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RESEARCH ARTICLE

Association of p53 Arg72Pro polymorphism with gastric cancer: a meta-analysis

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Abstract

Background: p53 tumor suppressor gene Arg72Pro polymorphism has been associated with gastric cancer. However, results were inconsistent. We performed this meta-analysis to estimate the association between p53 Arg72Pro polymorphism and gastric cancer.

Methods: An electronic search of PubMed was conducted to select studies. Studies containing available genotype frequencies of Arg72Pro were chosen, and the association was assess by pooled odds ratio (ORs) with 95% confidence interval (CIs).

Results: The meta-analysis suggested that the p53 Arg72Pro was associated with the gastric cancer risk (Additive model: OR = 1.149, 95% CI = 1.045–1.263, $p = 0.004$; Dominant model: OR = 1.18, 95% CI = 1.049–1.328, $p = 0.006$; Recessive model: OR = 1.202, 95% CI = 1.013–1.427, $p = 0.035$) in Asian subgroup.

Conclusion: This meta-analysis suggests that p53 Arg72Pro polymorphism is associated with increased risk of gastric cancer in Asians.

Keywords: p53, meta-analysis, gastric cancer

Introduction

Gastric cancer is one of the most common cancers of the gastrointestinal system, which is an important health problem worldwide (Bertuccio et al. 2009). Gastric cancer has been the most common cause of cancer death throughout the world. Its overall five-year survival rate is 15–20%. About 0.15 million new cases are expected all over the world in 2008 (Jemal et al. 2011). The pathogenesis of gastric cancer is not completely clear. Many studies have indicated the association between environmental factors such as smoking, drinking, dietary habits and Helicobacter pylori infection and the risk of gastric cancer. However, only a few individuals who infected with Helicobacter pylori may develop into gastric cancer. That is the specific disease induced by the infection is determined to a great degree by host genetic polymorphisms (Kim et al. 2010). The heritable factor may predispose to the risk of gastric cancer (Carneiro et al. 2010). The interaction between environmental and genetic factors remains to be illuminated. The polymorphisms in functionally critical genes have been suggested as risk factors for the development of many cancers, including gastric cancer (Oliveira et al. 2006, Milne et al. 2009, Asslaber et al. 2010, Santos et al.

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2011, Terrazzino et al. 2012). Tumor suppressor gene inactivation may play a critical role in the development of gastric cancer.

The p53 tumor suppressor gene is at the crossroads of a network of cellular pathways evolving to maintain the stability of the genome (Bennett et al. 1999). p53 is a stress sensor protein that functions primarily as a tetrameric sequence-specific DNA binding transcription activator of a lot of target genes in response to a variety of cellular insults, including DNA damage, oncogene activation and the other signals (Brosh & Rotter 2009). Activated p53 suppresses cellular transformation mainly by inducing cell cycle arrest, senescence, apoptosis, inhibition of angiogenesis, metastasis, DNA repair and differentiation in damaged cells (Brady & Attardi 2010). p53 is involved in both the pro-death response of apoptosis, and the pro-survival response of cell cycle arrest and DNA repair (Li et al. 2011). If a mutation presents, p53 may not only lose its normal tumor suppressive ability and acquire dominant-negative activities, but also gain new functions that promote carcinogenesis (Brosh & Rotter 2009). p53 is the most frequently mutated gene in all kinds of human tumors; more than half of human cancers harbor mutations in the p53 gene (Bennett et al. 1999). The p53 tumor suppressor gene (TP53; GenBank NM_000546.2) contains 11 exons, located on chromosome 17p13 and encoded a 53-kDa nuclear phosphor protein. A common polymorphism occurs at codon 72 of exon 4, with CGC to CCC transition causing an arginine (Arg) in codon 72 to proline (Pro) amino acidic substitution in the transactivation domain of the protein (Pinarbasi et al. 2007). Studies have reported the Arg72Pro polymorphism has been linked to an increased risk of cancer (Zhou et al. 2007).

