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Association Between *p21* Ser31Arg Polymorphism and Gastrointestinal Tract Tumor Risk: A Meta-analysis

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Human *p21* gene is characterized by a polymorphism at codon 31 leading to a Serine-to-Arginine (S/R), two different alleles of *p21* Ser31Arg (rs 1801270) polymorphism have been shown to differ significantly in their transcriptional efficiency. More and more investigations are now being carried out to examine a possible link between the *p21* Ser31Arg polymorphism and cancer. However, the results were inconclusive. Therefore, we carried out a systematic review and meta-analysis to examine whether this polymorphism is associated with gastrointestinal tract tumor in Asian. Seven studies (n = 2690), comprising 967 cases and 1723 controls in Asian population, were included in our study. The meta-analysis showed significant association between Ser-allele or Ser/Ser genotype and the susceptibility to gastrointestinal tract tumor in overall studies (Ser-allele vs. Arg-allele: OR = 1.17, 95% CI: 1.04-1.31; Ser/Ser vs. Arg/Arg: OR = 1.38, 95% CI: 1.09-1.75; Ser/Ser vs. Arg/Ser: OR = 1.27, 95% CI: 1.05-1.53; Ser/Ser vs. Arg/Ser + Arg/Arg: OR = 1.29, 95% CI: 1.07-1.54). Despite the limitations, the results of the present meta-analysis suggested that, in the *p21* Ser31Arg polymorphism, Ser-allele and Ser/Ser genotype might be risk factors for gastrointestinal tract tumor in Asian populations.

Key words: Asian; Codon 31; Gastrointestinal tract tumor; Meta analysis; *p21*.

Introduction

The gastrointestinal tract tumor is one of the common causes of death in Asia. According to the data from global cancer statistics in 2008 (GLOBOCAN2008), the esophageal cancer, gastric cancer and colorectal cancer ranked the top-ten incidence rate and mortality rate cancers in Asia (1). More than 70% of the gastric and esophageal cancer cases and deaths occurred in developing countries, and both the highest incidence rates of gastric cancer and esophageal cancer were in Eastern Asia (1, 2). Additionally, the incidence of colorectal cancer has more than doubled over the past few decades, and mortality continues to rise substantially in Asia (3). All these suggest that the gastrointestinal tract tumor may be an important problem of concern to human health in Asia.

The *p21* (also known as CDKN1A) is located on chromosome 6*p21*.2 and consists of three exons and two introns. The translation region of *p21* lies mainly in

Abbreviations: 95% CI: 95% Confidence Interval; OR: Odds Ratio; CNKI: China National Knowledge Infrastructure; CCT: Clinical Controlled Trials; ISTP: Index to Scientific & Technical Proceedings; CACP: Chinese Academic Conference Papers; CDDB: China Dissertation Database; HWE: Hardy-Weinberg Equilibrium; M-H Pooled: Mantel-Haenszel Pooled; D+L Pooled: DerSimonian-Laird Pooled.

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exon 2, which encodes a 21-kda protein (4, 5). As the cyclin-dependent kinase (CDK) inhibitor belonging to the Cip/Kip family, p21 was first described as a potent inhibitor of cell proliferation and DNA replication, both in physiological conditions and after DNA damage (6). As the main downstream regulator of tumor suppressor *p53*, *p21* functions as a unique link from p53 to cell-cycle arrest and DNA repair (5, 7). More recently, it was reported that p21 not only exhibits antioncogenic, but also oncogenic properties depending on its intracellular localization. Thus more and more investigations are now being carried out to unravel its true role in the cellular activities accordingly. Several studies showed that *p21* polymorphisms might affect protein expression and activity, and play a role in susceptibility to cancer (8, 9). Sun *et al.* reported a polymorphism in the *p21* codon31 (NM_000389.3:c.93 C>A, dbSNP rs 1801270) that produces a C to A transversion and causes a substitution from serine (Ser) to arginine (Arg), causing a loss of the restriction site and affecting the DNA binding zinc finger motif (10-12). It was found that *p21* codon 31 (*p21* Ser31Arg), which was later proved to be the only SNP in the 3-kb-long coding sequence of *p21*, both alone and/or in combination with other variants, might have an effect on carcinogenesis (8). A relatively large number of studies evaluated the association between *p21* Ser31Arg and the risk of cancers, such as lung cancer, breast cancer, cervical cancer and so on (13-16), but the results remain inconclusive. Especially there were very few studies about the correlation of *p21* Ser31Arg and gastrointestinal tract tumors in Asians reported. Therefore, to derive a more comprehensive and precise estimation of the relationship, we conducted a systematic meta-analysis by including all relevant gastrointestinal system studies focusing on the association between the *p21* Ser31Arg and the risk of gastrointestinal tract tumors in Asians.

