Association between $p21$ Ser31Arg polymorphism and cancer risk: a meta-analysis

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Abstract

$P21$ (CDKN1A), a key cell cycle regulatory protein that governs cell cycle progression from $G_0$ to $S$ phase, can regulate cell proliferation, growth arrest, and apoptosis. The Ser31Arg polymorphism is located in the highly conserved region of $p21$ and may encode functionally distinct proteins. Although many epidemiological studies have been conducted to evaluate the association between the $p21$ Ser31Arg polymorphism and cancer risk, the findings remain conflicting. This meta-analysis with 33,077 cases and 45,013 controls from 44 published case-control studies showed that the variant homozygous 31Arg/Arg genotype was associated with an increased risk of numerous types of cancers in a random-effect model (heterogeneity test: OR = 1.17, 95% CI = 0.99 to 1.37, $P = 0.0002$ for the heterogeneity test; recessive model comparison: OR = 1.16, 95% CI = 1.01 to 1.33, $P = 0.0001$ for the heterogeneity test). Stratified analysis revealed that increased cancer risk associated with the 31Arg/Arg genotype remained significant in subgroups of colorectal cancer, estrogen-related cancer, Caucasians, population-based studies, studies with matching information or a larger sample size. Heterogeneity analysis showed that tumor type contributed to substantial between-study heterogeneity (recessive model comparison: $\chi^2 = 21.83, df = 7, P = 0.003$). The results from this large-sample sized meta-analysis suggest that the $p21$ 31Arg/Arg genotype may serve as a potential marker for increased cancer risk.

Key words $p21$, cancer, risk, meta-analysis
alteration of p21 expression and/or activity, thereby affecting susceptibility to cancer.

Many molecular epidemiological studies have been conducted to evaluate the effect of the p21 Ser31Arg polymorphism on cancer risk\(^{[19,24-26]}\). The results, however, remain conflicting, and the underlying heterogeneity between studies still needs to be explored. To estimate the overall cancer risk associated with the p21 Ser31Arg polymorphism and to quantify potential between-study heterogeneity, we conducted a systematic meta-analysis by including the most recent and relevant studies focusing on the association between the p21 Ser31Arg polymorphism and cancer risk.

Materials and Methods

Identification and eligibility of relevant references

We included all references of the case-control studies written in English and published to date on the association between the p21 Ser31Arg polymorphism and cancer risk. Two electronic databases (MEDLINE and EMBASE) were searched (last search update October 2010, using the search terms “p21” or “CDKN1A”, “cancer” or “carcinoma”, and “polymorphism” or “variant”) to identify eligible references. Additional references were identified by a hand search of original papers or reviews. If studies had overlapping subjects, only the one with the larger or largest sample size was selected. Furthermore, the studies including subjects with family history or cancer-prone predisposition were excluded.

Data extraction

The following information was extracted from each report: author, year of publication, country of origin, ethnicity, demographics, cancer type, and detail genotyping information and source of controls (population-based and hospital-based). For studies including subjects of different racial descents, data were extracted separately for each race (categorized as Caucasian, Asian, and others).

Statistical analyses

Genotype frequency was collected from each study to evaluate the risk of cancers [odds ratios (ORs) and 95% confidence intervals (CI)]. For all studies, we evaluated the effects of variant genotypes including Arg/Ser and Arg/Arg, compared with the wild-type Ser/Ser genotype, respectively. Then we calculated the ORs and 95% CI for both dominant and recessive genetic models of the variant Arg allele. In addition, we conducted stratification analysis by tumor type (if one cancer type was investigated in less than 3 studies, it would be merged into the “other cancers” group), ethnicity, control source, matching status (yes or no), and sample size (< 500, 500 to 1000, and > 1000). Smoking-related cancers included lung, bladder, head and neck, kidney, and pancreatic cancers; estrogen-related cancers included breast, cervical, and ovarian cancers.

