Quantitative Assessment the Relationship between p21 rs1059234 Polymorphism and Cancer Risk

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Abstract

p21 is a cyclin-dependent kinase inhibitor, which can arrest cell proliferation and serve as a tumor suppressor. Though many studies were published to assess the relationship between p21 rs1059234 polymorphism and various cancer risks, there was no definite conclusion on this association. To derive a more precise quantitative assessment of the relationship, a large scale meta-analysis of 5,963 cases and 8,405 controls from 16 eligible published case–control studies was performed. Our analysis suggested that rs1059234 was not associated with the integral cancer risk for both dominant model \( ([T/T + C/T] \text{ vs } C/C, \text{ OR}=1.00, 95\% \text{ CI: } 0.84-1.18] \) and recessive model \( [T/T \text{ vs } (C/C + C/T), \text{ OR}=1.03, 95\% \text{ CI: } 0.93-1.15)] \). However, further stratified analysis showed rs1059234 was greatly associated with the risk of squamous cell carcinoma of head and neck (SCCHN). Thus, larger scale primary studies are still required to further evaluate the interaction of p21 rs1059234 polymorphism and cancer risk in specific cancer subtypes.

Keywords: p21 - cancer risk - polymorphism - meta-analysis

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Introduction

It has been suggested that environmental and genetic factors may affect the individual’s susceptibility to cancer (Derynck et al., 2001). An important gene identified as cancer susceptibility one is p21 (also known as CDKN1A), a member of the Cip/Kip family of cyclin-dependent kinase (CDK) inhibitors. Expression of p21 is up-regulated by wildtype p53 in response to DNA damage to induce cell cycle arrest at the G1 checkpoint (Xiong et al., 1993; Sherr, 1996). p21 can exerts tumor-suppressive effects by inhibiting PCNA-dependent DNA replication and mismatch repair (Li et al., 1994; Waga et al., 1997). Somatic mutations in the p21 gene are rare in human malignancies (Roninson, 2002). However, reduced p21 expression in tumors has been associated with poor prognosis in humans (Jiang et al., 1997; Wakasugi et al., 1997). Therefore, genetic polymorphisms in p21 may modulate its expression and thereby affect carcinogenesis.

p21 polymorphism rs1059234 (C70T) locates within the 3' untranslated region of p21 gene, causes a single C-to-T substitution 20 nt downstream of the stop codon at exon 3 (http://egp.gs.washington.edu). This polymorphic variant identified was thought to alter p21 function and maybe functionally associated with cancer susceptibility. Analysis of case-control studies is the most prevalent method of investigating the association between a disease and a specific gene polymorphism. Thus far, a number of studies have reported the role of p21 rs1059234 polymorphism in cancer risk (Li et al., 2005; Lei et al., 2010), but the results remain conflicting (Sivonova et al., 2013; Yin et al., 2015), partially because of the relatively small sample size in each of the published studies. Therefore, here we performed a large scale meta-analysis of all the published studies to derive a more precise quantitative assessment of the association between p21 rs1059234 polymorphism and the cancer risk.

Materials and Methods

Selection of studies

All of the case-control studies were identified by a computerized literature search of the PubMed, Web of Science, EBSCO, and CGEMS database (prior to March 2015) using the following words and terms: “p21”, “CDKN1A”, “polymorphism”, and “cancer”. References of the retrieved publications were also screened. Studies had to be based on an unrelated case-control design, so pedigree data were excluded. The following basic data were collected from the studies: first authors, journals, year of publications, cancer subtypes and ethnicity of the population.

Statistical analysis

For each study, the OR was first calculated to assess the association between the polymorphisms and the disease risk.
in Table 1. In meta-analysis, we examined the association between p21 rs1059234 polymorphism and the risk of cancer using recessive [T/T vs (C/C + C/T)] and dominant [(T/T + C/T) vs C/C] genetic models. There are three widely used methods of meta-analysis for dichotomous outcomes: two fixed effects methods (Mantel-Haenszel’s method and Peto’s method), which assume that studies are sampled from populations with the same effect size, making an adjustment to the study weights according to the in-study variance; and one random effects method (DerSimonian and Laird’s method), which assumes that studies are taken from populations with varying effect sizes, calculating the study weights both from the in-study and between-study variance, considering the extent of variation, or heterogeneity. In our study, both Mantel-Haenszel’s fixed effects method and DerSimonian and Laird’s random effects method were used in Stata 10.0 software. A chi-square-based Q-statistic test was performed to evaluate the between-study heterogeneity of the studies. If \( P < 0.10 \), the between-study heterogeneity was considered to be significant, we chose the random-effects model to calculate the OR. Otherwise, when \( P \geq 0.10 \), the between-study heterogeneity was not significant, then the fixed-effects model was suitable.