Materials and Methods

Literature Search and Inclusion/Exclusion Criteria

The workflow of our study was shown in Figure 1. We conducted a computerized literature search of the MEDLINE (Host: PubMed), EMBASE (Host: Ovid), Google Scholar, CNKI (China National Knowledge Infrastructure) and Chinese Biomedicine databases to retrieve all available papers up to May 2013. The uncompleted studies in the Cochrane Central Register of Controlled Trials, Clinical Controlled Trials (CCT), the conference proceedings published in Index to Scientific & Technical Proceedings (ISTP), Chinese Academic Conference Papers (CACP) and the academic dissertations in China Dissertation Database (CDDB) were also searched. The search terms included ("*P21*" OR "CDKN1A"), ("polymorphism" OR "variant"), and ("cancer" OR "carcinoma"). Hand searches including backward and forward searches were also conducted by reviewing the reference lists and prospective citation searches for all retrieved studies and relevant review articles to further extend our search. Then a total of 10 references were qualified for the analysis after we screened in the studies related to the gastrointestinal system tumors. All human-associated studies, regardless of sample size, were included if they met the following criteria: (1) evaluation of *p21* Ser31Arg polymorphism and cancer risk; (2) about gastrointestinal tract tumor; (3) case-control studies which use Asia's local population as objects; (4) sufficient data for examining an odds ratio (OR) with 95% confidence interval (95% CI). Studies were excluded if they were: (1) published duplicate data; (2) abstract, comment, review and editorial reviews or case reports; (3) no sufficient data were reported, or in which relevant raw data could not be abstracted; (4) were family-based genetic studies.

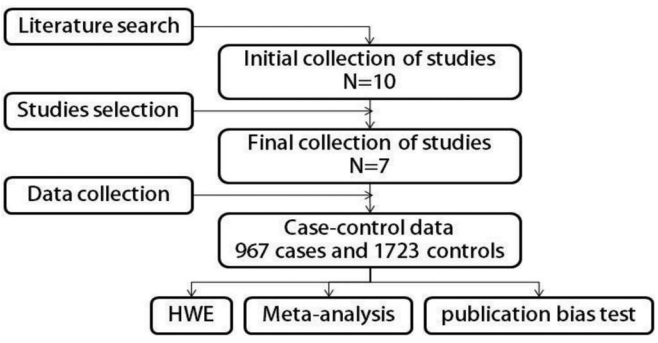

Figure 1: Workflow chart of this study.

Data Extraction

Two investigators (Y. Dong and X. Wang) extracted information from all eligible publications independently according to the inclusion criteria listed above. Disagreements between two investigators were resolved by discussion with the project group until consensus was obtained on every item. Seven papers (4, 11, 17-21) were included for the final analysis. The following characteristics were extracted from each study: First author, year of publication, country of the first or corresponding author, ethnicity, cancer type, source of control groups (population-based and hospital-based controls), genotyping methods, the number of cases and controls, and the number of three genotypes between cases and controls, respectively.