The \(\chi^2\)-based \(Q\) statistic test was used to assess between-study heterogeneity, and it was considered significant if \(P < 0.05\)^{[27]}. The fixed-effects model and the random-effects model were respectively performed to combine values from each of the studies based on the Mantel-Haenszel method and the DerSimonian and Laird method^{[28]}. When the effects were assumed to be homogenous, the fixed-effects model was then used; otherwise, the random-effects model was more appropriate. The inverted funnel plots and Egger’s test were used to investigate publication bias (linear regression analysis)^{[27]}\). The deviation of genotype distribution from Hardy-Weinberg equilibrium (HWE) among controls was also examined by a goodness-of-fit \(\chi^2\) test. All analyses were conducted using Review Manager (v.5.0) and Stata 10.0. \(P\) values were two-sided.

Results

Characteristics of studies

A total of 48 publications examined the relationship between p21 Ser31Arg polymorphism and cancer risk. Two studies \(^{[24,28]}\) were excluded because they investigated the same or a subset population of reported articles \(^{[25,30]}\). Another two were also excluded because they did not present detailed genotyping information \(^{[66]}\) or had cancer-prone predisposition \(^{[29]}\). The studies investigating different cancers \(^{[28]}\), multiple ethnicity \(^{[29]}\), or multi-center collaboration \(^{[39]}\) were separated into multiple studies in subgroup analysis. In addition, three studies \(^{[48,61,63]}\) that only provided the total number of variant genotypes (Arg/Ser and Arg/Arg) were included in the analysis for the dominant model but not for other genetic models. Finally, our meta-analysis consisted of 44 publications including 59 case-control studies: 20 breast cancer studies, 5 lung cancer studies, 6 head and neck cancer studies, 7 cervical cancer studies, 3 colorectal cancer studies, 3 skin cancer studies, 5 gastric and esophageal cancer studies, and 10 studies of other cancers (Table 1). Among the 59 studies, 28 were conducted in Caucasian descents, 28 were conducted in...
Asian descents, 2 were conducted in other descents, and the remaining one by Keshava et al. was divided into two subgroups (Caucasians and other ethnicity), because it included multiple ethnicities. In addition, 11 studies were population-based and 48 were hospital-based; 26 did not provide matching information, while 33 were matched by age, sex, and/or geographic region. The polymerase chain reaction-restriction fragment length polymorphism assay (PCR-RFLP) was the most frequently used method for genotyping. Some other methods were also applied, such as direct sequencing, Taqman, and SNAPSHOT (Table 1). Overall,

