Association between L55M polymorphism in Paraoxonase 1 and cancer risk: a meta-analysis based on 21 studies

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Abstract: L55M polymorphism in Paraoxonase 1 (PON1) has been regarded as a risk factor for many cancer types. Nevertheless, the results remain controversial and inconclusive. We therefore performed a meta-analysis of all eligible case–control studies to evaluate the association between L55M polymorphism and cancer risk. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess the strength of the associations. Finally, a total of 5,627 cases and 6,390 controls, arising from 21 case–control studies, were enrolled in our study. Significant associations between PON1-L55M polymorphism and overall cancer risk were identified in all genetic models. In the stratified analyses by cancer type, PON1-L55M polymorphism was a risk factor for breast cancer in all genetic models, prostate cancer in the heterozygote model (ML vs LL: OR = 1.304, 95% CI = 1.049–1.620, $P_{\text{heterogeneity}} = 0.067$), and ovarian cancer in the recessive model (MM vs ML/LL: OR = 1.526, 95% CI = 1.110–2.097, $P_{\text{heterogeneity}} = 0.464$). Similarly, an increased risk was also identified for the Caucasian population in the heterozygote comparison and homozygote models, and hospital-based controls in all genetic models. To sum up, our study suggests that the PON1-L55M allele increased the risk of cancer. Future well-designed studies with larger sample sizes are warranted to further verify these findings.

Keywords: Paraoxonase 1, L55M, polymorphism, cancer, meta-analysis

Introduction

Cancer is the most lethal factor in developed countries and the second most lethal factor in developing countries.1 According to GLOBOCAN 2012, the number of new cases increased from 12.7 to 14.1 million in 2012, and 8.2 million deaths occurred.1,2 Aging of the population and adoption of cancer-related lifestyle increased the burden of cancer in developing countries. Reducing the incidence of cancer morbidity was the preferred prevention strategy. New and sensitive biomarkers are urgently required for the detection of high-risk populations and as new strategies for early detection. Currently, the underlying mechanisms of carcinogenesis are poorly understood, and research studies have suggested that environmental factors combined with susceptibility genes may play a critical role in the process.3,4 Gene polymorphisms, which can decrease the activity of detoxifying carcinogenic substances, may contribute to the transformation of exposure effects.

PON1 is located on the long arm of chromosome 7. Two important common genetic polymorphisms, PON1-Q192R and PON1-L55M, were identified by the epidemiologic and molecular studies in the coding region of the PON1 gene at positions 192 and 55. Studies revealed that higher PON1 activity and mRNA levels were
related to the PON1-55L allele than to PON1-55M,\textsuperscript{5,6} and a decreased stability of the PON1-55M protein may lead to a lower activity of PON1.\textsuperscript{7} In addition, the association between the polymorphism and risk of different cancers, such as prostate cancer\textsuperscript{8} and breast cancer,\textsuperscript{9} was identified by case–control studies, whereas no significant association was identified between the polymorphism and cancer risk in renal cell carcinoma\textsuperscript{10} and ovarian cancer.\textsuperscript{11} Until now, these results remain inconclusive. Therefore, we conducted the present meta-analysis to precisely assess the association between PON1-L55M polymorphism and cancer risk.

**Materials and methods**

**Search strategy**

We searched the PubMed, Google Scholar, and Web of Science databases for studies published before November 30, 2015, by adopting keywords “cancer OR malignancy OR carcinoma OR tumor OR neoplasm” AND “polymorphism OR mutation OR SNP OR variant” AND “Paraoxonase 1 OR PON1”. We also conducted a hand search of references of original articles or reviews on this issue for additional studies. All the eligible studies were restricted to humans. And the articles should be presented in English. We extracted data separately when more than one cancer type or ethnicity was involved in one publication. In addition, we enrolled the report with the largest sample size when more than one report published the same data.