A number of studies have been conducted to investigate the potential association between p53 Arg72Pro polymorphism and gastric cancer in humans (Hamajima et al. 2002, Hiyama et al. 2002, Zhang et al. 2003, Shen et al. 2004, Wu et al. 2004, Lai et al. 2005, Mu et al. 2005, Pérez-Pérez et al. 2005, Belyavskaya et al. 2006, Chung et al. 2006, Sul et al. 2006, Yi & Lee 2006, Yang et al. 2007, Gomes de Souza et al. 2009, Kim et al. 2010, Zhou et al. 2010, Song et al. 2011, Ke-Xiang et al. 2012). However, the results were inconsistent. Therefore, we conducted a meta-analysis to assess the association between the p53 Arg72Pro polymorphism and the risk of gastric cancer.

Materials and methods

Publication search

PubMed was searched using the search terms "p53," "polymorphism" and "gastric cancer" (the last search update was on Feb 2, 2012). Case-control studies containing available genotype frequencies of Arg72Pro were chosen. Additional studies were identified by a manual search of the references of original studies.

Statistic analysis

For control group of each study, the observed genotype frequencies of the p53 Arg72Pro polymorphism were assessed for Hardy–Weinberg equilibrium using the χ^2 test. The strength of association between Arg72Pro polymorphism of p53 gene and gastric cancer was accessed by calculating crude odds ratios (ORs) with 95% confidence intervals (CIs). The pooled ORs were performed for dominant model (Pro/Pro + Pro/Arg vs. Arg/Arg), additive genetic model (Pro vs. Arg) and recessive model (Pro/Pro vs. Pro/Arg + Arg/Arg), respectively. Heterogeneity assumption was checked by a chi-square based Q-test. A significant Q-statistic ($p < 0.05$) indicated heterogeneity across studies. The summary OR estimate of each study was calculated by he fixed-effects model if there was not significant heterogeneity. Otherwise, the random-effects model was employed (Mantel & Haenszel 1959, DerSimonian & Laird 1986). The potential for publication bias was examined by a Begg's test (funnel plot method) and Egger's linear regression test ($p < 0.05$ considered representative of statistical significance) (Egger et al. 1997). All statistical analyses were performed with Stata software (version9.0; Stata Corporation, College Station, TX).

Results

Eligible studies

We identified 18 case–control studies on the association between p53 Arg72Pro polymorphism and gastric cancer (Table 1). The distribution of genotypes in the controls of all the studies was in agreement with Hardy–Weinberg equilibrium, except one study (Zhou et al. 2010). As lack of Hardy–Weinberg equilibrium indicates possible genotyping errors and/or population stratification, this study (Zhou et al. 2010) was excluded in the final meta-analysis. The final meta-analysis included 17 published studies with 5118 gastric cancer cases and 5897 controls.

Meta-analysis

The results of the association between the p53 Arg72Pro polymorphism and gastric cancer and the heterogeneity test were shown in Table 2 (Figures 1–3). The overall results suggested that the variant genotype was associated with the gastric cancer risk (Pro vs. Arg: OR = 1.109, 95% CI = 1.012–1.215, $p = 0.026$; Pro/Pro vs. Arg/Arg + Arg/Pro: OR = 1.207, 95% CI = 1.027–1.417, $p = 0.022$). In the stratified analysis, this polymorphism was significantly associated with this risk of gastric cancer in Asian subjects (additive model: OR = 1.149, 95% CI = 1.045–1.263, $p = 0.004$; dominant model: OR = 1.18, 95% CI = 1.049–1.328, $p = 0.006$; recessive model: OR = 1.202, 95% CI = 1.013–1.427, $p = 0.035$). However, the association was not significant between this polymorphism and gastric cancer in Caucasian subjects.

Publication bias

Funnel plot, Egger's test and the Begg's test were done to estimate the publication bias of literatures. The results of

Table 1. The distribution of the p53 codon 72 variant for cases and controls.