| Reference          | Year | Country | Ethnicity | Cancer type | Sample size (case/control) | Matching (yes/no) | Genotyping method | Source of control |
|--------------------|------|---------|-----------|-------------|-----------------------------|-------------------|------------------|-------------------|
| Keshava et al.     | 2002 | USA     | Multiple  | Breast cancer | 160/327                     | Yes               | PCR-RFLP          | Hospital          |
| Ma et al.          | 2006 | China   | Asian     | Breast cancer | 368/467                     | Yes               | PCR-RFLP          | Hospital          |
| Tarasov et al.     | 2006 | Russia  | Caucasian | Breast cancer | 151/191                     | No                | PCR-RFLP and dCAPs | Hospital          |
| Staalesen et al.   | 2006 | Norway  | Caucasian | Breast cancer | 547/1006                    | No                | Sequencing        | Hospital          |
| Cox et al.         | 2007 | USA     | Multiple  | Breast cancer | 18 290/22670                | Yes               | Multiple methods  | Both              |
| MARIE-GENICA       | 2010 | USA     | Caucasian | Breast cancer | 314/27472                  | Yes               | MALDI-TOF MS and PCR-based Population fragment analyses | Hospital          |
| Splandel et al.    | 1996 | Sweden  | Caucasian | Lung cancer     | 144/761                      | No                | PCR-RFLP          | Hospital          |
| Shih et al.        | 2000 | China   | Asian     | Lung cancer     | 155/189                      | Yes               | PCR-RFLP          | Hospital          |
| Su et al.          | 2003 | China   | Asian     | Lung cancer     | 1069/1220                   | No                | PCR-RFLP          | Hospital          |
| Popanda et al.     | 2007 | Germany | Caucasian | Lung cancer     | 402/403                     | No                | Fluorescence-based melting-curve | Hospital          |
| Choi et al.        | 2008 | Korea   | Asian     | Lung cancer     | 549/533                      | Yes               | PCR and sequencing | Hospital          |
| Sun et al.         | 1995 | China   | Asian     | Nasopharyngeal cancer | 76/66                       | No                | PCR-SSCP direct sequencing | Hospital          |
| Tsai et al.        | 2002 | China   | Asian     | Nasopharyngeal cancer | 47/119                      | No                | PCR-RFLP          | Hospital          |
| Rodrigues et al.   | 2003 | Brazil  | Caucasian | Head and neck cancer | 73/104;46/104               | No                | PCR-SSCP          | Hospital          |
| Li et al.          | 2005 | USA     | Caucasian | Head and neck cancer | 712/1222                   | Yes               | PCR-RFLP          | Hospital          |
| Bau et al.         | 2007 | USA     | Asian     | Oral cancer     | 137/105                      | Yes               | PCR-RFLP          | Hospital          |
| Gomes et al.       | 2008 | Brazil  | Mixed     | Oral cancer     | 80/80                       | Yes               | PCR-RFLP          | Hospital          |
| Roh et al.         | 2001 | Korea   | Asian     | Cervical cancer | 111/98                      | No                | PCR-RFLP          | Hospital          |
| Harima et al.      | 2001 | Japan   | Asian     | Cervical cancer | 66/108                      | No                | Sequencing        | Hospital          |
| Lee et al.         | 2004 | Korea   | Asian     | Cervical cancer | 185/345                     | No                | SNAPSHOT assay    |                   |
| Lee et al.         | 2004 | Korea   | Asian     | Cervical cancer | 81/86                       | No                | PCR-RFLP          |                   |
| Bhattacharya et al. | 2005 | India   | Asian     | Cervical cancer | 148/191                     | No                | PCR-RFLP          |                   |
| Tian et al.        | 2009 | China   | Asian     | Cervical cancer | 317/353                     | Yes               | MAMA-PCR          |                   |
| Roh et al.         | 2010 | Korea   | Asian     | Cervical adenocarcinoma | 53/286                     | No                | PCR-RFLP          |                   |
| Wu et al.          | 2003 | China   | Asian     | Esophageal cancer | 128/178                    | Yes               | PCR-RFLP          |                   |
| Wu et al.          | 2004 | China   | Asian     | Gastric cancer  | 89/192                      | Yes               | PCR-RFLP          |                   |
| Lai et al.         | 2005 | China   | Asian     | Gastric cancer  | 123/119                     | No                | PCR-RFLP          |                   |
| Taghavi et al.     | 2010 | Iran    | Asian     | Esophageal cancer | 126/100                    | Yes               | PCR-RFLP          |                   |
| Yang et al.        | 2010 | China   | Asian     | Esophageal cancer | 80/200                     | No                | Sequencing        |                   |
| Polakova et al.    | 2009 | Czech   | Asian     | Colorectal cancer | 612/611                     | Yes               | Taqman            |                   |
| Liu et al.         | 2009 | China   | Asian     | Colorectal cancer | 373/838                     | No                | PCR-RFLP          | Population        |
| Cacina et al.      | 2010 | Turkey  | Turkish   | Colorectal cancer | 53/64                      | Yes               | PCR-RFLP          |                   |
| Konishi et al.     | 2000 | Japan   | Asian     | Skin cancer     | 113/165                     | No                | PCR-RFLP          |                   |
| Li et al.          | 2008 | China   | Asian     | Cutaneous melanoma | 805/838                    | Yes               | PCR-RFLP          |                   |
| Hachiyama et al.   | 1999 | Japan   | Asian     | Endometrial cancer | 54/55                      | Yes               | Dot Blot Hybridization | Hospital          |
| Chen et al.        | 2002 | China   | Asian     | Bladder cancer  | 53/119                      | No                | PCR-RFLP          |                   |
| Roh et al.         | 2004 | Korea   | Asian     | Endometrial cancer | 95/285                     | No                | PCR-RFLP          |                   |
| Hishida et al.     | 2004 | Japan   | Asian     | Non-Hodgkin’s lymphoma | 103/440                    | No                | Duplex PCR-CTPP   |                   |
| Huang et al.       | 2004 | China   | Asian     | Prostate cancer | 200/247                     | Yes               | PCR-RFLP          |                   |
| Hirata et al.      | 2007 | Japan   | Asian     | Renal cell carcinoma | 200/200                    | Yes               | PCR-RFLP          |                   |
| Gayther et al.     | 2007 | USA     | Caucasian | Ovarian cancer | 1491/2463                   | Yes               | Taqman            | Population        |
| Rajaraman et al.   | 2007 | USA     | Mixed     | Brain tumor     | 594/529                     | Yes               | Taqman            |                   |
| Chung et al.       | 2008 | China   | Asian     | Urothelial carcinoma | 169/402                    | Yes               | PCR-RFLP          |                   |
| Chen et al.        | 2010 | China   | Asian     | Pancreatic cancer | 59/462                      | Yes               | Pyrosequencing and PCR-RFLP |                   |

PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphisms; dCAPs, derived cleaved amplified polymorphic sequences; MALDI-TOF MS, matrix assisted laser desorption ionisation time-of-flight mass spectrometry; SSCP, single strand conformation polymorphism; MAMA, mismatch amplification mutation assay; CTPP, confronting two-pair primers.
most studies indicated that the distribution of genotypes in controls was consistent with HWE with the exception of 6 studies.[19,26,40,43,47,59].

Quantitative synthesis

The p21 31Arg allele frequency varied in different ethnicities, ranging from 0.04 in a Caucasian population[30] to 0.54 in an Asian population[51]. When the eligible studies were pooled into the meta-analysis, the variant genotypes of p21 Ser31Arg were significantly associated with an increased cancer risk. Specifically, compared to the wild-type homozygotes (31Ser/Ser), the variant homozygotes (31Arg/Arg) had a borderline increased risk of all types of cancers (OR = 1.17, 95% CI = 0.99 to 1.37, P = 0.0002 for heterogeneity test), and the association was significant in the recessive genetic model [Arg/Arg vs. (Ser/Ser + Arg/Ser): OR = 1.16, 95% CI = 1.01 to 1.33, P = 0.0001 for heterogeneity test]. (Figures 1 and 2). However, such associations were not found for heterozygous comparison or for dominant model comparison (heterozygote comparison: OR = 1.01, 95% CI = 0.94 to 1.08, P < 0.0001 for the heterogeneity test; dominant model comparison: OR = 0.98, 95% CI = 0.89 to 1.08, P < 0.0001 for the heterogeneity test).

In stratified analysis by tumor type, recessive model comparison with the heterogeneity test showed that individuals with variant homozygous genotypes (31Arg/Arg) had a higher risk for colorectal cancer (OR = 1.39, 95% CI = 1.03 to 1.08, P = 0.25) and estrogen-related cancer (OR = 1.27, 95% CI = 1.01 to 1.60, P = 0.002), but not for other cancers (Table 2). Furthermore, recessive model comparison for the heterogeneity test showed that the risk effect of variant homozygotes (31Arg/Arg) remained significant in studies Hongxia Ma et al. p21 Ser31Arg polymorphism and cancer risk

Figure 1. Forest plot (random-effects model) of overall cancer risk associated with the p21 codon 31 polymorphism: Arg/Arg vs. Ser/Ser. Compared to Ser/Ser, Arg/Arg had a borderline association with increased risk of all types of cancer.
with Caucasian subjects (OR = 1.41, 95% CI = 1.14 to 1.73, \( P = 0.34 \)), population-based controls (OR = 1.36, 95% CI = 1.11 to 1.67, \( P = 0.06 \)), matching design (OR = 1.21, 95% CI = 1.01 to 1.45, \( P = 0.002 \)), and sample size more than 1000 (OR = 1.18, 95% CI = 1.01 to 1.37, \( P = 0.08 \)).

