivin -31G/C polymorphism and gastrointestinal cancers in both Asian and Caucasian under the five genotype comparison models (**Table 3**). Pooled OR under homozygous model comparison was given in **Figure 3**. In Asians, the strength of the association under different models were: allele model, OR=1.49, 95% CI: 1.15-1.94, P=0.003; dominant model, OR=1.46, 95% CI: 1.03-2.06, P=0.03; recessive model, OR=1.75, 95% CI: 1.29-2.37, P=0.0003; homozygous model, OR=2.03, 95% CI: 1.27-3.26, P=0.003; and heterozygous model, OR=1.60, 95% CI: 1.34-1.93, P<0.00001. In Caucasians, the strength of the association under different models were: allele model: OR=1.45, 95% CI: 1.16-1.80, P=0.0009; dominant model: OR=1.63, 95% CI: 1.21-2.19, P=0.001; recessive model: OR=1.53, 95% CI: 1.00-2.32, P=0.05; homozygous model: OR=1.89, 95% CI: 1.19-3.01, P=0.007; heterozygous model: OR=1.45, 95% CI: 1.10-1.90, P=0.008). Except the heterozygous model, heterogeneity was not significant in Caucasian, suggesting a relatively high consistency of the findings.

Publication bias

Funnel plot for OR of Homozygous model (CC vs. GG) and gastric or colorectal cancer risks were used to assess publication bias (**Figure 4**). The plots were nearly symmetric distributed, indicating a relatively low potential of publication bias. But only eight studies were included in this meta-analysis, it is difficult to estimate the publication bias accurately.

Discussion

Survivin, as member of the IAP family, plays an important role in regulation of cell cycle and inhibition of the apoptotic pathways. Aberrant expression of survivin was observed in various cancer type [21]. In addition, survivin overexpression is also closely related to multidrug resistance, cancer progression, poor prognosis

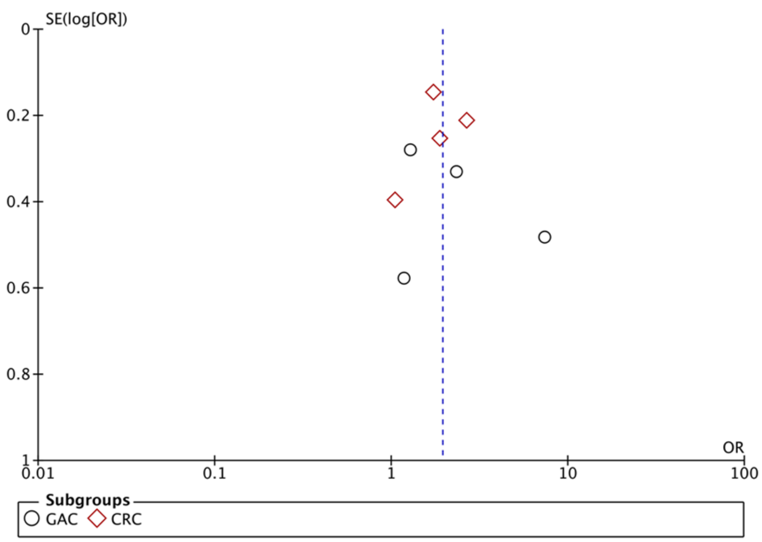

Figure 4. Funnel plot analysis of publication bias.

and survival in several malignancies [22]. Due to the complex regulation, the mechanism of survivin overexpression in different type of tumors is not well understood. Previous studies found that survivin expression could be regulated at the transcriptional level by interfering with the CDE/CHR at the promoter region [9, 23]. Survivin -31G/C polymorphism (rs9904-341), which is located in the CDE/CHR region, is associated with altered survivin expression [8] and thus might affect susceptibility to cancers. Previous studies explored this polymorphism and susceptibility to various types of cancers. But the findings were not consistent and conclusive. Concerning this SNP and gastrointestinal cancer risk, although one previous meta-analysis was conducted, the small number of the studies included made the findings not conclusive.

In this update meta-analysis, data from eight studies concerning the survivin -31G/C polymorphism and gastrointestinal cancer risks were extracted and analyzed. Based on data of 1,903 cases and 2,299 healthy controls, this study observed that this SNP was associated with significantly increased risk of gastrointestinal cancers. Although the following stratified analysis found this SNP was associated with increased risk of both gastric cancer and colorectal cancer, the strength of the association was different.

In gastric cancer, only homozygote CC carriers had significantly higher risk compared with wild-type homozygote GG, heterozygous GC, and combined GG/GC carriers. The allele mo-del comparison did not foundsignificant association. Therefore, single allele variant is insufficient to significantly increase gastric cancer susceptibility. However, in colorectal cancer subgroup, allele model comparison demonstrated that single variant is sufficient to increase gastric cancer susceptibility significantly. Thus, both homozygote CC and heterozygous GC had significantly higher risk of colorectal cancer. In addition, the small heterogeneity suggested consistent findings in colorectal cancer. Based on these findings, it was hypothesized that Allele Chad stronger risk inducing effect in colorectal cancer than in gastric cancer. The discrepancy between gastric and colorectal cancer risk could be partially explained by the different influence of gene-environment interaction in multistep process of carcinogenesis. In subgroup analysis by ethnicity, similar findings were observed in both Asian and Caucasian population. Variant allele C was associated with significantly higher risk of gastrointestinal cancer risk. In Asian population, between studies heterogeneity was quite significant under allele, dominant, recessive and homozygous model. However, in Caucasian population, significant heterogeneity was only observed under heterozygous model. This discrepancy might be explained by the different susceptibility of heterozygous GC carriers to gastrointestinal cancer due to population difference.

This study also has several limitations. Although the overall sample size is relatively large, the number of cases and control in gastric cancer subgroup is still relatively small and thus might not have sufficient statistical power to make persuasive conclusions. Secondly, although most of the studies used PCR-RFLP for genotyping, one studies used TaqMan method. Different methods have different sensitivity. The possible bias associated with the methods may affect the accuracy of pooled results.

Thirdly, data analysis is all based on unadjusted ORs. Thus, the influences of potential confounders were not considered in this study.

Conclusion

In conclusion, this study provided strong evidence about the association between survivin -31G/C polymorphism and the risk of gastrointestinal cancers in both Asian and Caucasian. However, single allele variant was insufficient to significantly increase gastric cancer risk, but was sufficient for colorectal cancer. To further verify these findings, more large well-designed epidemiological studies are required.

Disclosure of conflict of interest

None.

Address correspondence to: Guoxin Li, Department of General Surgery, Nanfang Hospital, Southern Medical University, Guangzhou 510515, Guangdong, China. E-mail: yangbairen1@126.com

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