Ethnicity	Author	Country	Design	Year	Gastric cancer			Control			p^a
					ArgArg	ArgPro	ProPro	ArgArg	ArgPro	ProPro	
Caucasian	Gomes (Gomes de Souza et al. 2009)	Brazil	HCC	2009	39	37	8	91	79	15	0.709
	Sul (Sul et al. 2006)	USA	HCC	2006	51	73	31	51	61	22	0.604
	Belyavskaya (Belyavskaya et al. 2006)	Russia	HCC	2006	18	1	11	60	46	19	0.050
	Pérez (Pérez-Pérez et al. 2005)	Mexico	PCC	2005	35	21	9	68	88	26	0.773
	Zhang (Zhang et al. 2003)	UK	HCC	2003	64	50	6	125	129	23	0.197
Asian	Ke-Xiang (Ke-Xiang et al. 2012)	China	HCC	2012	22	84	34	32	68	25	0.307
	Song (Song et al. 2011)	Korean	HCC	2011	939	977	279	734	776	190	0.481
	Zhou (Zhou et al. 2010)	China	HCC	2010	31	58	61	53	48	49	<0.001
	Kim (Kim et al. 2010)	Korean	PCC	2010	214	223	97	216	230	85	0.074
	Yang (Yang et al. 2007)	China	HCC	2007	123	245	132	316	486	198	0.652
	Chung (Chung et al. 2006)	Korea	HCC	2006	30	42	12	41	50	18	0.677
	Yi (Yi & Lee 2006)	Korea	HCC	2006	101	126	65	89	103	24	0.474
	Mu (Mu et al. 2005)	China	PCC	2005	42	88	64	118	178	94	0.098
	Lai (Lai et al. 2005)	China	PCC	2005	18	22	11	25	26	8	0.765
	Wu (Wu et al. 2004)	China	HCC	2004	11	53	25	40	95	57	0.971
	Shen (Shen et al. 2004)	China	PCC	2004	96	180	48	94	160	63	0.732
	Hiyama (Hiyama et al. 2002)	Japan	HCC	2002	49	52	16	50	52	14	0.932
	Hamajima (Hamajima et al. 2002)	Japan	HCC	2002	51	70	23	90	106	43	0.232

[a]p value for Hardy–Weinberg equilibrium in control group.
HCC, hospital-based case-control study; PCC, population-based case-control study.

Table 2. ORs and 95% CI for gastric cancer and the p53 Arg72Pro polymorphism under different genetic models.

Genetic model	Population	Pooled OR [95% CI]	p	Heterogeneity	Begg's test	Egger's test
				p value	p value	p value
Additive (Pro vs. Arg)	Caucasian	0.953 [0.75–1.212]	0.696	0.129	0.624	0.867
	Asian	1.149 [1.045–1.263]	0.004	0.04	0.891	0.399
	Overall	1.109 [1.012–1.215]	0.026	0.015	1	0.39
Dominant (Pro-carriers vs. Arg/Arg)	Caucasian	0.823 [0.588–1.152]	0.256	0.101	0.624	0.577
	Asian	1.18 [1.049–1.328]	0.006	0.183	0.273	0.046
	Overall	1.112 [0.978–1.265]	0.104	0.03	0.355	0.031
Recessive (Pro/Pro vs. Arg-carriers)	Caucasian	1.231 [0.749–2.021]	0.412	0.114	0.327	0.93
	Asian	1.202 [1.013–1.427]	0.035	0.04	1	0.821
	Overall	1.207 [1.027–1.417]	0.022	0.033	0.792	0.805

the Egger's test ($p > 0.05$), and the Begg's test ($p > 0.05$) provided statistical evidence for funnel plot symmetry in Asian and Caucasian subgroup (Table 2).

