p27^{Kip1} V109G Polymorphism and Cancer Risk: A Systematic Review and Meta-Analysis

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Abstract

Relationship between the p27^{Kip1} (here after referred to as p27) V109G polymorphism and cancer risk has been extensively studied; however, results from different studies were not fully consistent. Therefore, we carried out a meta-analysis to comprehensively assess the correlation between the p27V109G polymorphism and the cancer risk. Articles on the relationship of the p27V109G polymorphism with cancer risk were searched from Medline, Pub Med, and Web of science databases. A total of eight eligible studies with 3591 cases and 3799 controls were included in this meta-analysis. Overall, it seemed that the G allele was not associated with the elevated cancer risk (pooled odds ratio [OR]=0.98, 95% confidence interval [CI]: 0.88–1.09, $p=0.68$, fixed effects). Analyses in different populations revealed that no statistically significant associations between the G allele and cancer risk were demonstrated in Caucasians or Asians. When analyzed in different types of cancer that, from two studies, the G allele was found to be associated with a decreased risk of prostate cancer in a dominant genetic model (pooled OR=0.60, 95% CI=0.36–0.98, $p=0.04$, fixed effects), but did not alter the breast cancer risk from four studies. In conclusion, this meta-analysis indicated that the p27V109G polymorphism did not correlate with the overall cancer risk in the general population.

Key words: cancer, p27, polymorphism, risk, V109G

Introduction

Aberrant cell cycle control is one of the hallmarks of cancer.¹ The eukaryotic cell cycle progression is driven by cyclin-dependent kinases (CDKs) and negatively regulated by CDK inhibitors (CDKIs).^{2,3} In tumor cells, it seen frequently that abnormal function of CDKIs can cause the deregulation of proliferative activity.⁴ The p27, a CDKI belonging to the ciprofloxacin/kinase inhibitor protein family, inhibits the CDK2-cyclin E complex and regulates the cell cycle checkpoint at the G1-to-S transition, and it is a putative tumor suppressor.^{5,6} While mutations of p27 are frequently found in cancer,^{7,8} whether polymorphisms of this protein are associated with cancer risk is also not well understood and remains an interesting question in the field. According to the dbSNP database (www.ncbi.nlm.nih.gov/SNP), p27 has at least 59 variants. Previous studies have mainly focused on one of the important variants, namely p27V109G (single-nucleotide polymorphism [SNP] database: rs2066827), resulted from a

polymorphism at codon 109 (T to G), due to its potential functional alteration to the protein. This valine-to-glycine substitution variant may affect the interaction of the p27 protein with other cell cycle-regulating molecules, and consequently alter its expression or activation.⁹ For example, this polymorphism falls within a region that physically interacts with the Jun activation domain-binding protein 1 (JAB1), which triggers the proteolytic degradation of p27.^{10,11} It has been speculated that the p27V109G polymorphism enhances the degradation of this variant protein, and possibly leads to cell cycle dysregulation and tumorigenesis. Recently, many studies on the relationship between the p27V109G polymorphism and cancer risk have been reported, but the results were inconsistent. For instance, two studies showed that the G allele was associated with an increased risk of oral squamous cell carcinoma and prostate cancer,^{12,13} while one study suggested that the G allele of the p27V109G polymorphism was associated with a decreased risk of breast cancer,¹⁴ and in addition, other studies reported that there was no association

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FIG. 1. The crystal structures of the wild type and the mutant type with p27V109G. Threading, a popular protein structure-modeling technology, is used to build modeled structures for p27-109 Val (left) and p27-109 Gly (right). The superposition between the native structure of 109 Val (red) and 109 Gly (green) predicted by Threading. Color images available online at www.liebertpub.com/cbr

between the p27V109G polymorphism and breast cancer risk,^{15–18} pancreatic cancer risk,^{19,20} prostate cancer risk,²¹ and thyroid cancer risk.²² To investigate whether the p27V109G variant is indeed associated with cancer susceptibility, we performed a systematic review of the published articles, and conducted a meta-analysis to gain insights into the relationship between the p27V109G polymorphism and cancer risk.