**Inclusion criteria and exclusion criteria**

We selected studies according to the following criteria: 1) reports that assessed the association between PON1 polymorphisms and cancer risk; 2) case–control studies only; and 3) publications that could provide the specific genotype frequency of cases and controls directly or indirectly (can be calculated from the article text). Besides, we excluded studies that were: 1) case reports, case-only studies, or reviews; 2) publications without specific genotype frequency of L55M polymorphism in PON1; 3) animal studies; and 4) duplicate publications.

**Data extraction**

Two investigators (LC and WL) devoted themselves to the data extraction process, and the following details were captured: the name of the first author, year of publication, ethnicity of each population, cancer type, control source, genotyping method, total number of cases and controls, and \( P \)-value of HWE (Hardy–Weinberg equilibrium). We compared the data and reached consensus for all disagreements by the two investigators.

**Statistical analysis**

We used odds ratio (OR) and 95% confidence interval (CI) to assess the association between PON1-L55M polymorphism and cancer risk. ORs were calculated in five genetic models: allele contrast (M vs L), heterozygote comparison (ML vs LL), homozygote comparison (MM vs LL), recessive (MM vs ML/LL), and dominant (ML/MM vs LL). Between-study heterogeneity was assessed by \( \chi^2 \)-test-based \( Q \)-statistic test,\textsuperscript{12} and quantified by \( F \) values, as well as \( P \)-values.\textsuperscript{13} No significant heterogeneity was observed when \( F<0.50 \) and \( P>0.10 \), and ORs were pooled by a fixed-effects model. Otherwise, the random-effects model was used.\textsuperscript{14} Besides, stratified analyses by ethnicity, cancer type, genotyping method, and control source were performed. We combined any cancer type with less than two studies into the “other cancers” group. In addition, we also divided these cancer types into solid and hematological malignancies, individually. Sensitivity analysis was performed to assess the stability of these findings by removing one single study from the enrolled studies to reveal the influence of individual data sets on the pooled ORs. In the end, Begg’s funnel plot and Egger’s regression test were performed to assess the publication bias.\textsuperscript{13,15} We applied STATA software (version 12.0; StataCorp LP, College Station, TX, USA) to conduct all statistical analyses, and \( P<0.05 \) for any tests or genetic models was regarded as statistically significant.

**Results**

**Study characteristics**

After careful examination according to the inclusion criteria, a total of 21 case–control studies comprising 6,224 cases and 7,014 healthy controls were enrolled in our study (Table 1).\textsuperscript{8–11,16–32} The flow chart of the study selection process is shown in Figure 1. Among these studies, three studies were performed in Asians, 14 in Caucasians, and four in mixed group. A total of six cancer types were addressed: four studies on breast cancer; three on prostate cancer; two on colorectal cancer, lung cancer, and ovarian cancer; and eight on other cancers (one study each on acute leukemia, brain tumor, embryonal tumor, hepatocellular carcinoma, lymphohematopoietic cancer, osteosarcoma, renal cell carcinoma, and pancreatic cancer). All genotype frequencies were in HWE with the exception of Antognelli et al\textsuperscript{16} and Ahmed et al,\textsuperscript{2} and these two studies were excluded from the pooled analyses.

**Quantitative data synthesis**

Significant associations between the PON1-L55M polymorphism and cancer risk were identified in the allele contrast (M vs L: OR=1.221, 95% CI=1.066–1.398, \( P_{\text{heterogeneity}}=0.000 \)).
Association between PON1-L55M polymorphism and cancer risk