**Heterogeneity and sensitivity analyses**

In the recessive model comparison, heterogeneity among all studies on the \( p21 \) Ser31Arg polymorphism and cancer risk was observed (\( \chi^2 = 98.56, P = 0.0001 \)). We evaluated the source of heterogeneity by tumor type, ethnicity, control source, matching status, and sample size, and found that tumor type contributed to substantial heterogeneity (\( \chi^2 = 21.83, P = 0.003 \)), but not ethnicity, control source, matching status, and sample size. The leave-one-out sensitivity analysis indicated that no single study changed the pooled ORs qualitatively. Furthermore, the exclusion of 6 studies \([19,20,40,43,47,59]\), whose genotype distributions deviated from HWE, did not affect the results of the meta-analysis (OR = 1.16, 95% CI = 1.01...
### Table 2. Summary ORs for association between the p21 Ser31Arg polymorphism and cancer risk

| Subgroup               | Comparisons | Cases/Controls | Arg/Arg vs. (Arg/Ser + Ser/Ser) OR (95% CI) | P²  |
|------------------------|-------------|----------------|------------------------------------------|-----|
| Total^                 | 56          | 32 420/43 960  | 1.16 (1.01–1.33)                          | 0.0001 |
| Tumor type             |             |                |                                          |     |
| Breast cancer          | 20          | 22 656/30 133  | 1.25 (0.96–1.63)                          | 0.03 |
| Lung cancer            | 5           | 2319/3106      | 0.92 (0.73–1.17)                          | 0.88 |
| Head and neck cancer   | 6           | 1125/1696      | 1.16 (0.79–1.72)                          | 0.63 |
| Cervical cancer        | 6           | 908/1181       | 1.40 (0.85–2.28)                          | 0.005|
| Colorectal cancer      | 3           | 1038/1513      | 1.39 (1.03–1.87)                          | 0.25 |
| Skin cancer            | 3           | 964/1107       | 0.64 (0.36–1.16)                          | 0.15 |
| Gastric/esophageal cancer | 5        | 546/769        | 0.78 (0.58–1.03)                          | 0.25 |
| Other cancers          | 8           | 2864/4455      | 1.43 (1.16–1.73)                          | 0.06 |
| Smoking–related cancer | 12          | 3574/4936      | 1.05 (0.88–1.27)                          | 0.10 |
| Estrogen–related cancer| 29          | 25 065/33 777  | 1.27 (1.01–1.60)                          | 0.002|
| Ethnicity              |             |                |                                          |     |
| Caucasian              | 28          | 27 184/36 960  | 1.41 (1.14–1.73)                          | 0.34 |
| Asian                  | 26          | 4495/6251      | 1.09 (0.92–1.28)                          | <0.0001 |
| Others                 | 3           | 741/749        | 0.87 (0.53–1.42)                          | 0.11 |
| Control source         |             |                |                                          |     |
| Population             | 11          | 17623/26454    | 1.36 (1.11–1.67)                          | 0.06 |
| Hospital               | 45          | 14797/17506    | 1.15 (0.99–1.33)                          | 0.0008|
| Matching status        |             |                |                                          |     |
| Yes                    | 32          | 23 809/27 929  | 1.21 (1.01–1.45)                          | 0.002|
| No                     | 24          | 8611/16031     | 1.09 (0.88–1.35)                          | 0.01 |
| Sample size            |             |                |                                          |     |
| < 500                  | 25          | 2653/3827      | 1.05 (0.85–1.30)                          | 0.002|
| 500–1000               | 8           | 2455/3522      | 1.21 (0.87–1.68)                          | 0.01 |
| > 1000                 | 23          | 27 312/36 611  | 1.18 (1.01–1.37)                          | 0.08 |

OR, odds ratio; CI, confidence interval. *Three references that only provided the total number of Arg/Ser and Arg/Arg were excluded from the analysis for the recessive comparison [Arg/Arg vs. (Arg/Ser+Ser/Ser)]. *One study by Keshava et al included multiple ethnicities. *Random effect model was used when P value for heterogeneity test < 0.05; otherwise, fix effect model was used. *Test for heterogeneity.

The risk effect of Arg/Arg was more prominent in studies with Caucasian subjects, population-based controls, matching design, and larger sample sizes.

