The Association between PON1 (Q192R and L55M) Gene Polymorphisms and Risk of Cancer: A Meta-Analysis Based on 43 Studies

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Q192R and L55M polymorphism were considered to be associated with the development of multiple cancers. Nevertheless, the results of these researches were inconclusive and controversial. Therefore, we conducted a meta-analysis of all eligible case-control studies to assess the association between PON1 (Q192R and L55M) gene polymorphisms and risk of cancer. With the STATA 14.0 software, we evaluated the strength of the association by using the odds ratios (ORs) and 95% confidence intervals (CIs). A total of 43 case-control publications 19887 cases and 23842 controls were employed in our study. In all genetic models, a significant association between PON1-L55M polymorphisms and overall cancer risk was observed. Moreover, in the stratified analyses by cancer type, polymorphism of PON1-L55M played a risk factor in the occurrence of breast cancer, hematologic cancer, and prostate cancer. Similarly, an increased risk was observed in the Caucasian and Asian population as well as hospital-based group and population-based group. For PON1-Q192R polymorphisms, in the stratified analyses by cancer type, PON1-Q192R allele was associated with reduced cancer risks in breast cancer. Furthermore, for racial stratification, there was a reduced risk of cancer in recession model in Caucasian population. Similarly, in the stratification analysis of control source, the overall risk of cancer was reduced in the heterozygote comparison and dominant model in the population-based group. In conclusion, PON1-Q192R allele decreased the cancer risk especially breast cancer; there was an association between PON1-L55M allele and increased overall cancer risk. However, we need a larger sample size, well-designed in future and at protein levels to confirm these findings.

1. Introduction

Cancer is one of the diseases caused by a combination of genetic and environmental factors [1]. The PON1 gene, located on the long arm of chromosome 7q21.3, is an antioxidant enzyme that has strong lipophilic antioxidant properties, which can maintain the balance of antioxidant-oxidant [2, 3]. Simultaneously, PON1 is also an esterase involved in scavenging reactive oxygen species by binding to high-density lipoprotein (HDL). Studies have shown that oxidative stress may participate in the process of cell proliferation and malignant transformation and damage DNA as well as other biological molecules, resulting in the occurrence of tumors [4]. The ability of PON1 detoxification of carcinogenic oxidative stress products makes it possible for researchers to predict PON1 gene polymorphism in cancer susceptibility [5].

At present, with the deep development of genetic studies of PON1, studies have found that PON1-Q192R and PON1-L55M, the two most common functional genetic polymorphisms in PON1, were identified at positions 192 and 55 [6]. PON1-Q192R polymorphism (rs662A > G) was caused by the glutamine (Q genotype) substituted for the arginine (R genotype) 192 of the gene 6 exon of the PON 1 gene [7]. PON1-L55M (rs854560) was originated from the replacement of 55 leucines (L genotype) by methionine (M genotype) at
third exon 55[8]. In addition, it has been shown that the two functional SNP Q192R and L55M, were associated with the risk of multiple tumors [9, 10], such as oral cancer [11], lung cancer [12], and embryonal tumors [13].

According to the important role of PON1 in the development of tumor and the correlation between genotype and phenotype, we speculate that the variation of PON1 gene Q192 R and L55M may be related to tumor susceptibility. However, the data of many studies are contradictory and uncertain at present. Therefore, a comprehensive meta-analysis should be conducted to determine the relationship between Q192R and L55M polymorphism and cancer risk.

2. Materials and Methods

2.1. Search Strategy. We conducted a systematic literature search in the PubMed, Embase, and Web of Science for all related studies before June 10, 2019 via utilizing the following terms: “polymorphism OR paraoxonase 1 OR PONI” AND “tumor OR malignancy OR cancer OR carcinoma OR neoplasm”. In addition, we extracted the reference of the original articles on this issue to carry out a hand search for extra studies. The results deduced from these articles were limited to humans. When the publication referred to more than one cancer type or ethnicity, we deleted with data respectively. Besides, if different authors published articles based on the same population or one author used similar data in an article, we picked out the report with the latest study and largest sample size.

2.1.1. Inclusion Criteria and Exclusion Criteria. The enrolled studies must contain the following inclusion criteria: (1) publication that evaluated the association between PON1-L55M, or PON1-Q192R polymorphism and the risk of cancer. (2) The genotype frequency may be obtainable from cases and controls, or we could gain it via computing. In addition, studies were excluded when they would meet these exclusion criteria: (1) reviews, case reports, or case-only studies; (2) studies with deficient genotype frequency data; (3) animals reports; and (4) replicate studies.

2.2. Data Extraction. The authors were able to excerpt relevant data from these qualified studies independently, and the following information would be seized: first author's last name, publishing year, the ethnicity of each population, the genotyping methods, the control of source, cancer types, number of cases and controls, and P value of Hardy–Weinberg equilibrium. When encountering divergences, we analyzed the report and reached a consistent agreement lastly.

2.3. Statistical Analysis. 95% confidence interval (CI) and odds ratio (OR) were utilized to estimate the relation between PON1-Q192R, or PON1-L55M polymorphism and the risk of cancer with five genetic models: heterozygote comparison (ML versus LL; RR versus QQ), allele contrast (M versus L; R versus Q), homozygote (MM versus LL; RR versus QQ), recessive (MM versus ML+LL; RR versus RQ+QQ), and dominant (ML+MM versus LL; RR+RQ versus QQ). Besides, stratified analyses were conducted via ethnicity, cancer type, control source, and genotyping method. However, when any cancer type is less than two studies, we would segment it into the “other cancers” group. In addition, \( \chi^2 \)-test-based Q-statistic test [14] was taken to assess the research heterogeneity while \( I^2 \) values and \( P \) values [15] were used for quantifying. When \( I^2 < 50\% \) and \( P>0.10 \), it indicates that there was no significant heterogeneity, and ORs could be pooled by a fixed-effects model. Otherwise, the random effects model would be adopted [16]. Furthermore, sensitivity analysis, from the qualified removing a single research study and revealing the individual data set to merge OR influence, was applied to estimate the stability of these data. (\( P<0.05 \) was regarded as statistically significant [17].) Finally, potential publication bias was estimated by symmetry of funnel plot of Begg’s test as well as Egger’s test [15, 18], and being statistically significant was considered when \( P<0.05 \). All statistical tests were performed with STATA Software (version 14.0, state Corp), and \( P<0.05 \) for any genetic models or tests was identified as statistically significant.