Methods

Identification and eligibility of relevant studies

We searched for relevant studies published in English before October 2011, by using the electronic databases of Medline, Pub Med, and Web of science with the following terms: p27, p27 or CDKN1B, V109G or Val109Gly, cancer, tumor, polymorphism, and risk. References of the retrieved articles were also screened for original studies. We included all the case-control studies that investigated the association between the p27V109G polymorphism and cancer risk with genotyping data. Abstracts, unpublished reports, and articles written in non-English language were not considered. Additionally, when the same case-control case series were used

for multiple times in different studies, we only selected the study that included the largest number of individuals.

Data extraction

We extracted the following information from each article: author, year of publication, country of origin, cancer type, ethnicity, genotyping information, genotype method, and source of control groups (population-based, hospital-based, or mixed controls). For studies, including subjects of different ethnicities, data were extracted separately and categorized as Asians, Caucasians, and others.

Statistical analysis

We performed a meta-analysis to estimate the risk (odds ratio [OR]) and 95% confidence interval [95% CI] of cancer associated with the p27V109G polymorphisms. In addition to the comparison among all subjects, we also performed stratification analyses by ethnicity, cancer type, and source of controls. We investigated the interstudy heterogeneity by using the Cochran's Q -test,²³ and the heterogeneity was considered significant if $p < 0.05$.²⁴ When $p < 0.05$ of Q -test for

FIG. 2. Flow chart for the study selection.

heterogeneity, we used a random effects model (DerSimonian Laird), conversely a fixed effects model (Mantel-Haenszel). Inverted funnel plots and the Egger's test were used to examine the influence of publication bias (linear regression analysis).²⁵⁻²⁷ We checked deviation from the Hardy-Weinberg equilibrium (HWE) among controls for each of p27V109G polymorphism by a χ^2 -test, with one degree of freedom. All the *p*-values were two sided, and all analyses were done in Statistical Analysis System software Stata11.0 and Review Manager 5.0.

Results

Protein structure

Protein, a peptide connection of a long chain of amino acids, can produce specific biological function only in the

shape of folding into a specific structure. Therefore, to understand the function of protein, understanding the structure of protein is significantly important. The classic biological means of protein structure determination cannot keep up with the speed of DNA and Gene sequencing prediction and cannot meet the demand of structure prediction on a proteome scale. Therefore, researchers want to shorten the above gap by computer prediction methods. Those prediction methods can help to understand the mechanism of protein folding, and to shorten the design process. As above points, accurate prediction of a protein structure starting from the sequence has become the urgent requirement of people.

The classic means of protein prediction are homology modeling, threading, and ab initio. The core idea of threading is looking for the protein that has the same structure fold type with the targeted sequence, but without significant

TABLE 1. CHARACTERISTICS OF STUDIES INCLUDED IN THE META-ANALYSIS

First author (year of publication)	Country	Ethnicity	Cancer type	Source of control	Genotype method
Li G (2004)	American	Caucasian	Oral squamous cell cancer	Mixed	PCR-RFLP
Kibel AS (2003)	American	Caucasian	Prostate cancer	Hospital	Not defined
Figueiredo JC (2007)	Canada	Asian	Breast cancer	Population	5'nuclease Taqman
Naidu R (2007)	Malaysia	Asian	Breast cancer	Population	PCR-RFLP
Ma H (2006)	China	Asian	Breast cancer	Hospital	PCR-RFLP
Onay VU (2006)	Canada	Asian	Breast cancer	Population	5'nuclease Taqman
Chen J (2010)	American	Caucasian	Pancreatic cancer	Population	PCR-RFLP Pyrosequencing
Huang SP (2007)	China	Asian	Prostate cancer	Hospital	PCR-RFLP

PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism.