| First author            | Year | Ethnicity | Genotyping method | Control source | Cancer type          | Case MM | Case LM | Case LL | Control MM | Control LM | Control LL | Y or N (HWE) |
|-------------------------|------|-----------|-------------------|----------------|----------------------|---------|---------|---------|------------|------------|------------|--------------|
| Antognelli et al⁸       | 2005 | Caucasian | PCR-RFLP          | H-B            | Prostate cancer      | 67      | 197     | 120     | 43         | 169        | 148        | Y            |
| Van Der Logt et al⁹     | 2005 | Caucasian | PCR-RFLP          | P-B            | Colorectal cancer    | 59      | 166     | 139     | 50         | 162        | 140        | Y            |
| Stevens et al²²         | 2006 | Caucasian | PCR-RFLP          | P-B            | Breast cancer        | 77      | 230     | 176     | 58         | 223        | 202        | Y            |
| Stevens et al⁹         | 2008 | Mixed     | TaqMan            | P-B            | Prostate cancer      | 165     | 609     | 481     | 189        | 575        | 498        | Y            |
| Lurie et al¹⁷           | 2008 | Mixed     | TaqMan            | P-B            | Ovarian cancer       | 192     | 65      | 14      | 276        | 145        | 24         | Y            |
| Arpaci et al¹¹          | 2009 | Caucasian | PCR-RFLP          | H-B            | Ovarian cancer       | 5       | 19      | 27      | 2          | 27         | 25         | Y            |
| Antognelli et al¹⁶      | 2009 | Caucasian | PCR-RFLP          | P-B            | Breast cancer        | 325     | 115     | 107     | 231        | 125        | 188        | N            |
| Martinez et al¹³        | 2010 | Caucasian | TaqMan            | H-B            | Brain tumor          | 30      | 32      | 11      | 88         | 94         | 38         | Y            |
| Naidu et al¹⁷           | 2010 | Asian     | PCR-RFLP          | P-B            | Breast cancer        | 50      | 178     | 159     | 17         | 109        | 126        | Y            |
| Uyar et al¹⁹            | 2011 | Caucasian | PCR-RFLP          | P-B            | Renal cell carcinoma | 6       | 25      | 29      | 10         | 29         | 21         | Y            |
| Ergen et al¹⁹           | 2011 | Caucasian | PCR-RFLP          | P-B            | Osteosarcoma         | 3       | 23      | 24      | 9          | 20         | 21         | Y            |
| Aksoy-Sagirli et al²⁶   | 2011 | Caucasian | PCR-RFLP          | H-B            | Lung cancer          | 10      | 94      | 119     | 14         | 102        | 118        | Y            |
| Hussein et al⁹          | 2011 | Caucasian | PCR-RFLP          | P-B            | Breast cancer        | 60      | 21      | 19      | 6          | 23         | 35         | Y            |
| Vecka et al¹⁷           | 2012 | Caucasian | PCR-RFLP          | H-B            | Pancreatic cancer    | 10      | 39      | 24      | 8          | 37         | 28         | Y            |
| Kokouva et al²⁰         | 2013 | Caucasian | PCR-RFLP          | H-B            | Lymphohematopoietic cancers | 60   | 139     | 117     | 50         | 159        | 142        | Y            |
| de Aguiar Goncalves et al²³ | 2012 | Mixed     | TaqMan            | H-B            | Acute leukemia       | 34      | 99      | 104     | 19         | 75         | 131        | Y            |
| Wang et al²⁰           | 2012 | Asian     | PCR-RFLP          | P-B            | Lung cancer          | 2       | 47      | 307     | 0          | 18         | 166        | Y            |
| Akkiz et al²⁰           | 2013 | Caucasian | PCR-RFLP          | P-B            | Hepatocellular cancer | 31    | 81      | 105     | 27         | 89         | 101        | Y            |
| Antognelli et al²⁴      | 2013 | Caucasian | PCR-RFLP          | H-B            | Prostate cancer      | 100     | 291     | 180     | 131        | 540        | 497        | Y            |
| Vasconcelos et al²⁹     | 2014 | Mixed     | TaqMan            | P-B            | Embryonal tumor      | 15      | 56      | 85      | 25         | 134        | 177        | Y            |
| Ahmed et al²¹           | 2015 | Asian     | PCR-RFLP          | P-B            | Colorectal cancer    | 2       | 10      | 38      | 16         | 24         | 40         | N            |

Abbreviations: PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; HWE, Hardy–Weinberg equilibrium; Y, polymorphisms conformed to HWE in the control group; N, polymorphisms did not conform to HWE in the control group; H-B, hospital based; P-B, population based; L allele, leucine; M allele, methionine.