3. Result

3.1. Publication Characteristics. According to the inclusion criteria after detailed examination, a total of 43 case-control publications including 19977 cases and 23932 controls were employed in our study [11–13, 19–59]. The flow chart of the study screening process was summarized in Figure 1. Moreover, there were 43 studies with 14142 cases and 13936 controls for PON1-Q192R polymorphism (Table 1), and, for PON1 L55M polymorphism, 28 studies involved a total of 8565 cases and 9996 controls (Table 2). For PON1 Q192R polymorphism, a total of 8 cancer types were processed, including breast cancer [21, 27, 31, 32, 37, 39, 50], prostate cancer [22, 23, 40, 41], gastrointestinal cancer [19, 20, 48, 59, 60], hematologic tumor [25, 29, 33, 44], lung cancer [11, 12, 54], brain tumors [30, 35, 38, 45, 56, 57], ovarian cancer [34, 43] and other cancers [13, 26, 28, 42, 53, 58] (uterine leiomyoma, childhood embryonal tumors, metastatic gastric cancer, bladder cancer,
Table 1: Characteristics of qualified case-control studies included in the meta-analysis of PON1-Q192R.

| Author                  | Year  | Ethnicity | Genotyping Method | Control of source | Cancer Type          | Case | Control | pHWE |
|-------------------------|-------|-----------|-------------------|-------------------|----------------------|------|---------|------|
| Stevens et al.          | 2006  | Caucasian | PCR-RFLP          | P-B               | Breast Cancer        | 259  | 42      | 0.38 | 0.54 Y |
| Gallicchio et al.       | 2007  | Caucasian | PCR-RFLP          | P-B               | Breast Cancer        | 38   | 15      | 1.93 | 0.19 Y |
| Antognelli et al.       | 2009  | Caucasian | PCR-RFLP          | P-B               | Breast Cancer        | 484  | 13      | 2.71 | 0.00 N |
| Hussein et al.          | 2011  | Caucasian | PCR-RFLP          | P-B               | Breast Cancer        | 51   | 8       | 0.25 | 0.62 Y |
| Naidu et al.            | 2010  | Asian     | PCR-RFLP          | H-B               | Breast Cancer        | 200  | 29      | 0.81 | 0.37 Y |
| Tang et al.             | 2017  | Asian     | TaqMan            | P-B               | Prostate Cancer      | 24   | 8       | 0.06 | 0.80 Y |
| Ulici et al.            | 2017  | Asian     | PCR-RFLP          | H-B               | Breast Cancer        | 155  | 54      | 3.42 | 0.06 Y |
| Kaya et al.             | 2016  | Caucasian | TaqMan            | H-B               | Breast Cancer        | 10   | 11      | 0.88 | 0.35 Y |
| Tomatir et al.          | 2015  | Caucasian | PCR-RFLP          | P-B               | Hematologic Cancer   | 36   | 20      | 0.07 | 0.79 Y |
| Tomatir et al.          | 2015  | Caucasian | PCR-RFLP          | H-B               | Hematologic Cancer   | 33   | 21      | 0.07 | 0.08 Y |
| Attar et al.            | 2015  | Caucasian | PCR-RFLP          | H-B               | Uterine Leiomyoma    | 60   | 8       | 1.39 | 0.24 Y |
| Eom et al.              | 2015  | Asian     | PCR-RFLP          | H-B               | Lung Cancer          | 37   | 109     | 0.01 | 0.92 Y |
| Ahmed et al.            | 2015  | Asian     | PCR-RFLP          | P-B               | Colorectal Cancer    | 30   | 4       | 0.76 | 0.38 Y |
| Akkiz et al.            | 2013  | Caucasian | PCR-RFLP          | P-B               | Hepatocellular Carcinoma | 109  | 13      | 0.27 | 0.60 Y |
| Vasconcelos et al.      | 2014  | Mixed     | TaqMan            | H-B               | Embryonal Tumors     | 83   | 33      | 0.51 | 0.48 Y |
| Conesa-Zamora et al.    | 2013  | Caucasian | TaqMan            | H-B               | Lymphomas            | 161  | 52      | 0.59 | 0.44 Y |
| Zha et al.              | 2012  | Asian     | TaqMan            | H-B               | Glioma               | 158  | 52      | 0.59 | 0.44 Y |
| De Aguiar Goncalves et al. | 2012   | Caucasian | TaqMan            | H-B               | Hematologic Tumor    | 102  | 40      | 1.79 | 0.180 Y |
| Kokouva et al.          | 2012  | Caucasian | PCR-RFLP          | H-B               | Hematologic Tumor    | 213  | 88      | 0.04 | 0.83 Y |
| Aksoy-Sagirli et al.    | 2011  | Caucasian | PCR-RFLP          | H-B               | Lung Cancer          | 93   | 11      | 0.13 | 0.72 Y |
| Uyar et al.             | 2011  | Caucasian | PCR-RFLP          | H-B               | Renal Cell Cancer    | 38   | 21      | 0.04 | 0.84 Y |
| Lurie et al.            | 2008  | Mixed     | TaqMAN            | P-B               | Ovarian Cancer       | 120  | 86      | 1.07 | 0.30 Y |
| Ergen et al.            | 2010  | Caucasian | PCR-RFLP          | H-B               | Osteosarcoma         | 27   | 21      | 0.06 | 0.80 Y |
| Martinez et al.         | 2010  | Caucasian | TaqMan            | H-B               | Brain Tumor          | 31   | 33      | 0.37 | 0.54 Y |
| Ozurtk et al.           | 2009  | Caucasian | PCR-RFLP          | H-B               | Bladder Cancer       | 53   | 15      | 0.10 | <0.001 N |
| Gold et al.             | 2009  | Mixed     | PCR-RFLP          | P-B               | Multiple Myeloma     | 19   | 13      | 0.91 | 0.91 Y |
| Arpac et al.            | 2009  | Caucasian | PCR-RFLP          | P-B               | Ovarian Cancer       | 38   | 6       | 1.46 | 0.23 Y |
| Rajaraman et al.        | 2008  | Mixed     | TaqMan            | H-B               | Brain Tumor          | 266  | 207     | 4.10 | 0.04 N |
| Searies Nielsen et al.  | 2005  | Mixed     | TaqMan            | P-B               | Brain Tumor          | 32   | 8       | 6.04 | 0.23 Y |
| Van der Logt et al.     | 2005  | Caucasian | PCR-RFLP          | P-B               | Colorectal Cancer    | 180  | 24      | 0.87 | 0.35 Y |
| Lincz et al.            | 2004  | Caucasian | PCR-RFLP          | P-B               | Multiple Myeloma     | 41   | 16      | 2.35 | 0.13 Y |
| Kerridge et al.         | 2002  | Caucasian | PCR-RFLP          | P-B               | Lymphoma             | 73   | 30      | 2.35 | 0.13 Y |
| Antognelli et al.       | 2005  | Caucasian | PCR-RFLP          | H-B               | Prostate Cancer      | 197  | 120     | 67.85 <0.001 N |
| Herrera et al.          | 2015  | Mixed     | TaqMan            | H-B               | Brain Tumor          | 15   | 20      | 0.64 | 0.42 Y |
| Kafadar et al.          | 2006  | Caucasian | PCR-RFLP          | P-B               | Brain Tumor          | 43   | 15      | 1.96 | 0.16 Y |
| J De Roos et al.        | 2006  | Mixed     | TaqMan            | P-B               | Hematologic Cancer   | 540  | 137     | 1.53 | 0.22 Y |
| Stevens et al.          | 2005  | Mixed     | TaqMan            | P-B               | Prostate Cancer      | 624  | 95      | 4.74 | 0.03 Y |
| Antognelli et al.       | 2013  | Caucasian | PCR-RFLP          | H-B               | Prostate Cancer      | 291  | 30      | 2.44 | <0.001 N |
| Wang et al.             | 2012  | Asian     | PCR-RFLP          | P-B               | Lung Cancer          | 36   | 17      | 0.93 | 0.33 Y |
| Lee et al.              | 2005  | Asian     | TaqMan            | P-B               | Lung Cancer          | 24   | 73      | 4.99 | 0.025 N |
| Agachan et al.          | 2006  | Caucasian | PCR-RFLP          | P-B               | Breast Cancer        | 17   | 4       | 1.46 | 0.230 Y |
| Hemati et al.           | 2019  | Asian     | PCR-RFLP          | H-B               | Gastric Cancer       | 39   | 10      | 0.03 | 0.87 Y |