TABLE 2. p27-CODON 109 GENOTYPE DISTRIBUTION IN INCLUDED STUDIES

First author (year of publication)	Case			Control			OR (95% CI)	HWE
	TT	TG	GG	TT	TG	GG		
Li G (2004)	422	241	50	718	440	66	1.77 (1.03-3.04)	0.8950
Kibel AS (2003)	67	24	5	57	38	10	2.24 (1.02-4.95)	0.3312
Figueiredo JC (2007)	668	366	53	405	243	29	0.70 (0.52-0.93)	0.3218
Naidu R (2007)	171	46	13	159	34	7	1.26 (0.75-2.12)	0.006
Ma H (2006)	345	23	0	442	25	0	1.05 (0.57-1.93)	0.5523
Onay VU (2006)	256	125	17	235	122	15	1.00 (0.70-1.30)	0.8665
Chen J (2010)	299	210		280	182		2.20 (1.32-3.68)	N/A
Huang SP (2007)	183	7	0	280	12	0	1.95 (1.09-3.47)	0.7180

CI, confidence interval; OR, odds ratio; HWE, Hardy-Weinberg equilibrium; N/A, not available.

FIG. 3. Association of the p27V109G polymorphism with overall cancer risks.

TABLE 3. ASSOCIATIONS BETWEEN THE p27V109G POLYMORPHISM AND CANCER RISKS

Variables	Sample size case-control	Homozygote (GG vs. TT)		Dominant (TG+GG vs. TT)		Recessive (GG vs. TG+TT)	
		OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
All	3591–3799	0.93 (0.72–1.20)	0.59	0.98 (0.88–1.09)	0.68	1.19 (0.92–1.53)	0.18
Cancer type							
Breast	2083–1716	1.17 (0.81–1.68)	0.40	0.99 (0.85–1.15)	0.90	1.19 (0.83–1.70)	0.35
Prostate	286–397	0.43 (0.14–1.32)	0.14	0.60 (0.36–0.98)	0.04	0.52 (0.17–1.59)	0.25
Ethnicity							
Caucasian	1318–1791	1.13 (0.79–1.63)	0.50	0.97 (0.84–1.12)	0.67	1.19 (0.83–1.70)	0.34
Asian	2273–2008	1.28 (0.89–1.83)	0.19	0.99 (0.85–1.14)	0.87	1.19 (0.83–1.70)	0.35
Source of control							
Hospital	654–864	0.43 (0.14–1.32)	0.14	0.79 (0.54–1.15)	0.22	0.52 (0.17–1.59)	0.25
Population	2224–1711	1.17 (0.81–1.68)	0.40	1.00 (0.88–1.15)	0.95	1.19 (0.83–1.70)	0.35

homologous relation. Threading can make full using of the template library of structure information and sequence-structure comparing calculation to get the most likely alignment. Therefore, threading can get a more accurate prediction than other methods. In this article, we found that the p27V109G polymorphism resulted in an amino acid change from valine (V) to glycine (G) (Fig. 1) by Threading software.

Meta-analyses database

A flowchart of relevant study identification was shown in Figure 2. Briefly, 263 articles were obtained in the primary search. After initial screening, we identified a total of 34 relevant publications. Among these, 11 publications appeared to meet the inclusion criteria and were subjected to a detailed full-text review.^{12–22} We further excluded three publications because they did not provide detailed genotype data of cases and controls.^{18,20,22} Therefore, our final data pooling consisted of eight publications (Table 1).^{12–17,19,21} Three of the eight case-control studies were conducted in Caucasians, and the remaining five studies were conducted in Asians. Overall, there were four breast cancer studies, two prostate cancer studies, one pancreatic cancer study, and one oral squamous cell cancer study. Cancers were confirmed histologically or pathologically in all the studies. Of the eight studies, four were population-based, three were hospital-based, and one was with mixed controls. Different genotyping methods were used in these studies, including polymerase chain reaction-restriction fragment length polymorphism in five studies, the 5'-nuclease TaqMan assay in two studies, and Pyrosequencing in one study (Table 1).