In stratified analyses by cancer type, the PON1-55M allele was a risk factor for breast cancer in all genetic models (allele contrast: M vs L: OR = 2.120, 95% CI = 1.066–4.218, OR = 1.218, 95% CI = 1.054–1.407, $P_{\text{heterogeneity}}$ = 0.000) models (Table 2, Figure 2).

Figure 1 Flow chart presenting the publication selection process.
Table 2 Results of meta-analysis for PON1-L55M polymorphism and cancer risk

| Variables          | Case/control | M vs L | OR (95% CI) | P-value | P (%) | MM vs LL | OR (95% CI) | P-value* | P (%) | ML vs LL | OR (95% CI) | P-value* | P (%) | ML + MM vs LL | OR (95% CI) | P-value* | P (%) | MM vs ML + LL | OR (95% CI) | P-value* | P (%) |
|--------------------|--------------|--------|-------------|----------|-------|----------|-------------|----------|-------|----------|-------------|----------|-------|----------------|-------------|----------|-------|----------------|-------------|----------|-------|
| Total              | 5,627/6,390  | 1.211  | 1.463       | 0.000    | 79.5  | 1.161    | 0.162       | 24.4     | 0.000 | 62.9     | 1.381       | 0.000    | 69.0 |
| Prostate cancer    | 2,210/2,790  | 1.244  | 1.521       | 0.000    | 89.6  | 1.258    | 0.067       | 63.0     | 0.003 | 83.1     | 1.293       | 0.000    | 87.0 |
| Breast cancer      | 970/799      | 2.120  | 3.666       | 0.000    | 94.7  | 1.252    | 0.703       | 0.0      | 1.887 | 0.001    | 3.187       | 0.000    | 90.7 |
| Ovarian cancer     | 322/499      | 1.268  | 1.305       | 0.000    | 97.2  | 0.713    | 0.764       | 0.0      | 0.831 | 0.000    | 1.523       | 0.000    | 4.0 |
| Lung cancer        | 579/418      | 1.095  | 0.718       | 0.000    | 66.2  | 1.047    | 0.215       | 34.8     | 0.014 | 80.6     | 1.523       | 0.000    | 0.0 |
| Other cancers      | 1,182/1,532  | 1.072  | 1.249       | 0.124    | 53.5  | 1.062    | 0.268       | 20.3     | 0.098 | 42.1     | 1.219       | 0.000    | 20.7 |
| Cancer type 2      |              |        |             |          |       |          |             |          |       |          |             |          |       |
| Solid tumor        | 5,074/5,814  | 1.201  | 1.420       | 0.000    | 88.8  | 1.148    | 0.208       | 21.1     | 0.000 | 63.8     | 1.356       | 0.000    | 71.7 |
| Hematological      | 553/576      | 1.336  | 1.717       | 0.262    | 65.3  | 1.280    | 0.089       | 65.4     | 0.079 | 67.6     | 1.531       | 0.000    | 0.0 |
| Ethnicity          |              |        |             |          |       |          |             |          |       |          |             |          |       |
| Caucasian          | 2,965/3,686  | 1.199  | 1.461       | 0.000    | 82.2  | 1.170    | 0.185       | 25.6     | 0.000 | 67.7     | 1.371       | 0.000    | 69.4 |
| Asian              | 743/436      | 1.428  | 2.344       | 0.925    | 84.9  | 1.324    | 0.797       | 0.0      | 0.938 | 0.0      | 2.068       | 0.000    | 0.0 |
| Mixed              | 1,919/2,268  | 1.113  | 1.252       | 0.052    | 76.7  | 1.104    | 0.093       | 53.3     | 0.053 | 60.9     | 1.265       | 0.012    | 72.7 |
| Control source     |              |        |             |          |       |          |             |          |       |          |             |          |       |
| Population-based   | 3,699/3,705  | 1.221  | 1.374       | 0.000    | 85.2  | 1.082    | 0.574       | 0.0      | 1.162 | 0.001    | 65.1        | 1.376    | 0.000 | 79.3 |
| Hospital-based     | 1,928/2,685  | 1.303  | 1.714       | 0.303    | 48.0  | 1.293    | 0.139       | 36.3     | 0.059 | 48.6     | 1.484       | 0.050    | 0.0 |
| Genotyping method  |              |        |             |          |       |          |             |          |       |          |             |          |       |
| PCR-RFLP           | 3,635/3,902  | 1.239  | 1.558       | 0.000    | 80.9  | 1.188    | 0.208       | 22.6     | 0.000 | 65.7     | 1.463       | 0.000    | 67.0 |
| TaqMan             | 1,992/2,488  | 1.171  | 1.221       | 0.100    | 68.9  | 1.112    | 0.169       | 37.9     | 0.103 | 48.0     | 1.212       | 0.027    | 63.6 |