**Abbreviations:** PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; HWE, Hardy–Weinberg equilibrium; Y, polymorphisms conforming to HWE in the control group; N, polymorphisms not conforming to HWE in the control group; H-B, hospital based; P-B, population based.
Table 2: Characteristics of qualified case-control studies included in the meta-analysis of PON1-L55M.

| Author                | Year | Ethnicity | Genotyping Method | Control of source | Cancer Type          | Case Control | Cancer Type          | Case Control | HWE   | p | p(HWE) |
|-----------------------|------|-----------|-------------------|-------------------|----------------------|--------------|----------------------|--------------|-------|---|--------|
| Stevens et al.        | 2006 | Caucasian | PCR-RFLP          | P-B               | Breast Cancer        | 176          | 230                  | 77           | 202   | 233| 58     | 0.88 | 0.77 | Y    |
| Antognelli et al.     | 2009 | Caucasian | PCR-RFLP          | P-B               | Breast Cancer        | 107          | 115                  | 325          | 188   | 125| 231    | 157.2 | 0.0001 | N    |
| Hussein et al.        | 2011 | Caucasian | PCR-RFLP          | P-B               | Breast Cancer        | 19           | 21                   | 60           | 35    | 23 | 6     | 0.58 | 0.44 | Y    |
| Naidu et al.          | 2010 | Asian     | PCR-RFLP          | P-B               | Breast Cancer        | 159          | 178                  | 50           | 126   | 109| 17    | 1.04 | 0.308 | Y    |
| Tang et al.           | 2017 | Asian     | TaqMan             | P-B               | Esophagogastric Cancer | 971          | 69                   | 1            | 1573  | 99 | 2     | 0.12 | 0.73 | Y    |
| Uluocak et al.        | 2017 | Caucasian | PCR-RFLP          | H-B               | Prostate Cancer      | 19           | 24                   | 6            | 43    | 45 | 10    | 0.13 | 0.72 | Y    |
| Wu et al.             | 2017 | Asian     | TaqMan             | H-B               | Breast Cancer        | 284          | 72                   | 9            | 346   | 30 | 2     | 3.24 | 0.064 | Y    |
| Akkiz et al.          | 2013 | Caucasian | PCR-RFLP          | P-B               | Hepatocellular Carcinoma | 105          | 81                   | 31           | 101   | 89 | 27    | 1.12 | 0.29 | Y    |
| Geng et al.           | 2014 | Asian     | TaqMan             | H-B               | Metastatic Gastric Cancer | 11           | 7                    | 0            | 82    | 7  | 0     | 0.15 | 0.7  | Y    |
| Vasconcelos et al.    | 2012 | Mixed     | TaqMan             | H-B               | Embryonal Tumors     | 85           | 56                   | 15           | 177   | 134| 25    | 0.032 | 0.95 | Y    |
| Metin et al.          | 2013 | Caucasian | PCR-RFLP          | H-B               | Ovarian Cancer       | 33           | 22                   | 0            | 33    | 19 | 2     | 0.13 | 0.72 | Y    |
| Vecka et al.          | 2012 | Caucasian | PCR-RFLP          | H-B               | Pancreatic Cancer    | 24           | 39                   | 10           | 28    | 37 | 8     | 0.67 | 0.41 | Y    |
| De Aguiar Goncalves et al. | 2012 | Mixed     | TaqMan             | H-B               | Acute Leukemia       | 104          | 99                   | 34           | 131   | 75 | 19    | 2.91 | 0.09 | Y    |
| Kokouva et al.        | 2012 | Caucasian | PCR-RFLP          | H-B               | Hematologic Cancer   | 117          | 139                  | 60           | 142   | 159| 50    | 0.26 | 0.61 | Y    |
| Aksoy-Sagirli et al.  | 2011 | Caucasian | PCR-RFLP          | H-B               | Lung Cancer          | 119          | 94                   | 10           | 118   | 102| 14    | 1.75 | 0.39 | Y    |
| Uyar et al.           | 2011 | Caucasian | PCR-RFLP          | P-B               | Renal Cell Cancer    | 29           | 25                   | 6            | 21    | 29 | 10    | 4.96 | 0.998 | Y    |
| Lurie et al.          | 2008 | Mixed     | TaqMan             | P-B               | Ovarian Cancer       | 14           | 65                   | 192          | 24    | 145| 276   | 0.74 | 0.39 | Y    |
| Ergen et al.          | 2010 | Caucasian | PCR-RFLP          | H-B               | Osteosarcoma         | 24           | 23                   | 3            | 21    | 20 | 9     | 1.14 | 0.29 | Y    |
| Martinez et al.       | 2010 | Caucasian | TaqMan             | H-B               | Brain Tumor          | 11           | 32                   | 30           | 38    | 94 | 88    | 2.15 | 0.14 | Y    |