Statistical Analysis

All meta-analyses were performed using STATA software, version 11.0 (STATA Corp., College Station, TX, USA). Odds ratios (ORs) and 95% CI were used to assess the strength of association between *p21* Ser31Arg polymorphism and gastrointestinal tract tumor. The selection of fixed or random effects model was based on the

heterogeneity test. For the heterogeneity test, we performed Cochran's Q test and Higgins's I^2 test. When $P > 0.05$ (for Q test) and $I^2 < 50.0\%$ indicated no heterogeneity across studies, the fixed effects model (Mantel-Haenszel pooled, M-H pooled) was chosen for meta-analysis. On the contrary, when $P \leq 0.05$ and $I^2 \geq 50.0\%$, the random effects model (DerSimonian-Laird pooled, D+L pooled) would be chosen (22).

The pooled ORs were performed for allelic contrast (Ser-allele vs. Arg-allele), homozygote comparison (Ser/Ser vs. Arg/Arg), heterozygote comparison (Ser/Ser vs. Arg/Ser, Arg/Ser vs. Arg/Arg), dominant genetic model (Ser/Ser + Arg/Ser vs. Arg/Arg) and recessive genetic model (Ser/Ser vs. Arg/Ser + Arg/Arg).

Before doing our meta-analysis, we tested whether the genotype frequencies of controls were in Hardy-Weinberg equilibrium (HWE) using the χ^2 test. Sensitivity analysis was mainly performed by sequential omission of individual studies. The funnel plot asymmetry was assessed with Egger's test. Publication bias was investigated by Egger's and Begg's tests ($P < 0.05$ was considered statistically significant).

Results

Eligible Studies

Overall, seven case-control studies were available for this analysis. Study characteristics were summarized in Table I. All the investigations were case-control studies including 967 cases and 1723 controls that examined the relationship between *p21* Ser31Arg polymorphism and gastrointestinal tract tumor risk. There were 5 hospital-based studies and 2 population-based studies. Among 7 eligible studies, patients with esophageal cancer (3 studies), gastric cancer (3 studies) and colorectal cancer (1 study) were used as cases. The genotype distributions among the controls of all studies were consistent with HWE.

Meta-analysis Results

All chi-squared P-values for Q test were above 0.05 and I^2 values were between 0 and 50.0%, which suggested that there was no statistical heterogeneity among the studies (Table II). A summary of the meta-analysis findings of the association between *p21* Ser31Arg polymorphism and gastrointestinal tract tumor was listed in Table II. The *p21* Ser31Arg polymorphism analysis showed a significant association between Ser-allele and susceptibility to gastrointestinal tract tumor (OR = 1.17, 95% CI: 1.04-1.31) using the fixed effects model ($P = 0.010$, $I^2 = 15.4\%$). In the homozygote model comparison, Ser/Ser genotype was more likely to increase gastrointestinal tract tumor risk than Arg/Arg genotype (OR = 1.38, 95% CI: 1.09-1.75). In addition, similar results with Ser/Ser genotype were also found in heterozygote model comparison and recessive genetic model (OR = 1.27, 95% CI: 1.05-1.53, OR = 1.29, 95% CI: 1.07-1.54). However, no statistically significant association was found under the other comparisons (Arg/Ser + Ser/Ser vs. Arg/Arg: OR = 1.16, 95% CI: 0.95-1.41; Arg/Ser vs. Arg/Arg: OR = 1.02, 95% CI: 0.83-1.27). (Table II, Figure 2)

Sensitivity Analysis and Publication Bias

Sensitivity analysis was performed to assess the influence of each individual study on the pooled ORs by sequential omission of individual studies. The significance of pooled ORs under recessive model of *p21* Ser31Arg polymorphism were not influenced excessively by omitting any single study (Figure 3), and the results were stable according to the ORs of fixed effects model and random effects model (Table II). Publication bias of the literatures was accessed by Begg's funnel plot and Egger's test. The graphical funnel plots of included studies appeared to be almost symmetrical. The results of Begg's and Egger's tests also showed that there was no statistical significance for the evaluation of publication bias. (Figure 4, Table II).

Table I
Main characteristics of studies included in the meta-analysis.