Notes: P: 0%–25%, no heterogeneity; 25%–50%, modest heterogeneity; >50%, high heterogeneity; P-value: P-value of Q test for heterogeneity test; *statistically significant (P<0.05).

Abbreviations: OR, odds ratio; CI, confidence interval; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; L, allele, leucine; M allele, methionine.
Figure 2 Meta-analysis of the association between PON1-l55M polymorphism and cancer risk in the dominant model (MM/ML vs LL).

Note: Weights are from random effects analysis.

Abbreviations: CI, confidence interval; OR, odds ratio; ID, identification; NA, not available; L allele, leucine; M allele, methionine.

$P_{\text{heterogeneity}}$=0.000; homozygote: MM vs LL: OR = 3.666, 95% CI = 1.159–11.600, $P_{\text{heterogeneity}}$=0.000; heterozygote comparison: ML vs LL: OR = 1.252, 95% CI = 1.020–1.536, $P_{\text{heterogeneity}}$=0.703; recessive: MM vs ML/LL: OR = 3.187, 95% CI = 1.052–9.661, $P_{\text{heterogeneity}}$=0.000; and dominant: MM/ML vs LL: OR = 1.887, 95% CI = 1.064–3.349, $P_{\text{heterogeneity}}$=0.001), prostate cancer in the heterozygote comparison model (ML vs LL: OR = 1.304, 95% CI = 1.049–1.620, $P_{\text{heterogeneity}}$=0.067), and ovarian cancer in the recessive model (MM vs ML/LL: OR = 1.526, 95% CI = 1.110–2.097, $P_{\text{heterogeneity}}$=0.464).

Similarly, an increased risk was observed in the Caucasian population (homozygote: MM vs LL: OR = 1.461, 95% CI = 1.041–2.051, $P_{\text{heterogeneity}}$=0.000; and heterozygote comparison: ML vs LL: OR = 1.170, 95% CI = 1.050–1.303, $P_{\text{heterogeneity}}$=0.185) and the Asian population (allele contrast: M vs L: OR = 1.428, 95% CI = 1.143–1.784, $P_{\text{heterogeneity}}$=0.849; homozygote: MM vs LL: OR = 2.344, 95% CI = 1.304–4.214, $P_{\text{heterogeneity}}$=0.925; recessive: MM vs ML/LL: OR = 2.068, 95% CI = 1.175–3.638, $P_{\text{heterogeneity}}$=0.880; MM/ML vs LL: OR = 1.443, 95% CI = 1.092–1.907, $P_{\text{heterogeneity}}$=0.938), and hospital-based group (allele contrast: M vs L: OR = 1.303, 95% CI = 1.194–1.423, $P_{\text{heterogeneity}}$=0.062; homozygote: MM vs LL: OR = 1.714, 95% CI = 1.369–2.147, $P_{\text{heterogeneity}}$=0.303; heterozygote comparison: ML vs LL: OR = 1.293, 95% CI = 1.134–1.474, $P_{\text{heterogeneity}}$=0.139; recessive: MM vs ML/LL: OR = 1.484, 95% CI = 1.248–1.764, $P_{\text{heterogeneity}}$=0.510; and dominant: MM/ML vs LL: OR = 1.314, 95% CI = 1.083–1.594, $P_{\text{heterogeneity}}$=0.059). In addition, we conducted a stratification analysis by genotyping method, and an increased risk for the PCR-RFLP (polymerase chain reaction-restriction fragment length polymorphism) group was identified (Table 2). We divided these tumors into solid and hematological tumor.
groups, and the results of subgroup analyses were not completely consistent with those of overall cancer analyses (Table 2). We observed an increased risk of solid cancer in the allele contrast, homozygote, heterozygote comparison, and dominant models, and hematological tumor in the allele contrast, homozygote, and recessive models (Table 2).