Discussion

It was thought that gastric cancer was a result of a combination of the accumulation of genetic variation and environmental factors. The genetic susceptibility to gastric cancer may be attributed to the SNP of major genetic pathways including DNA repair and cell-cycle control pathways. Recently, p53 gene variants in the etiology of cancers have drawn increasing attention. Some studies have attempted to discover a possible association between the p53 Arg72Pro polymorphism and the risk of gastric cancer (Hiyama et al. 2002, Hamajima et al. 2002, Zhang et al. 2003, Wu et al. 2004, Shen et al. 2004, Pérez-Pérez et al. 2005, Mu et al. 2005, Lai et al. 2005, Yi & Lee 2006, Sul et al. 2006, Chung et al. 2006, Belyavskaya et al. 2006, Gomes de Souza et al. 2009, Zhou et al. 2010, Kim et al. 2010, Song et al. 2011, Ke-Xiang et al. 2012). A significant association between this polymorphism and gastric cancer has been shown in Caucasian (Pérez-Pérez et al. 2005), Japanese (Hiyama et al. 2002), Korean (Yi & Lee 2006, Chung et al. 2006, Song et al. 2011) and Chinese (Shen et al. 2004, Lai et al. 2005, Zhou et al. 2010, Ke-Xiang et al. 2012). It was observed a positive correlation between the frequency of Arg72 p53 and the age of gastric adenocarcinoma patients but not the age of no cancer patients (Zhang et al. 2003). On the contrary, the other studies did not demonstrate any significant difference in the prevalence of the p53 Arg72Pro genotype between gastric cancer patients and controls, indicated an insignificant association between this polymorphism and gastric cancer risk in Chinese (Wu et al. 2004, Mu et al. 2005), Japanese (Hamajima et al. 2002) and Caucasian (Sul et al. 2006, Belyavskaya et al. 2006, Gomes de Souza et al. 2009). Some new statistical concerns for case–control studies were rose, which showed sensitivity and specificity had different

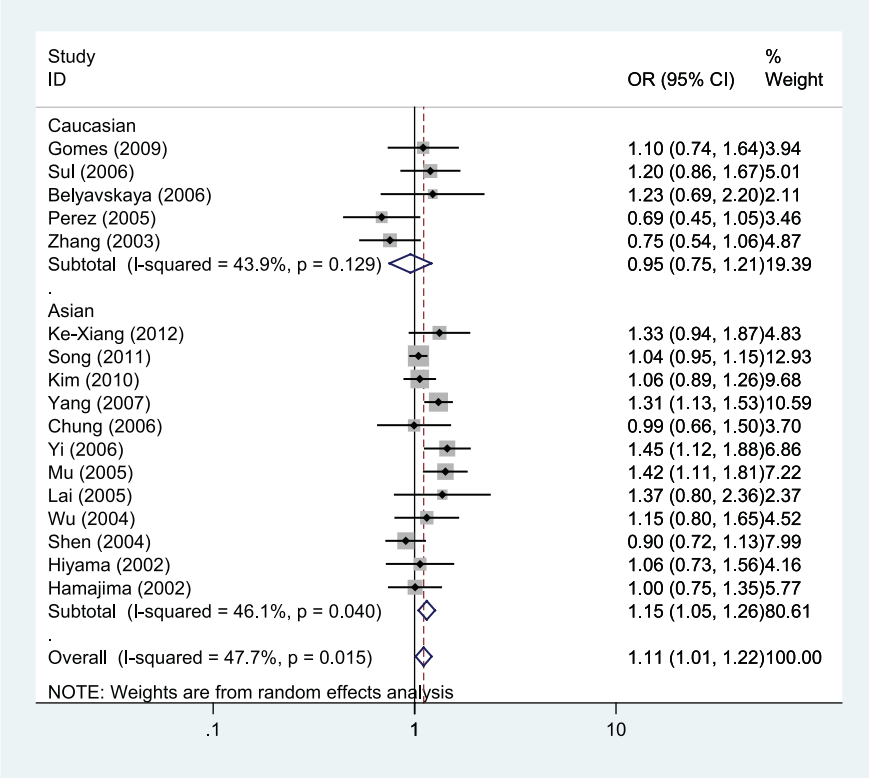

Figure 1. Forest plot of ORs of gastric cancer Pro allele when compared to the Arg allele (Additive model). The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the study-specific weight. The diamond represents the pooled OR and 95% CI.