Information about genotyping methods was missing in one publication.¹⁹ A summary of genotype data was listed in Table 2. Overall, the distribution of genotypes in the controls was consistent with HWE, except for one breast cancer study by Naidu et al.¹⁵

Quantitative synthesis

The eight studies^{12–17,19,21} included a total of 3591 cases and 3799 controls. When all eligible studies were pooled into the meta-analysis, there was no statistical evidence of an association between the p27V109G polymorphism and the increased cancer risk (homozygote genetic model, GG vs. TT: OR=0.93, 95% CI=0.72–1.20, $p=0.59$; dominant genetic model, TG+GG vs. TT: OR=0.98, 95% CI=0.88–1.09, $p=0.68$; recessive genetic model, GG vs. TG+TT: OR=1.19, 95% CI=0.92–1.53, $p=0.18$) (Fig. 3 and Table 3). Considering that in one study, the genotype frequencies in controls significantly deviated from HWE,¹⁵ whereas in another study, the numbers of each individual genotype were not sufficiently provided¹⁹; we did a reanalysis with these two studies excluded, and association between the p27V109G polymorphism and the cancer risk was again not found (homozygote genetic model: OR=1.11, 95% CI=0.85–1.45, $p=0.43$; dominant genetic model: OR=0.94, 95% CI=0.83–1.06, $p=0.29$; recessive genetic model: OR=0.97, 95% CI=0.32–2.97, $p=0.96$, random effect model) (Fig. 4).

In the stratified analysis by a cancer type as shown in Table 3, we found that the p27V109G polymorphism had not significantly increased the risk of breast cancer (homozygote genetic model: OR=1.17, 95% CI=0.81–1.68, $p=0.40$; dominant genetic model: OR=0.99, 95% CI=0.85–1.15, $p=0.90$;

FIG. 4. Association of the p27V109G polymorphism with overall cancer risks in a reanalysis (excluded two cases, see text for detail).

FIG. 5. Association of the p27V109G polymorphism with breast cancer and prostate cancer risks.

recessive genetic model: OR=1.19; 95% CI=0.83–1.70; $p=0.35$). Interestingly, the G allele was found to be associated with a decreased risk of prostate cancer in a dominant genetic model (OR=0.60, 95% CI=0.36–0.98, $p=0.04$), but not in other genetic models (homozygote genetic model: OR=0.43; 95% CI=0.14–1.32, $p=0.14$; recessive genetic model: OR=0.52, 95% CI=0.17–1.59, $p=0.25$) (Fig. 5).

In terms of subgroup analysis by ethnicity, the p27V109G polymorphism was not found to be associated with the cancer risk in either Caucasians (homozygote genetic model: OR=1.13, 95% CI=0.79–1.63, $p=0.50$; dominant genetic

model: OR=0.97, 95% CI=0.84–1.12, $p=0.67$; recessive genetic model: OR=1.19, 95% CI=0.83–1.70, $p=0.34$) or Asians (homozygote genetic model: OR=1.28, 95% CI=0.89–1.83, $p=0.19$; dominant genetic model: OR=0.99, 95% CI=0.85–1.14, $p=0.87$; recessive genetic model: OR=1.19, 95% CI=0.83–1.70, $p=0.35$) (Fig. 6 and Table 3).

For the studies with population-based controls, it was indicated that there was no association between the p27V109G polymorphism and the cancer risk (homozygote genetic model: OR=1.17, 95% CI=0.81–1.68, $p=0.40$; dominant genetic model: OR=1.00, 95% CI=0.88–1.15, $p=0.95$;

FIG. 6. Association of the p27V109G polymorphism with cancer risks in Caucasians and Asians.

