RESEARCH ARTICLE

Paraoxonase 1 (PON1) Q192R Gene Polymorphism and Cancer Risk: A Meta-Analysis Based on 30 Publications

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Abstract

Common genetic variation Q192R in the paraoxonase 1 (PON1) gene has been considered to be implicated in the development of many cancers. Nevertheless, results from the related studies were inconsistent. To elucidate the association, we performed a meta-analysis for 8,112 cases and 10,037 controls from 32 published case-control studies. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess the strength of the association by STATA 12.0 software. Overall, we revealed that the PON1-192R allele was associated with a reduced risk of the overall cancers. Moreover, in the stratified analysis by cancer types (breast cancer, prostate cancer, brain cancer etc.), the results showed that PON1-192R allele was associated with a decreased risk in breast cancer (R vs Q: OR=0.605, 95% CI=0.378-0.967, \(P_{\text{heterogeneity}}=0.000\); RR vs QQ: OR=0.494, 95% CI=0.275-0.888, \(P_{\text{heterogeneity}}=0.002\); RQ vs QQ: OR=0.465, 95% CI=0.259-0.835, \(P_{\text{heterogeneity}}=0.000\), and associated with prostate cancer in homozygote (RR vs QQ: OR=0.475, 95% CI=0.251-0.897, \(P_{\text{heterogeneity}}=0.001\) and recessive models (RR vs RQ+QQ: OR=0.379, 95% CI=0.169-0.853, \(P_{\text{heterogeneity}}=0.000\)), while an increased risk was identified in lymphoma (R vs Q: OR=1.537, 95% CI=1.246-1.896, \(P_{\text{heterogeneity}}=0.944\); RR vs QQ: OR=2.083, 95% CI=1.861-4.795, \(P_{\text{heterogeneity}}=0.350\); RR+RQ vs QQ: OR=1.840, 95% CI=1.021-1.796, \(P_{\text{heterogeneity}}=0.056\); and RR vs RQ+QQ: OR=2.934, 95% CI=1.869-4.605, \(P_{\text{heterogeneity}}=0.433\)) and an increased risk in prostate cancer under heterozygote comparison (RQ vs QQ: OR=1.782, 95% CI=1.077-2.950, \(P_{\text{heterogeneity}}=0.000\)) and dominant models (RR+RQ vs QQ: OR=1.281, 95% CI=1.044-1.573, \(P_{\text{heterogeneity}}=0.056\)). When subgroup analysis that performed by the control source (hospital based or population based), a decreased risk of the overall cancers was revealed by homozygote (RR vs QQ: OR=0.601, 95% CI=0.366-0.987, \(P_{\text{heterogeneity}}=0.000\)) and dominant models (RR vs RQ+QQ: OR=0.611, 95% CI=0.384-0.973, \(P_{\text{heterogeneity}}=0.000\)) in hospital based group. Stratifying by ethnicity, a significantly reduced risk of the overall cancers under allele contrast model (R vs Q: OR=0.788, 95% CI=0.626-0.993, \(P_{\text{heterogeneity}}=0.000\)) was uncovered in Caucasian. In summary, these findings suggested that PON1 Q192R polymorphism was associated with a reduced risk of the overall cancers, nevertheless, it might increase cancer susceptibility of prostate and lymphoma risk. Large well-designed epidemiological studies will be continued on this issue of interest.

Keywords: Paraoxonase 1 - Q192R - polymorphism - cancer - meta-analysis

Asian Pac J Cancer Prev, 16 (10), 4457-4463

Introduction

About 14.1 million cancer cases and 8.2 million cancer deaths were reported in the GLOBOCAN 2012, indicating that cancer has already been a critical public health problem around the world (Torre et al., 2015). It is known to us that cancer is a disorder arising from complex interactions between genetic predispositions and environmental factors (Pharoah et al., 2004; Bredberg, 2011). And gene PON1 is located on the long arm of the chromosome 7q21.3 (Humbert et al., 1993), and the protein encoded by this gene is responsible for the hydrolysing organophosphate pesticides and nerve gasses process. Studies indicated that the activity of PON1 can be influenced by the polymorphisms of the PON1. Besides, several variants in PON1, such as Q192R, L55M etc., have been uncovered as biologically plausible candidates for effects on cancer. The first polymorphism (rs662A>G) was arising from the substitution of glutamine (Q genotype) by arginine (R genotype) at position 192 in exon 6 of the PON1 genes. Previous studies suggested that the PON1 activity of the PON1 192R allele carriers was identified to be higher than that of the Q carriers (Davies et al., 1996; Mackness et al., 1997; Li et al., 2003).
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Recently, several studies have uncovered the association between Q192R polymorphism and malignant tumor susceptibility, including bladder cancer (Ozturk et al., 2009), renal cancer (Uyar et al., 2011) and glioma (Zhao et al., 2012). In the study conducted by Aygac et al. (2009), they investigated the association between PON1 Q192R polymorphism and ovarian cancer risk in a small sized case-control study of 51 cases and 54 controls in a Turkish Population, and revealed that this polymorphism increased the risk of ovarian cancer. Nevertheless, a lack of association between this polymorphism and brain astrocytoma or meningioma risk was also obtained by Martinez et al. (2010).

Based on the significant role of PON1 in cancer carcinogenesis and the genotype-phenotype correlation, we hypothesized that genetic variant Q192R in PON1 might be associated with cancer susceptibility. Awkward, the data reported are conflicting and inconclusive. Thus, we conducted a meta-analysis aiming to define the association between the Q192R polymorphism and cancer risk.