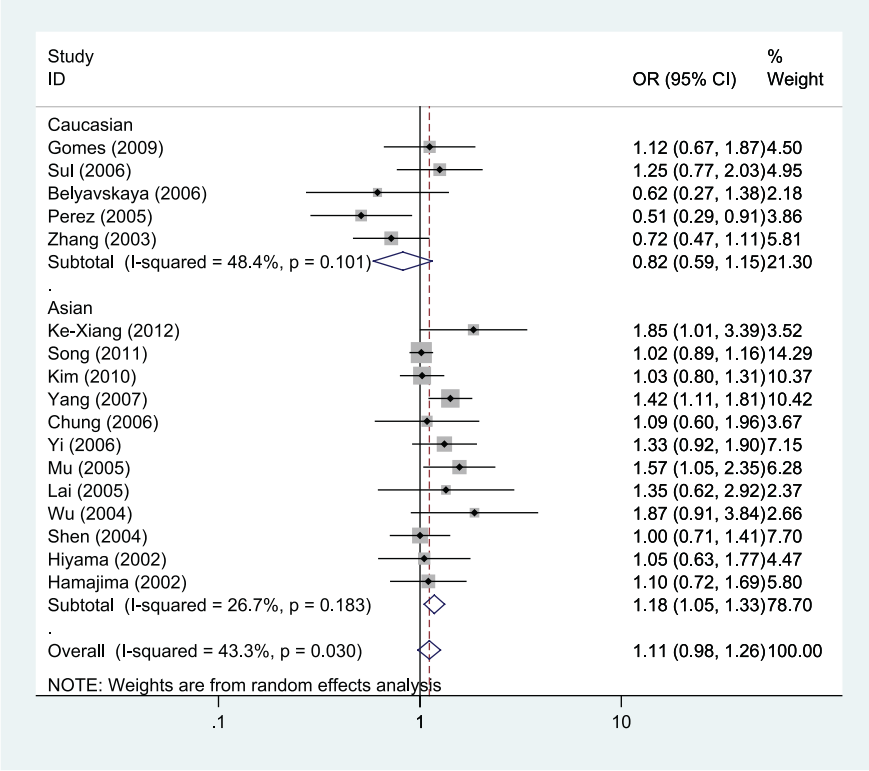

Figure 2. Forest plot of ORs of gastric cancer Pro allele carriers (Pro/Pro + Pro/Arg) when compared to the Arg/Arg genotype (Dominant model). The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the study-specific weight. The diamond represents the pooled OR and 95% CI.