| Arpac et al.          | 2009 | Caucasian | PCR-RFLP          | H-B               | Ovarian Cancer       | 27           | 19                   | 5            | 25    | 27 | 2     | 2.65 | 0.103 | Y    |
| Van der Logt et al.   | 2005 | Caucasian | PCR-RFLP          | P-B               | Colorectal Cancer    | 139          | 166                  | 59           | 140   | 162| 50    | 0.08 | 0.78 | Y    |
| Antognelli et al.     | 2005 | Caucasian | PCR-RFLP          | H-B               | Prostate Cancer      | 120          | 197                  | 67           | 148   | 169| 43    | 0.65 | 0.35 | Y    |
| Herrera et al.        | 2015 | Mixed     | TaqMan             | H-B               | Brain Tumor          | 46           | 17                   | 4            | 42    | 14 | 2     | 0.37 | 0.56 | Y    |
| J. De Roos et al.     | 2006 | Mixed     | TaqMan             | P-B               | Hematologic Cancer   | 299          | 307                  | 100          | 282   | 260| 69    | 0.59 | 0.44 | Y    |
| Stevens et al.        | 2008 | Mixed     | TaqMan             | P-B               | Prostate Cancer      | 481          | 609                  | 165          | 498   | 575| 189   | 1.18 | 0.28 | Y    |
| Wang et al.           | 2012 | Asian     | PCR-RFLP          | P-B               | Lung Cancer          | 307          | 47                   | 2            | 166   | 18 | 0     | 0.49 | 0.49 | Y    |
| Antognelli et al.     | 2013 | Caucasian | PCR-RFLP          | H-B               | Prostate Cancer      | 180          | 291                  | 100          | 497   | 540| 131   | 0.75 | 0.39 | Y    |
| Hemati et al.         | 2019 | Asian     | PCR-RFLP          | H-B               | Gastric Cancer       | 41           | 40                   | 9            | 34    | 49 | 7     | 0.027 | 0.87 | Y    |

Abbreviations: PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; HWE, Hardy–Weinberg equilibrium; Y, polymorphisms conforming to HWE in the control group; N, polymorphisms not conforming to HWE in the control group; H-B, hospital based; P-B, population based.
and renal cell cancer). Besides, we disposed a total of 7 cancer types when dealing with PON1-L55M polymorphism nearly like PON1 Q192R polymorphism. In addition, For PON1 Q192R polymorphism, 9 publications were conducted in Asians, 9 in mixed group, and 25 publications in Caucasians. Besides, there were 15 studies divided by TaqMan assay, while 28 studies conducted by PCR-RFLP. Moreover, the majority of control groups in the case group are gender and age matching, including 23 hospital based and 20 population based. For PON1 L55M polymorphism, we also conducted 6, 6, and 16 studies in Asian, mixed group, Caucasians, respectively. Moreover, 10 studies were divided by TaqMan assay as well as 18 studies conducted by PCR-RFLP.

3.2. Meta-Analysis

3.2.1. Association between PON1-Q192R and Cancer Susceptibility. In summary, in allele contrast model, we have found that there were not association between PON1-Q192R allele and reduced overall cancer risk (Table 3). In the subgroup analysis of cancer type, we identified a decreased risk in breast cancer (R versus Q: OR=0.643, 95%CI=0.440-0.942; RR versus QQ: OR=0.542, 95%CI=0.331-0.886; RQ versus QQ: OR=0.529, 95%CI=0.325-0.861; and RR+RQ versus QQ: OR=0.534, 95%CI=0.330-0.865). Nevertheless, an increased risk was confirmed in prostate cancer in the dominant model (RR+RQ versus QQ: OR=0.744, 95%CI=0.557-0.993) among Caucasian population. Similarly, in the stratification analysis of control source, the overall risk of cancer is reduced in the heterozygote comparison and dominant model (RR versus QQ: OR=0.793, 95%CI=0.638-0.984; RR+RQ versus QQ: OR=0.789, 95%CI=0.630-0.988) in the population-based group. In addition, we did not observe any risk factor by stratified analysis using genotyping method. Figure 2 showed the meta-analysis of the association between PON1-Q192R polymorphism and cancer risk (R versus Q)

3.2.2. Association between PON1-L55M and Cancer Susceptibility. Our study had uncovered that the PON1-L55M polymorphism was significantly associated with an increased risk of the overall cancers under all the genetic models (Table 4) (M versus L: OR=1.277, 95% CI=1.127-1.448; MM versus LL: OR=1.507, 95% CI=1.205-1.885; ML versus LL: OR=1.192, 95%CI =1.064-1.337; MM versus ML+LL: OR=1.288, 95%CI=0.557-0.993) in the population-based group. In addition, we did not observe any risk factor by stratified analysis using genotyping method. Figure 3 showed the meta-analysis of the association between PON1-Q192R and cancer risk (R versus Q)