Main results

For each study we investigated the association between p21 rs1059234 polymorphism and cancer risk, assuming different inheritance models of the C70T allele. Overall, when all the eligible studies were pooled into the meta-analysis, no associations between p21 rs1059234 polymorphism and cancer susceptibility were observed in all genetic models. No significant associations were found for T/T vs C/C (OR=1.02; 95% CI: 0.83–1.26; \( P=0.010 \) for heterogeneity), C/T vs C/C (OR=0.98; 95% CI: 0.82–1.16; \( P=0.000 \) for heterogeneity), T/T+C/T vs C/C (OR=1.00; 95% CI: 0.84–1.18; \( P=0.000 \) for heterogeneity) and T/T vs C/T+C/T (OR=1.03; 95% CI: 0.93–1.15; \( P=0.135 \) for heterogeneity)(Table 2). However, subgroup analyses by cancer type showed rs1059234 polymorphism might associate with the risk of SCCHN for T/T+C/T vs C/C.

### Table 1. Characteristics of Studies Included in the Meta-Analysis

| Author | Cancer subtype | Genotype distribution of p21 rs1059234 polymorphism | OR (95% CI) | HWE (control P value) |
|--------|----------------|-----------------------------------------------|------------|-----------------------|
|        |                | Case                                      | Control    | T/T vs (C/C + C/T)     | T/T+C/T vs C/C     |
|        |                | C/C C/T T/T                               | C/C C/T T/T |                        |                      |
| Li et al., 2005 | SCCHN | Caucasian | 596 110 6 | 1080 136 6 | 1.72(0.55-5.36) | 1.48(1.14-1.93) | 0.445 |
| Wu et al., 2006 | bladder cancer | Caucasian | 513 86 3 | 506 82 3 | 0.98(0.20-4.88) | 1.03(0.75-1.42) | 0.8692 |
| Ma et al., 2006 | breast cancer | Asian | 87 211 70 | 129 253 85 | 1.06(0.74-1.50) | 1.23(0.90-1.69) | 0.444 |
| Guo et al., 2006 | ESCC | Asian | 94 154 51 | 166 221 50 | 1.59(1.04-2.43) | 1.34(0.98-1.82) | 0.0655 |
| Guo et al., 2006 | gastric cancer | Asian | 95 121 50 | 166 221 50 | 1.79(1.17-2.74) | 1.10(0.80-1.51) | 0.0655 |
| Driver et al., 2008 | prostate cancer | Caucasian | 167 18 1 | 181 39 1 | 1.19(0.07-19.14) | 0.51(0.29-0.92) | 0.4711 |
| Polakova et al., 2009 | Colorectal Cancer | Caucasian | 534 69 4 | 520 89 1 | 1.04(0.45-36.25) | 0.79(0.57-1.10) | 0.1603 |
| Lei et al., 2010 | SCCHN | Caucasian | 93 25 2 | 1009 139 14 | 1.39(0.31-6.19) | 1.91(1.21-3.04) | 0.0004 |
| Liu et al., 2010 | Colorectal Cancer | Asian | 100 197 76 | 223 438 177 | 0.96(0.71-1.29) | 0.99(0.75-1.30) | 0.1603 |
| Taghavi et al., 2010 | ESCC | Caucasian | 99 27 0 | 82 18 0 | Excluded | 0.61(0.45-0.83) | 0.3227 |
| Wang et al., 2012 | cervical cancer | Asian | 131 160 102 | 102 221 111 | 1.02(0.75-1.39) | 1.05(0.80-1.38) | 0.6942 |
| Liu et al., 2013 | hepatocellular cancer | Asian | 134 224 118 | 153 255 188 | 1.14(0.85-1.52) | 2.15(1.23-3.76) | 0.5493 |
| Carvalho et al., 2013 | retinoblastoma | Mixed (Braz) | 90 49 2 | 95 23 2 | 0.85(0.12-6.12) | 0.88(0.60-1.13) | 0.6599 |
| Sivenova et al., 2013 | prostate cancer | Caucasian | 104 14 0 | 108 22 0 | Excluded | 0.78(0.58-1.05) | 0.2919 |
| Zheng et al., 2014 | ESCC | Asian | 172 321 107 | 170 340 141 | 0.79(0.59-1.04) | 0.56(0.39-0.81) | 0.2342 |
| Shao et al., 2014 | gastric cancer | Asian | 99 158 56 | 154 301 126 | 0.79(0.55-1.12) | 1.24(0.64-2.41) | 0.3527 |
| Yin et al., 2015 | Endometrial Cancer | Asian | 88 110 65 | 69 165 81 | 0.95(0.65-1.38) | 0.66(0.32-1.36) | 0.3831 |