First author (yr)	Cancer types	Country	Source of controls	Case/control				HWE	
				n	Arg/Arg	Arg/Ser	Ser/Ser	χ^2	P
Wu (2003)	Esophageal	Taiwan China	Hospital	128/178	23/51	62/84	43/43	0.524	0.469
Wu (2004)	Gastric	Taiwan China	Hospital	89/192	26/49	36/94	27/49	0.083	0.773
Xi (2004)	Gastric	China	Population	48/96	10/21	16/47	22/28	0.023	0.879
Lai (2005)	Gastric	China	Hospital	123/119	30/38	63/60	30/21	0.103	0.748
Liu (2010)	Colorectal	China	Population	373/838	77/183	193/436	103/219	1.513	0.219
Taghavi (2010)	Esophageal	Iran	Hospital	126/100	0/0	27/18	99/82	0.978	0.323
Yang (2010)	Esophageal	China	Hospital	80/200	19/49	33/109	28/42	1.668	0.196

Table II

Results of meta-analysis for *p21* Ser31Arg and the risk of gastrointestinal tract tumors in Asians.

	Heterogeneity test			Results			Public bias	
Meta-analysis	P^a	I^2 (%)	M-H pooled OR (95% CI)	P^b	D + L pooled OR (95% CI)	P^c	Begg's $Pr > \|z\|$	Egger's $P > \|t\|$
Ser-allele vs. Arg-allele	0.312	15.4	1.17(1.04,1.31)	0.010	1.19(1.03,1.36)	0.014	0.764	0.492
Dominant model[d]	0.416	0.0	1.16(0.95,1.41)	0.154	1.15(0.94,1.41)	0.164	1.000	0.745
Recessive model[e]	0.205	29.3	1.29(1.07,1.54)	0.006	1.39(1.07,1.70)	0.012	0.548	0.228
Ser/Ser vs. Arg/Arg	0.400	2.5	1.38(1.09,1.75)	0.008	1.38(1.08,1.77)	0.009	0.707	0.160
Ser/Ser vs. Arg/Ser	0.188	31.5	1.27(1.05,1.53)	0.016	1.33(1.04,1.72)	0.026	0.548	0.179
Arg/Ser vs. Arg/Arg	0.344	11.1	1.02(0.83,1.27)	0.789	1.02(0.81,1.30)	0.848	0.386	0.434

[a]*P* value for Q statistic.
[b]*P* value for M-H pooled.
[c]*P* value for D+L pooled.
[d]Ser/Ser+Arg/Ser vs. Arg/Arg.
[e]Ser/Ser vs. Arg/Ser + Arg/Arg.