FIG. 7. Funnel plot of publication bias analysis for the associations between the polymorphism of p27V109G and cancer risks (TG+GG vs. TT, fixed effect model). OR, odds ratio.

recessive genetic model: OR=1.19, 95% CI=0.83–1.70, $p=0.35$). This was also true for those studies with hospital-based controls (homozygote genetic model: OR=0.43, 95% CI=0.14–1.32, $p=0.14$; dominant genetic model: OR=0.79, 95% CI=0.54–1.15, $p=0.22$; recessive genetic model: OR=0.52, 95% CI=0.17–1.59, $p=0.25$) (Table 3).

There were no substantial interstudy heterogeneities in the above analyses (Fig. 3). In addition, no publication bias was detected by either the funnel plot (Fig. 7) or the Egger's test ($p=0.682$).

Discussion

To the best of our knowledge, our study is the first available meta-analysis that comprehensively evaluated the associations between the p27V109G polymorphism and the overall cancer risk. With eight case-control studies containing 3591 cases and 3799 controls, we report that the polymorphism of p27V109G was not associated with the cancer risk. Analyses in different cancer types revealed that the p27V109G polymorphism does not associate with the breast cancer risk, but it seemed to be associated with a decreased prostate cancer risk in a dominant genetic model (TG+GG vs. TT). However, the latter one needs to be interpreted with caution for two reasons. First, the sample size used for this analysis is relatively limited (286 cases and 397 controls); second, if the G allele is indeed associated with a decreased prostate cancer risk, one would expect the p -value from a homozygote genetic model-based analysis to be also statistically significant, which was not the case. Collectively, we conclude that the p27V109G polymorphism does not correlate with the overall cancer risk in the general population.

Functional polymorphisms of p27, a putative tumor suppressor, cancer prognostic factor, and a therapeutic target,^{28–30} can influence the expression of protein, and then contribute to the susceptibility and severity of cancer. Several SNPs of p27 have been found, and some of them were confirmed to be correlated with a low level of p27 protein, especially the V109G polymorphism. The p27V109G polymorphism is located at a region that physically interacts with the JAB1. It has been speculated that the p27V109G polymorphism can lead cell

cycle to out of control and more cells to transit from the G1 to S phase by enhancing protein degradation of p27 triggered by JAB1, so the p27V109G polymorphism can enhance the tumor genesis and development. The associations between the p27V109G polymorphism and the risk of cancer have been extensively studied, and inconsistent results have been reported. Therefore, we employed a meta-analysis to explore a more precise evaluation for the associations.

Although we are reporting a negative association, it is necessary to point out that a few drawbacks may mask a potential true association. First, we only included studies published in English. Second, populations included in this meta-analysis consisted exclusively of Caucasians and Asians. The distribution of genetic alleles may greatly vary by geography (genetic alleles frequencies of T, G were 0.768, 0.232 and 0.839, 0.161 in Caucasians and Asians populations), so the results of this meta-analysis might be biased. Third, only breast cancer, prostate cancer, pancreatic cancer, and oral squamous cell cancer are included in this meta-analysis, whereas many other types of cancer (lung cancer, gastric cancer, colorectal cancer, etc.) are not, due to availability. Fourth, our results are based on unadjusted OR estimates, because not all studies included in this meta-analysis provided adjusted ORs, and the ORs were not adjusted by the same potential confounders (such as TNM stage, age, sex, and other environmental factors) in those did. Since the susceptibility of cancer is influenced by numerous factors, the adjustments can be very important. Fifth, meta-analysis is a type of retrospective study, and limited by the quality of primary studies.

Overall, our meta-analysis does not support that the p27V109G polymorphism increases the cancer risk. However, future prospective studies with large sample sizes and better study designs are required to confirm our findings.

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Disclosure Statement

The authors declare that there are no financial or other conflicting interests in the present work.

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