3.2.3. Publication Bias and Sensitivity Analysis. A sensitivity analysis was carried out to detect the impact of individual papers on whole data by getting rid of one report at a time from the pooled analysis. And no individual report has been significantly affected by the pooled OR. Figure 4 showed the plot of the sensitivity analysis for evaluating the association between PON1-Q192R and cancer risk (RR versus QQ). Besides, we perform Egger’s test and Begg’s funnel plot to evaluate publication bias (Figure 5). And the results of Egger’s test and Begg’s funnel plot did not uncover publication bias in PON1 (Q192R and L55M) gene polymorphisms (PON1 Q192R: R versus Q: Begg’s test: z=2.034; ML versus LL: OR=1.222, 95%CI=1.122-1.331). In addition, we identified an increased risk by stratified analysis using genotyping method.

4. Discussion

Several studies have indicated that PON1, which is one of xenobiotic metabolising enzymes, plays a crucial role in the detoxification of carcinogenic compounds and decreases oxidative stress. Genetic polymorphisms can influence the enzyme and modify its activity, resulting in an impact on individual sensitivity to certain pathologies [61]. Indeed, a great deal of researches have showed that polymorphisms
| Study ID | OR (95% CI) | Weight |
|----------|-------------|---------|
| Breast cancer | | |
| Stevens et al (2006) | 0.88 (0.72, 1.07) | 2.79 |
| Gallicchio et al (2007) | 0.69 (0.44, 1.08) | 2.08 |
| Antognelli et al (2009) | 0.24 (0.18, 0.32) | 2.60 |
| Hussain et al (2011) | 0.81 (0.53, 1.24) | 2.16 |
| Naidu et al (2010) | 0.84 (0.66, 1.07) | 2.67 |
| Wu et al (2017) | 1.04 (0.84, 1.29) | 2.75 |
| Loyo et al (2016) | 0.52 (0.26, 1.05) | 1.45 |
| Agachan et al (2006) | 0.48 (0.26, 0.90) | 1.62 |
| Subtotal (I-squared = 91.4%, p = 0.000) | 0.64 (0.44, 0.94) | 18.13 |
| Gastrointestinal cancer | | |
| Tang et al (2017) | 1.05 (0.94, 1.18) | 2.95 |
| Lyrer et al (2015) | 0.29 (0.16, 0.50) | 1.80 |
| Akkör et al (2013) | 1.06 (0.79, 1.43) | 2.53 |
| Van Der Logt et al (2005) | 1.10 (0.86, 1.41) | 2.67 |
| Hemati et al (2019) | 2.56 (1.56, 4.22) | 1.95 |
| Subtotal (I-squared = 89.2%, p = 0.000) | 1.01 (0.70, 1.45) | 11.90 |
| Prostate cancer | | |
| Ulusak et al (2017) | 1.05 (0.63, 1.75) | 1.91 |
| Antognelli et al (2005) | 0.88 (0.71, 1.11) | 2.72 |
| Stevens et al (2006) | 1.01 (0.89, 1.14) | 2.93 |
| Antognelli et al (2013) | 0.94 (0.80, 1.10) | 2.87 |
| Subtotal (I-squared = 0.0%, p = 0.748) | 0.97 (0.89, 1.05) | 10.44 |
| Hematologic tumor | | |
| Tomatir et al (2015) | 1.52 (0.85, 2.73) | 1.72 |
| Tomatir et al (2015) | 1.90 (1.07, 3.33) | 1.76 |
| Conesa-Zamora et al (2013) | 1.53 (1.15, 2.03) | 2.57 |
| De Aguiar Goncalves et al (2012) | 0.73 (0.57, 0.95) | 2.64 |
| Kokouva et al (2012) | 0.58 (0.45, 0.75) | 2.64 |
| Guld et al (2009) | 0.80 (0.45, 1.52) | 1.75 |
| Lince et al (2004) | 1.62 (1.02, 2.43) | 2.33 |
| Kerridge et al (2002) | 1.55 (1.14, 2.11) | 2.50 |
| De Reus et al (2006) | 0.89 (0.78, 1.02) | 2.99 |
| Subtotal (I-squared = 85.5%, p = 0.000) | 1.11 (0.85, 1.45) | 20.82 |
| Other cancers | | |
| Attar et al (2015) | 0.47 (0.27, 0.79) | 1.87 |
| Vasconcelos et al (2014) | 1.29 (0.99, 1.68) | 2.62 |
| Lüer et al (2011) | 0.49 (0.27, 0.89) | 1.70 |
| Ergen et al (2010) | 0.57 (0.31, 1.04) | 1.66 |
| Ozturk et al (2009) | 1.70 (1.14, 2.53) | 2.23 |
| Subtotal (I-squared = 85.1%, p = 0.000) | 0.81 (0.48, 1.36) | 10.08 |
| Lung Cancer | | |
| Eom et al (2015) | 1.25 (1.02, 1.54) | 2.77 |
| Aksoy-Sagrit et al (2011) | 1.26 (0.95, 1.67) | 2.58 |
| Wang et al (2012) | 1.43 (1.11, 1.85) | 2.64 |
| Lee et al (2005) | 0.81 (0.59, 1.10) | 2.49 |
| Subtotal (I-squared = 63.8%, p = 0.040) | 1.18 (0.95, 1.46) | 10.48 |
| Brain tumor | | |
| Zhao et al (2012) | 0.98 (0.79, 1.21) | 2.76 |
| Martinez et al (2010) | 0.23 (0.16, 0.35) | 2.25 |
| Rajaraman et al. (2008) | 1.00 (0.82, 1.21) | 2.78 |
| Sevles Nielsen et al (2005) | 0.79 (0.52, 1.20) | 2.19 |
| Herrera et al (2015) | 1.08 (0.66, 1.78) | 1.95 |
| Kafadar et al (2006) | 0.97 (0.58, 1.64) | 1.88 |
| Subtotal (I-squared = 89.2%, p = 0.000) | 0.76 (0.51, 1.14) | 13.81 |
| Ovarian Cancer | | |
| Lurie et al. (2008) | 1.22 (0.98, 1.51) | 2.75 |
| Arpaci et al. (2009) | 0.34 (0.18, 0.64) | 1.58 |
| Subtotal (I-squared = 92.7%, p = 0.000) | 0.67 (0.19, 2.34) | 4.33 |
| Overall (I-squared = 86.8%, p = 0.000) | 0.90 (0.80, 1.01) | 100.00 |

NOTE: Weights are from random effects analysis.