Publication bias and sensitivity analysis
Each time, one single study was removed from the enrolled assembly to validate the effect of individual studies on the pooled analysis, and no individual study obviously affected the pooled OR observed (Figure 3). Egger’s test and Begg’s funnel plot were performed to assess the publication bias. The shape of the funnel plot was symmetrical (Figure 4). In addition, the results of Egger’s test did not show statistical evidence for bias (PON1-L55M MM vs LL: Egger’s test: $t=0.53; P=0.604$). Thus, no obvious publication bias was found in our meta-analysis, and our results were credible.

Discussion
Previous studies suggested that lifestyle, estrogens, dietary habits, and oxidative and carbonyl stresses potentially play a critical role in the tumorigenesis and progression of cancers. Decreased expression of PON1 was identified in lung cancer and pancreatic cancer by previous studies. M variants decreased the stability of the PON1 enzyme. Subsequently, the concentration of PON1 in the blood was lowered, which can influence the activity of the enzyme. The LM genotype was identified as having a PON1 activity level between LL and MM genotypes.
Previous studies suggested that PON1-L55M polymorphism was associated with an increased risk for many cancer types, such as breast and prostate cancers, while a decreased risk was identified in renal cell carcinoma and ovarian cancer. These results were controversial and inconclusive. In our present work, we identified that the PON1-55M allele was associated with an increased risk of cancer. In stratified analyses by cancer type, PON1-L55M polymorphism was a risk factor for breast cancer in all the five genetic models. Previous studies indicated that PON1, which is a part of lipid peroxidation scavenging systems, may affect the cell proliferation and malignant conversion process associated with the development of breast cancer. In addition, we also observed an increased risk of prostate cancer in the heterozygote comparison model and ovarian cancer in the recessive model. Similarly, an increased risk was observed in the Caucasian population (homozygote and heterozygote comparison models), the Asian population (allele contrast, homozygote, and recessive and dominant models), and the hospital-based group (all the five genetic models). The controls enrolled in our study were not uniformly defined. Some studies adopted the population-based group as the control source, while others adopted the hospital-based group. As a result, once the polymorphism was considered to influence the risk of other diseases, the control source would not always be representative of the underlying source populations. In addition, we observed an increased risk of solid cancer in the allele contrast, homozygote, heterozygote comparison, and dominant models, and hematological tumor in the allele contrast, homozygote, and recessive models. The cause of these differences may be related to the origin of the tumor.

Although we have presented a comprehensive study of the association between PON1-L55M polymorphism and cancer risk, several limitations should be noted. First, a limited number of publications were enrolled in our study and the sample size of each report was relatively small. Second, most of the enrolled publications were Caucasian, and none of them was African. Third, our results were based on single-factor estimates, which may result in a serious confounding bias, for the reason of lack of original data, without adjustment for age, sex, and other risk factors.

To sum up, our study identified that PON1-L55M polymorphism is a risk factor for cancers, particularly breast cancer, prostate cancer, and ovarian cancer. Further well-designed studies with large sample sizes will be continued on this issue of interest.

Author contributions
All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

Disclosure
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