**Publication bias**

Funnel plot and Egger's test were conducted to access the publication bias of all studies. The shapes of the funnel plots seemed symmetrical (Figure 3), suggesting that there was no obvious publication bias. Egger's test was used to provide further statistical evidence; similarly, we did not find significant publication bias in this meta-analysis (t = 0.95, P = 0.345).

**Discussion**

On the basis of 44 independent publications, our meta-analysis provided statistical evidence that variant homozygous Arg/Arg genotype of p21 was significantly associated with an increased risk of cancers, particularly of colorectal cancer and estrogen-related cancer. The stratification analysis also showed that the risk effect of
transcriptional efficiency. For example, individuals carrying the \textit{p21}-Arg-encoding allele manifest a lower \textit{p21} expression \cite{75}. Our meta-analysis supports that individuals carrying the Arg/Arg genotype have a higher cancer risk as assessed in a recessive model.

Because of the paradoxical role of \textit{p21} contributing to both cancer suppressive and promoting effects, it is biologically plausible that multiple tumors with different carcinogenic mechanisms may reflect different susceptibilities conferred by the \textit{p21} Ser31Arg polymorphism. In our meta-analysis, we found that the effect of the \textit{p21} 31Arg/Arg genotype was unfavorable toward the development of breast, head and neck, cervical, and colorectal cancer, but appeared to be favorable toward the development of lung, skin, gastric, and esophageal cancer. Heterogeneity analysis also showed that tumor type contributed to substantial between-study heterogeneity. Thus, inconsistent results among different cancers may involve the mechanisms by which \textit{p21} regulates cell proliferation or apoptosis in different cancer cells. However, this difference could also be due to limited statistical power as a result of a small sample size in subgroup analysis. Recently, a meta-analysis investigated the association between the \textit{p21} Ser31Arg polymorphism and breast cancer risk among 22 109 cases and 29 127 controls, but no significant associations were found \cite{76}, which is consistent with our results in breast cancer-including additional studies (22 656 cases and 30 133 controls). Moreover, studies have reported that estrogen stimulates cell mitotic activity and carcinogenesis in breast, endometrial, and ovarian cancer\cite{77,78}. In subgroup analysis, we found that the \textit{p21} Ser31Arg polymorphism was significantly associated with risk toward the development of estrogen-related cancer, possibly due to different carcinogenic mechanisms of different cancer types including gene-environment interactions.

Ethnicity may affect tumor susceptibility by different genetic factors and environmental exposures through gene-gene and gene-environment interactions. In our meta-analysis, we observed that the association between the \textit{p21} 31Arg/Arg genotype and overall cancer risk was significant in Caucasians but not in Asians. Furthermore, our results indicated that the association of significantly increased cancer risk with the \textit{p21} 31Arg/Arg genotype was more pronounced in studies with population-based controls, matching design, or larger sample sizes. The possible explanation may be that population-based controls were more representative of the general population and that studies with matching design or larger sample sizes may eliminate some bias and thus have a greater reliability or statistical power to detect the moderate effect of this single nucleotide polymorphism, suggesting that some characteristics should be carefully considered in genetic association studies, such as the selection of controls, matching status, ethnicity information, and sample size.

Several potential limitations of the present meta-analysis warrant consideration. First, although the funnel plot and Egger’s test showed no publication bias,
selection bias might have occurred because only studies published in English were included in our meta-analysis. Second, in the stratification analyses, the numbers of individuals carrying the Arg/Arg genotype in some subgroups were relatively small because of its low allele frequency in Caucasian subjects, which might have a small statistical power to detect the real association. Third, our results were based on unadjusted estimates, because ORs in all studies were not adjusted by the same potential confounders, such as age, sex, and exposure. Thus, a more precise analysis should be conducted, if individual data were available, which would allow for the adjustment by some co-variants and further evaluation of potential gene-environment interactions.

In summary, this meta-analysis provides statistical evidence that the p21 Ser31Arg polymorphism may contribute to individual susceptibility to cancer. Future well-designed large studies were warranted to validate our findings in different ethnic populations.

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