Figure 2: Meta-analysis of the association between PON1-Q192R polymorphism and cancer risk (R versus Q). Abbreviations: ID, identification; CI, confidence interval; NA, not available; OR, odds ratio; weights come from random effects analysis.
### Table 3: Results of meta-analysis for PON1-Q192R polymorphism and cancer risk.

| Variables                  | Case/control | R vs. Q | RR vs. QQ | RQ vs. QQ | RR+RQ vs. QQ | RR vs. RQ+QQ | RR vs. QQ+QQ |
|----------------------------|--------------|---------|-----------|-----------|--------------|--------------|--------------|
|                            | OR(95% CI)   | p       | OR(95% CI) | p         | OR(95% CI)   | p            | OR(95% CI)   |
| Total                      | 0.897(0.798-1.008) | 0 86.8 | 0.855(0.683-1.075) | 0 81.1 | 0.861(0.724-1.023) | 0 86.7 | 0.857(0.730-1.008) | 0 86.7 |
| Breast cancer              | 2005/2748    | 0.643(0.440-0.942) | 0 91.4 | 0.542(0.331-0.886) | 0 74 | 0.529(0.325-0.861) | 0 89.1 | 0.534(0.330-0.865) | 0 90.6 |
| Gastrointestinal cancer    | 1752/2356    | 1.008(0.700-1.450) | 0 88.1 | 0.969(0.463-2.025) | 0.000 | 80.2 | 1.079(0.748-1.529) | 0.002 | 75.7 | 1.038(0.682-1.580) | 0.000 | 83.0 | 0.968(0.547-1.711) | 0.013 | 68.5 |
| Prostate cancer            | 2261/2891    | 0.967(0.886-1.055) | 0 74.8 | 0.563(0.313-1.015) | 0.001 | 83 | 1.544(0.969-2.458) | 0.009 | 90.9 | 1.249(1.030-1.514) | 0.083 | 55 | 0.498(0.235-1.053) | 0 90.3 |
| Hematologic tumor          | 2303/2355    | 1.13(0.852-1.453) | 0 85.5 | 1.38(0.787-2.34) | 0 82 | 0.94(0.740-1.202) | 0 80.7 | 1.04(0.774-1.397) | 0 78.2 |
| Lung cancer                | 1172/1011    | 1.17(0.949-1.464) | 0.04 | 63.8 | 1.24(0.665-2.326) | 0.005 | 76.6 | 1.24(0.704-2.094) | 0.004 | 77.5 | 1.26(0.741-2.149) | 0.003 | 78.6 |
| Brain tumor                | 1173/1395    | 0.759(0.505-1.140) | 0 89.2 | 0.576(0.266-1.248) | 0 85.9 | 0.778(0.339-1.124) | 0.016 | 69 | 0.696(0.431-1.123) | 0 84.4 | 0.698(0.388-1.256) | 0 79.4 |
| Ovarian cancer             | 322/496      | 0.665(0.189-2.337) | 0 92.7 | 0.94(0.314-2.813) | 0.087 | 65.8 | 0.528(0.030-3.572) | 0 94.6 | 0.44(0.060-3.283) | 0 94.5 | 1.359(0.985-1.875) | 0 65.8 |
| Other cancers              | 424/684      | 0.809(0.481-1.362) | 0 85.1 | 1.26(0.353-3.77) | 0.022 | 65 | 0.67(0.250-1.790) | 0 89.4 | 0.74(0.299-1.030) | 0 89.1 | 1.352(0.797-2.94) | 0 20.9 |
| Ethnicities                |              |         |         |         |         |         |         |         |
| Caucasian                  | 442/6292     | 0.85(0.658-1.101) | 0 90.1 | 0.78(0.516-1.193) | 0 84.5 | 0.73(0.528-1.010) | 0 91.1 | 0.74(0.557-0.993) | 0 90.3 | 0.89(0.608-1.31) | 0 83.5 |
| Asian                      | 3253/3629    | 0.84(0.840-1.244) | 0 89.9 | 1.01(0.689-1.506) | 0 78.5 | 1.02(0.779-1.337) | 0 76.3 | 1.02(0.758-1.377) | 0 83.0 | 1.05(0.850-1.303) | 0 025 | 54.4 |
| Mixed                      | 3735/4015    | 0.98(0.877-1.098) | 0.035 | 51.6 | 0.91(0.727-1.145) | 0.062 | 46.2 | 1.02(0.873-1.174) | 0.019 | 38.8 | 0.99(0.831-1.153) | 0.057 | 47 | 0.92(0.770-1.119) | 0.035 | 38.1 |
| Control source             |              |         |         |         |         |         |         |         |
| Population based           | 6871/8354    | 0.89(0.717-1.104) | 0 88.8 | 0.80(0.641-1.065) | 0 79.1 | 0.79(0.638-0.988) | 0 85 | 0.79(0.630-0.988) | 0 87.9 | 0.92(0.749-1.130) | 0 70.3 |
| Hospital based             | 4309/5667    | 0.89(0.798-1.018) | 0 85.1 | 0.94(0.655-1.754) | 0 83.2 | 0.92(0.704-1.22) | 0 87.3 | 0.92(0.726-1.175) | 0 85.5 | 0.96(0.696-1.342) | 0 83.3 |
| Genotype method            |              |         |         |         |         |         |         |         |
| PCR-RFLP                   | 5445/6900    | 0.88(0.735-1.064) | 0 88.4 | 0.88(0.735-1.064) | 0 88.4 | 0.81(0.650-1.094) | 0 90.4 | 0.83(0.646-1.091) | 0 89.4 | 0.93(0.692-1.27) | 0 80.5 |
| TaqMan                     | 5967/7036    | 0.92(0.801-1.060) | 0 83 | 0.83(0.662-1.071) | 0 81.4 | 0.95(0.824-1.099) | 0.008 | 61.1 | 0.90(0.762-1.078) | 0 76.7 | 0.91(0.736-1.139) | 0 73.5 |