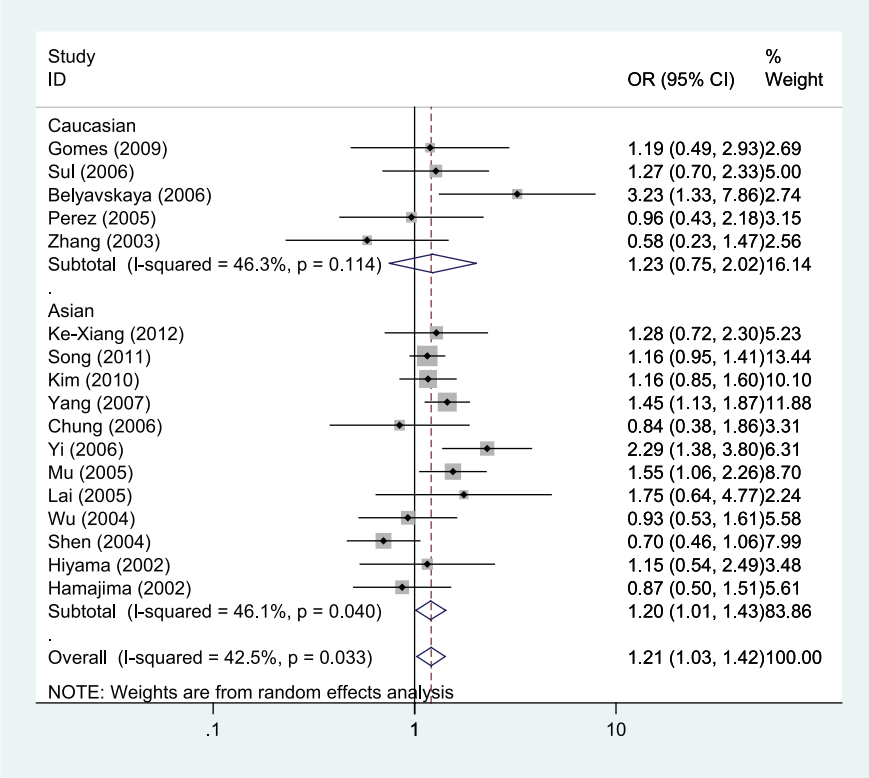

Figure 3. Forest plot of ORs of gastric cancer Pro/Pro genotype when compared to the Arg allele carriers (Pro/Arg + Arg/Arg)(Recessive model). The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the study-specific weight. The diamond represents the pooled OR and 95% CI.

relationships with disease prevalence (Li & Fine 2011). Usually, a case–control study selects subjects according to their disease status and thus does not provide a valid estimate for the prevalence. This meta-analysis reveal a significant association between p53 codon 72 polymorphism and gastric cancer risk (Pro vs. Arg: OR = 1.149, 95% CI = 1.045–1.263, p = 0.004; Pro-carriers vs. Arg/Arg: OR = 1.18, 95% CI = 1.049–1.328, p = 0.006; Pro/Pro vs. Arg-carriers: OR = 1.202, 95% CI = 1.013–1.427, p = 0.035) in Asian subjects, but not in Caucasian. A few studies showed that p53 mutations in tumor DNA had a potential prognostic role for disease recurrence in NSCLC patients (Ludovini et al. 2008). But Lim's study did not support the role of p53 as a prognostic indicator in advanced-stage NSCLC in Singapore population (Lim et al. 2009). Arg72Pro of p53 gene is a common coding polymorphism that results in either proline (Pro) or arginine (Arg) at 72nd amino-acid position. Significant ethnic differences were found in the codon 72 polymorphism. The Pro72 allele frequency increasing in populations as they near the equator is closely linked to latitude (Själander et al. 1995). There is a tight association between cold winter temperature and p53 Arg72 in Eastern Asia that suggests causative selection (Shi et al. 2009). Besides small sample size, the heterogeneity in ethnicity may be one major reason for the controversy.

p53 has been recently found to have broader roles in controlling apoptosis and cell cycle arrest and maintaining genomic stability. Significant differences in the p53 gene Arg72Pro polymorphic form might affect it biological activity. The Pro72 variant of p53 protein induces a markedly higher level of G1 arrest than the Arg72 form (Dumont et al. 2003, Sullivan et al. 2004, Bergamaschi et al. 2006), while the Arg72 form is significantly better than the Pro72 form in suppressing cellular transformation and inducing apoptosis (Pim & Banks 2004). These suggested that p53 gene variants might have different activities in cell cycle regulation. Deregulation of apoptosis plays a vital role in tumor genesis. Furthermore, carcinogenesis might be induced by genomic instability on account of failure in DNA repair. A great number of human cancers show mutations in p53 gene that lead to loss tumor suppression ability and cell cycle deregulation function. It is reported that p53 may be an independent prognostic factor in gastric cancer. It was reported no interaction between the p53 Arg72Pro polymorphism and alcohol consumption or smoking for gastric cancers (Sul et al. 2006). Similarly, it was found no interaction between the p53 Arg72Pro polymorphism and age, smoking, or drinking in gastric cancer in a Korean population (Song et al. 2011). Gastric carcinogenesis is a complex and multifactorial process. The genetic factors in the etiology of gastric cancer are still relatively unknown. Large genetic screenings can be useful for elucidating the molecular pathogenesis of gastric cancer.

In conclusion, this meta-analysis suggests the p53 Arg72Pro polymorphism may be associated with the risk of gastric cancer in Asians. Future well designed large

studies might be necessary to validate this association in different populations incorporated with environmental factors in the susceptibility of gastric cancer.

Declaration of interest

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