*OR: Odds ratio, CI: confidence interval, HWE: Hardy–Weinberg equilibrium, SCCHN: Squamous cell carcinoma of the head and neck, ESCC: esophageal squamous cell carcinoma
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Table 2. Summary of the Meta-analysis of Case-control Studies Examining the Association between p21 rs1059234 Polymorphism and Cancer Risk

| OR(95%CI)        | T/T vs C/C | C/T vs C/C | T/T vs (C/C+C/T) | (T/T+C/T) vs T/T |
|------------------|------------|------------|------------------|------------------|
| Studies          |            |            |                  |                  |
| All of studies   | 1.02(0.83–1.26) | 0.98(0.82–1.16) | 1.03(0.93–1.15) | 1.00(0.84–1.18) |
| All of SCCHN studies | 1.72(0.70–4.23) | 1.56(1.23–1.98) | 1.60(0.65–3.92) | 1.57(1.25–1.98) |
| All of ESCC studies | 1.14(0.48–2.70) | 1.06(0.87–1.28) | 1.10(0.55–2.19) | 1.05(0.87–1.27) |
| All of colorectal Cancer studies | 1.00(0.71–1.43) | 0.89(0.71–1.11) | 0.99(0.74–1.33) | 0.90(0.73–1.11) |
| All of gastric cancers studies | 1.09(0.44–2.71) | 0.88(0.70–1.11) | 1.17(0.53–2.63) | 0.92(0.74–1.14) |
| All of Caucasian studies | 1.67(0.82–3.37) | 1.02(0.74–1.41) | 1.61(0.80–3.25) | 1.03(0.75–1.42) |
| All of Asian studies | 0.98(0.78–1.25) | 0.89(0.75–1.07) | 1.05(0.89–1.24) | 0.92(0.77–1.10) |

Figure 1. Forest Plot of Cancer Risk Associated with the p21 rs1059234 Polymorphism. The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and 95% CI.

Figure 2. Begg’s Funnel Plot of the Egger’s Test for Publication Bias in Comparison of rs1059234 Polymorphism C70T Allele T vs allele C

(OR=1.57; 95% CI: 1.25–1.98; P=0.342 for heterogeneity) and T/T vs C/T+C/T (OR=1.60; 95% CI: 0.65–3.92; P=0.823 for heterogeneity) (Table 2).

Sensitivity analyses and publication bias

The results suggested the influences of the individual data set to the pooled ORs are all not significant. Funnel plots and Egger’s test were performed to assess publication bias (Figure 2). The data suggested that there is no publication bias for the comparison of rs1059234 polymorphism C70T allele T vs allele C (t=1.03, P=0.318).

Discussion

Cell cycle control is crucial for normal cell growth and differentiation and is regulated by cyclin-dependent kinases (CDKs). p21 is one of the universal inhibitors of cyclin-dependent kinases (CDK2, CDK3, CDK4, and CDK6)(Gartel and Tyner, 2002). It was initially discovered as a p53-target gene, but also has been suggested to play a role as a tumor suppressor in other cellular pathways including TGF-β and Wnt (Englert et al., 1997; Suzuki et al., 2012). Given the functional importance of p21 in carcinogenesis, genetic alteration of p21 could be associated with cancer risk.

So far, the functional role of the p21 rs1059234 variant has not yet to be well interpreted, several published clinic studies reported this variant was at increased risk of developing various cancer(Li et al., 2005; Lei et al., 2010; Liu et al., 2013). However, a number of published clinic studies reported this variant was not involved in the risk of cancer (Wu et al., 2006; Zheng et al., 2014; Yin et al., 2015). These conflicting studies based their conclusions on a small number of samples, so a meta-analysis of all available studies will help to establish a more convincing result. From our meta-analysis, p21 rs1059234 polymorphism in the combined population did not associate with cancer risk. There is no publication bias among the total studies. However, in the stratified analysis by ethnicity and subtype of cancer, significant association between p21 rs1059234 polymorphism and the risk of SCCHN was detected.

In conclusion, the research of the relationship of p21 rs1059234 polymorphism and cancer is very popular but remain conflicting at present. Our meta-analysis suggested that under recessive, dominant and other genetic models,
the p21 rs1059234 polymorphism did not associated with integral cancer risk. However, the studies included in the subgroups analysis are still limited and the results are sensitive to study selection. Since p21 also has a dual role can assume both pro- or anti-apoptotic functions in response to anti-tumor agents, depending on the cell type and context (Liu et al., 2003; Gartel, 2005). More comparative studies are needed to evaluate interactions of p21 rs1059234 polymorphism and cancer risk in specific cancer subtypes, especially in SCCHN.

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