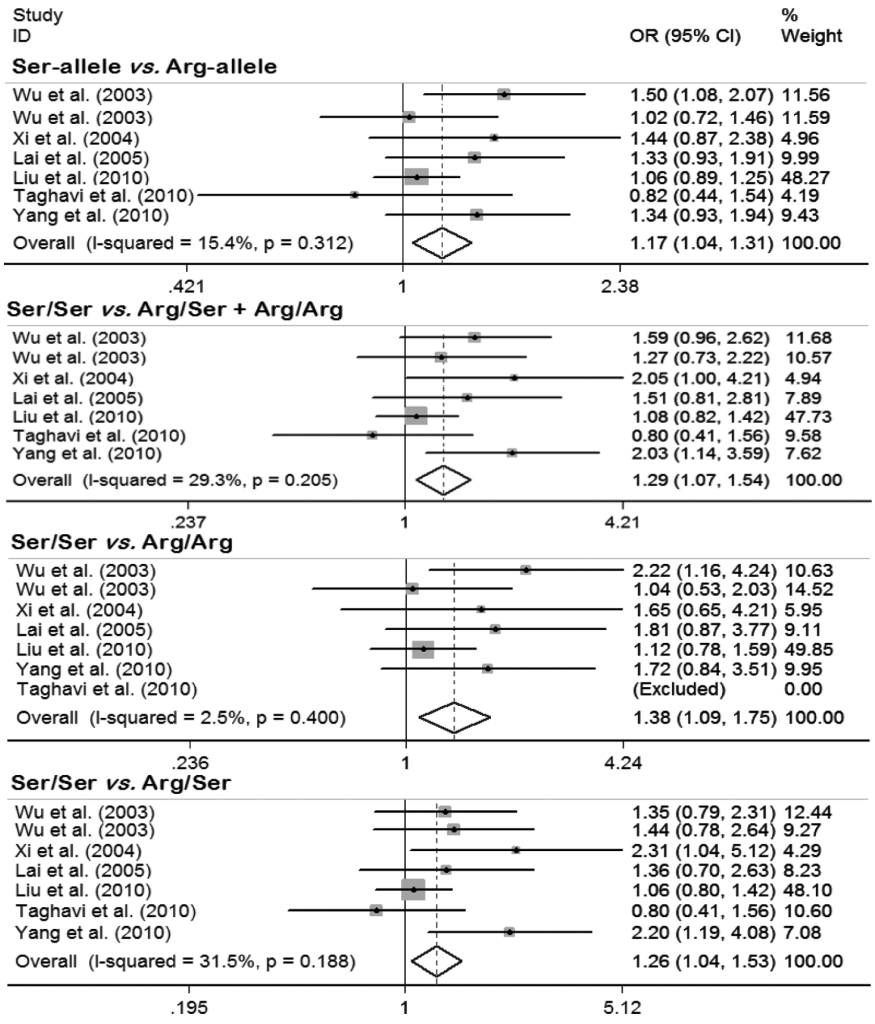

Figure 2: Forest plots of relationship between *p21* Ser31Arg and the risk of gastrointestinal tract tumors in Asians. The size of the gray square corresponding to each study is proportional to the sample size, and the black point in the center of each square represents the OR. The horizontal line shows the corresponding 95% CI of the OR. The pooled OR was obtained using fixed effects model and is represented by hollow diamonds, where its center indicates the OR, and its ends correspond to the 95% CI.

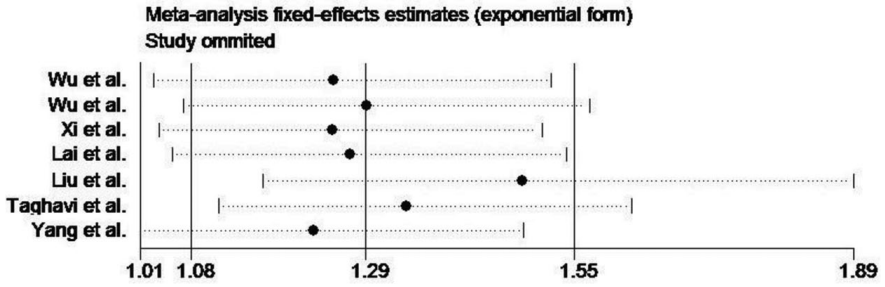

Figure 3: Sensitivity analyses of the summary odds ratio coefficients on the association between *p21* Ser31Arg polymorphism and gastrointestinal tract tumor risk among Asians under the recessive genetic model (Ser/Ser *vs.* Arg/Ser + Arg/Arg).

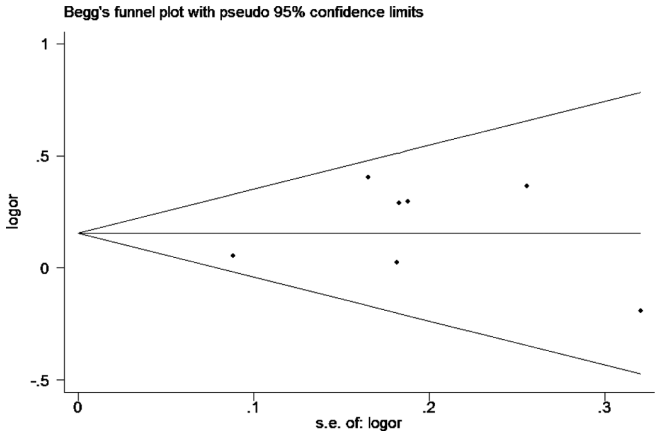

Figure 4: Funnel plot analysis to detect publication bias of the allelic contrast by Begg's test. Each point represents a separate study for the indicated association. The OR is plotted on a logarithmic scale against the precision (the reciprocal of the SE).