Notes: ∗statistically significant (P<0.05); P value: P value of Q test for heterogeneity test; I²: 0%–25% means no heterogeneity, 25%–50% means modest heterogeneity, and 50% means high heterogeneity. Abbreviations: CI, confidence interval; OR, odds ratio; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism.
Table 4: Results of meta-analysis for PON1-L55M polymorphism and cancer risk.

| Variables                     | Case/control | M vs. L (OR(95% CI)) | p² | I² (%) | MM vs. LL (OR(95% CI)) | p² | I² (%) | ML vs. LL (OR(95% CI)) | p² | I² (%) | ML+MM vs. LL (OR(95% CI)) | p² | I² (%) | MM vs. ML+LL (OR(95% CI)) | p² | I² (%) |
|-------------------------------|--------------|----------------------|----|--------|------------------------|----|--------|------------------------|----|--------|-------------------------|----|--------|---------------------------|----|--------|
| Total                         | Total        | 1.277 (1.126-1.448)* | 0  | 81.6   | 1.192 (1.064-1.333)*   | 0  | 90.6   | 1.288 (1.120-1.480)*   | 0  | 70.9   | 1.417 (1.176-1.708)*      | 0  | 64.2   |
| Breast cancer                 | 2.186 (1.438-3.323)* | 0  | 92.5   | 3.215 (1.756-5.886)*   | 0  | 81.8   | 1.579 (1.145-2.177)*   | 0  | 69.9   | 2.110 (1.397-3.188)*      | 0  | 81.9   |
| Gastrointestinal cancer       | 1.111 (0.898-1.375) | 0.071 | 50.7   | 1.165 (0.848-1.601) | 0.988 | 0  | 1.097 (0.794-1.515) | 0.023 | 61.5   | 1.120 (0.829-1.512) | 0.032 | 59.0   | 1.185 (0.881-1.594) | 0.996 | 0  |
| Prostate cancer               | 2.129 (1.071-2.557)* | 0  | 95.1   | 1.507 (1.205-1.885)*   | 0  | 85.3   | 1.192 (1.064-1.333)*   | 0  | 90.6   | 1.288 (1.120-1.480)*      | 0  | 70.9   |
| Hematologic tumor             | 1.214 (1.031-1.428) | 0.012 | 69.9   | 1.057 (0.851-1.314) | 0.848 | 0  | 1.133 (0.922-1.401) | 0.190 | 62.5   | 1.192 (1.064-1.333)*      | 0  | 90.6   |
| Lung cancer                   | 1.074 (0.711-1.622) | 0.194 | 41.5   | 1.070 (0.711-1.622) | 0.215 | 31  | 0.907 (0.682-1.206) | 0.801 | 0  | 0.910 (0.696-1.190) | 0.025 | 47.5   |
| Other cancers                 | 0.932 (0.763-1.155) | 0.333 | 12.6   | 0.884 (0.905-1.548) | 0.215 | 31  | 0.907 (0.682-1.206) | 0.801 | 0  | 0.910 (0.696-1.190) | 0.025 | 47.5   |
| Ethnicities                   |              |                      |    |        |                        |    |        |                        |    |        |                        |    |        |                        |    |        |
| Caucasian                     | 1.231 (1.028-1.474)* | 0  | 85.8   | 1.737 (1.509-1.986)*   | 0  | 72  | 1.170 (1.034-1.324)*   | 0.199 | 22.4   | 1.334 (1.125-1.545)*      | 0  | 70.7   | 1.407 (1.092-1.813)*      | 0  | 678   |
| Asian                         | 1.604 (1.049-2.363)* | 0  | 80.7   | 2.093 (1.295-3.381) | 0.441 | 0  | 1.550 (0.995-2.417) | 0.000 | 79.7   | 1.624 (1.041-2.353)*      | 0  | 80.8   | 1.967 (1.238-3.125)*      | 0  | 65.6   |
| Mixed                         | 1.177 (1.004-1.379) | 0.019 | 63.1   | 1.137 (0.953-1.364) | 0.088 | 47.8 | 1.112 (0.953-1.297) | 0.268 | 22.1   | 1.126 (1.006-1.261)*      | 0.165 | 36.3   | 1.262 (1.057-1.505) | 0.034 | 58.4   |
| Control source                |              |                      |    |        |                        |    |        |                        |    |        |                        |    |        |                        |    |        |
| Population based              | 1.325 (1.085-1.618) | 0  | 88.7   | 1.568 (1.091-2.233) | 0  | 81.9 | 1.275 (1.051-1.548) | 0.401 | 4.5   | 1.275 (1.051-1.548) | 0  | 75.7   | 1.503 (1.100-2.034)*      | 0  | 80.5   |
| Hospital based                | 1.240 (1.056-1.456)* | 0  | 68.9   | 1.531 (1.199-1.955) | 0.132 | 29.8 | 1.255 (1.020-1.543) | 0.000 | 62.3   | 1.288 (1.120-1.480)*      | 0  | 66.7   | 1.411 (1.173-1.698) | 0.324 | 11.6   |
| Genotype method               | 1.243 (1.053-1.466)* | 0  | 82.2   | 1.571 (1.183-2.047) | 0  | 70.1 | 1.164 (1.033-1.311) | 0.145 | 26.5   | 1.246 (1.045-1.487) | 0  | 69.3   | 1.483 (1.167-1.884)*      | 0  | 62.7   |
| TaqMan                        | 1.330 (1.091-1.622)* | 0  | 79.5   | 1.309 (0.988-1.735) | 0.091 | 41.4 | 1.307 (1.026-1.665) | 0.014 | 71.5   | 1.370 (1.073-1.748) | 0  | 74.7   | 1.264 (0.986-1.620) | 0.05 | 48.5   |