Discussion

The present meta-analysis, including 967 cases and 1723 controls from 7 publications with 7 case-control studies, explored that the *p21* Ser31Arg Ser-allele was significantly associated with an increased gastrointestinal tract tumor risk in Asians. The significant associations were maintained in homozygote model comparison, heterozygote model comparison, and recessive genetic model. These findings indicated that *p21* Ser31Arg polymorphism may play a role, although modest, in cancer development. It was biologically plausible that the *p21* Ser31Arg polymorphism may modulate the risk of cancers, as *p21* plays an important role in cell cycle arrest at the G1 to S phase checkpoint, allowing cells to repair damaged DNA and there by inhibit carcinogenesis. Two different alleles of *p21* Ser31Arg polymorphism have been shown to differ significantly in their transcriptional efficiency. For example, individuals carrying the Arg encoding allele manifest a lower expression (23).

In a previous meta-analysis, Liu *et al*. showed a significantly increased risk for cancer in white population but decreased risk of esophageal cancer and gastric cancer in Asian population with Arg/Arg genotype (24). It actually consisted with our meta-analysis result, in which we found that the effect of the *p21* Ser31Arg Ser/Ser genotype was unfavorable toward the development of esophageal, gastric and colorectal cancers in Asians. The main reason for the difference between the whites and Asians may come from either the ethnicity or cancer types or both. In addition, although Lin *et al.* (15) reported that their overall meta-analysis did not observe any significant association between *p21* Ser31Arg polymorphism and lung cancer risk, a significantly increased cancer risk with Ser/Ser genotype in a subgroup existed, which was also in accordant with our analysis results. The difference between the overall and subgroup analysis could be due to limited statistical power as a result of a small sample size in subgroup analysis. Another meta-analysis from Qiu *et al.* (16) investigated the association between the *p21* Ser31Arg and breast cancer risk among 22109 cases and 29127 controls, but no significant association was found. Interestingly, when stratifying by cancer types, significantly increased risks were observed for colorectal cancer among the whites. The difference could arise from both limited statistical power as a result of a small sample size in subgroup analysis and cancer types. However, there were some exceptions. For example, the results from Ma *et al*. suggested that the *p21* codon 31Arg/Arg genotype might serve as a potential marker for increased cancer risk (25). Overall, inconsistent results among different cancers may involve the mechanisms by which cell proliferation or apoptosis in different cancer cells were regulated. However, the difference could also be due to limited statistical power as a result of a small sample size in subgroup analysis. Additionally, ethnicity may affect tumor susceptibility by different genetic factors and environmental exposures through gene-gene and gene-environment interactions. Therefore, some characteristics should be carefully considered in genetic association studies such as sample size, ethnicity information and cancer types.

Several potential limitations of the present meta-analysis warrant consideration. Firstly, though the retrieved literature comprised almost all relevant studies, there may still be some relevant literatures could not be included in our analysis due to the language restriction. Secondly, the small sample sizes limited the ability to draw more solid conclusions. Thirdly, many other factors such as age, parity, smoking, and alcohol consumption may participate in the progression of diseases. We didn't carry out subgroup analysis based on these factors due to limited data.

In summary, this meta-analysis provided statistical evidence that the *p21* Ser/Arg polymorphism may contribute to individual susceptibility to gastrointestinal tract tumor in Asians. Moreover, further studies with large sample size of different ethnic populations would be necessary to combine genetic factors together with age, parity, smoking, and alcohol consumption.

Conflict of Interest Statement

We certify that regarding this paper, no actual or potential conflicts of interests exist; the work is original, has not been accepted for publication nor is concurrently under consideration elsewhere, and will not be published elsewhere without the permission of the Editor and that all the authors have contributed directly to the planning, execution or analysis of the work reported or to the writing of the paper.

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