Notes: * statistically significant (P<0.05); P value a: P value of Q test for heterogeneity test; I²: 0%–25% means no heterogeneity, 25%–50% means modest heterogeneity, and 50% means high heterogeneity.
Abbreviations: CI, confidence interval; OR, odds ratio; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism.
encoding the gene of these enzymes have been linked to the progression of cancer [49, 62]. Furthermore, several variants of PON1, including Q192R and L55M, have been found to be a biologically reasonable candidate which has an obvious influence on cancer. PON1 (Q192R and L55M) gene polymorphisms were related to many types of cancer, such as breast, prostate, and hepatocellular carcinoma [20, 50, 63]. For instance, PON1-L55M polymorphism may increase the risk in multiple cancer types, such as prostate and breast cancers but decrease renal cell carcinoma and ovarian cancer risk. As for PON1-Q192R, it has been revealed to suppress expression in lung [64] and pancreatic cancer [65] and reduce the risk of breast and prostate cancers. And the results of these researches were inconclusive and controversial.

In our work, in all genetic models we have identified the significant association between PON1-L55M polymorphism...
and overall cancer risk, while PON1-Q192R allele was not associated with reduced overall cancer risks. In the stratified analysis, we observed an increased risk in the Caucasian population and the Asian population, as well as the hospital-based group and population-based group under all the five genetic models in the PON1-L55M polymorphism. Similarly, a significantly increased risk of the overall cancers under the homozygote, allele contrast, recessive, and dominant models was uncovered in hematological tumor in the PON1-L55M polymorphism. Nevertheless, in the PON1-Q192R polymorphism, we also observe a reduced risk of the overall cancers in the allele contrast and dominant models. Meanwhile, we could obtain an interesting phenomenon that PON1-L55M polymorphism acts as a risk factor in all the five genetic models and there was an association between Q192R polymorphism and a reduced risk for cancer progression (except recessive model) after stratified analyses by cancer type, especially breast cancer. Thus, we can obtain that PON1

Figure 4: Sensitivity analysis of PON1-Q192R in overall OR coefficients (RR versus QQ). Abbreviations: OR, odds ratio CI, confidence interval. Sequentially calculated results of each study are omitted. Both ends of the broken line represent 95% of the CI.

Figure 5: Funnel figure of PON1-Q192R in overall OR coefficients (RR versus QQ). Abbreviations: OR, odds ratio.
(Q192R and L55M) gene polymorphisms play a vital role in the development of breast cancer, whose mechanism may be as follows: there was a critical association between L allele and higher PON1 serum concentrations while M variant decreased the stability of this enzyme. Therefore, the blood concentration of PON1 was reduced in this way; then, the activity of the enzyme was influenced, which may increase the vulnerability to genomic damage by reducing the inflammatory oxidant and the detoxifying ability of dietary carcinogens, thereby increasing the risk of breast cancer [5]. Furthermore, breast cancer becomes more susceptible to genomic damage as a result of lower levels of PON1 which could decrease the ability to detoxify inflammatory oxidants and dietary carcinogens [5]. Similarly, the exchange of Q and R could produce an enzyme which has a higher detoxification activity when there were potential carcinogenic products of oxidative stress and lipid peroxidation [66, 67]. In addition, not only genetic factors but also other contributors including nutrition and lifestyle can significantly affect PON1 enzyme activity, thereby reducing the risk of breast cancer [68]. To sum up, PON1, as a member of lipid peroxidation scavenging systems, may have an impact on malignant transformation and cell proliferation in the progression of breast cancer [69]. In the ethnographic analysis, we found ethnic groups having different results, which may be due to ethnic living habits, living environment, and genetic factors.

Previous meta-analysis also reported the association of PON1 polymorphism with cancer risk [10, 70]. As far as we know, we are the first of the typical functional polymorphism of the PON1 gene including all the published and defined case-control studies that have been conducted in a comprehensive meta-analysis. Compared with previous researches, our report was more persuasive and we have carried out a more detailed analysis to demonstrate our results. First and most obviously, the data we collected in our study was up-to-date, and we could keep up with the research front. Secondly, we included more qualified studies and larger sample size, which indicates that we are relatively more accurate in assessing that association between the PON1 gene SNPs and the risk of cancer.

Despite the association between PON1 (Q192R and L55M) gene polymorphism and cancer risk which has been studied in detail, we should note some limitations at the same time. First of all, the quantity of publications collected in our study was limited and there was a relatively small sample size of the report. What is more, Caucasian accounted for the most of the registered publications and there were no Africans. Furthermore, some of publications would only publish positive results, which could make the meta-analysis less credible. Lastly, our results were based on the estimates of single-factor, which could lead to serious confusion and bias due to the lack of raw data, and there is a need to adjust the effect size with possible confounders related to lifestyle risk factors, such as age, obesity, alcohol consumption, and smoking.

In conclusion, our study has demonstrated that PON1-Q192R can significantly reduce the risk of cancer and the polymorphism of PON1-L55M is a risk factor leading to cancer, especially breast cancer. Next, we need a larger sample size at protein levels to confirm whether PON1 polymorphisms may be potential genetic markers of tumor prognosis and identify its role in the risk of women developing breast cancer.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Authors’ Contributions

Bo Zhu, Lingsha Huang, and Jinfeng Liu conceived and designed the experiments; Xiaolan Pan, Lei Huang, and Meiqin Li conducted literature review and data abstraction; Xiaolan Pan and Bo Zhu analyzed data; and Dan Mo, Yihua Liang, and Zhaodong Huang conducted a hand search for extra studies. Xiaolan Pan, Bo Zhu, Lingsha Huang, and Meiqin Li wrote the manuscript. All authors reviewed and approved the manuscript. Xiaolan Pan, Lei Huang, and Meiqin Li have contributed equally to this work.

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