Materials and Methods

Search strategy

We searched the PubMed, Web of Science, Google Scholar and Embase for all relevant articles before March 22, 2015, by using the keywords “paraoxonase 1” or “PON1,” “polymorphism,” “tumor,” or “malignancy,” or “cancer,” or “carcinoma.” Additional reports on this issue were uncovered by conducting a hand search of the references extracting from the reviews or original research articles. All the retrieved results were confined to human populations and the genotype frequency can be obtained from these reports. When different authors published more than one of the same population or the same authors reported the overlapping data, we will select the most recent or comprehensive study into our meta-analysis. Besides, when one publication reported more than one cancer type or populations, we will extract the data separately.

Inclusion criteria and exclusion criteria

Reports were enrolled in our study keeping to the following criteria: i) Reports that assessed the association between the Q192R polymorphisms in PON1 and cancer risk; ii) Reports that designed in case-control study; iii) The genotype frequency was available for the cases and controls, or we can get it through calculating. Reports were removed from our report when they were: i) Case-only study, review or case report; ii) Reports without efficient genotype frequency data; iii) Overlapping reports; iv) Reports related to Animals.

Data extraction

Three of the authors (Meng Zhang, Hu Xiong and Lu Fang) extracted the detailed data from these eligible reports independently. Consensus for any controversy was reached and all the case-control studies followed the inclusion criteria. For each report, the following data will be gathered: the last name of the first author, the publication year, the ethnicity of each population, the genotype frequency for the cases and controls, the control source, the genotyping methods and cancer types. The ethnic descents can be divided into Caucasian, Asian, African or Mixed ethnicity group (more than one ethnic descent).

Statistical analysis

We used the OR and 95% CI to estimate the strength of the associations between Q192R polymorphism in PON1 and the cancer risk under five genetic models: allele contrast (R vs Q), homozygote (RR vs QQ), heterozygote comparison (RQ vs QQ), recessive (RR vs RQ/QQ), and dominant (RR/RQ vs QQ) models. We also performed stratified analysis by ethnicity and the type of cancers. Nevertheless, when only one cancer type encompassed less than two case-control studies, we will subdivide it into the group of “Other Cancers”. Besides, we calculated the heterogeneity via a chi-square based Q statistic test. By calculating F and P values, the effect of heterogeneity can be quantified. Once the F value <50 % and P>0.10, suggesting that no significant heterogeneity was uncovered, and ORs can be pooled by a fixed-effects model. If not, we will select a random-effects model (DerSimonian and Laird, 1986). In addition, a professional web-based program can be used to tested the Hardy-Weinberg equilibrium (HWE) (http://ihg2.helmholtz-muenchen.de/cgibin/hw/hwa1.pl) for the control group (Zamora-Ros et al., 2013); if P>0.05, suggesting that the control group accords with the HWE balance. We further performed sensitivity analysis to evaluate the stability of these data.

When HWE disequilibrium existed, we will apply sensitivity analysis to evaluate the stability of these data by removing a single study from the enrolled publications to uncover the impression of the separate data set on the pooled ORs (P<0.05 was considered statistically significant) (Tobias and Campbell, 1999). Finally, possibility of the publication bias was investigated by using Beggs’s test and Egger’s test(Begg and Mazumdar, 1994; Egger et al., 1997), and P<0.05 was considered as statistically significant. All the statistical tests can be conducted by STAATA Software (version 12.0, stata Corp), and P<0.05 for any tests or genetic models were regarded as statistically significant.

Results

Publication characteristics

After elaborated examination according to the inclusion criteria, a total of 30 publications enrolled in our meta-analysis comprising 8,112 cases and 10,037 controls (Kerridge et al., 2002; Linicz et al., 2004; Antognelli et al., 2005; Lee et al., 2005; Searles Nielsen et al., 2005; Van Der Logt et al., 2005; Kafadar et al., 2006; Gallicchio et al., 2007; Lurie et al., 2008; Rajaraman et al., 2008; Stevens et al., 2008; Antognelli et al., 2009; Arpaci et al., 2009; Ozturk et al., 2009; Martinez et al., 2010; Naidu et al., 2010; Aksoy-Sagirdir et al., 2011; Ergen et al., 2011; Hussein et al., 2011; Uyar et al., 2011; de Aguiar Goncalves et al., 2012; Vecka et al., 2012; Wang et al.,
Meta-analysis

To sum up, our results have revealed that the PON1-192R allele was associated with a reduced risk of the overall cancers in allele contrast model (R vs Q: OR = 0.843, 95% CI = 0.725-0.979, \( P_{\text{heterogeneity}} = 0.000 \)) (Table 2, Figure 2a). In the cancer type subgroup analysis, we identified an increased risk in lymphoma (R vs Q: OR = 1.537, 95% CI = 1.246-1.896, \( P = 0.944; \text{RR} \)).

Table 1. Characteristics of Eligible Case-control Studies Included in the Meta-analysis

| First Author       | Year | Ethnicity | Genotyping Method | Control of Cancer Type | Case (OR, 95% CI) | Control (OR, 95% CI) | HWE | \( p \) (HWE) |
|--------------------|------|-----------|-------------------|------------------------|------------------|---------------------|-----|----------|
| Lee et al.         | 2005 | Asian     | TaqMan            | Lung Cancer            | 24 (80, 73)      | 11 (89, 77)         | 5   | 0.025 N  |
| Wang et al.        | 2012 | Asian     | PCR-RFLP          | Lung Cancer            | 36 (173, 143)   | 83 (84, 62)         | 0.93 | 0.33 Y   |
| Ahmed et al.       | 2015 | Asian     | PCR-RFLP          | Colorectal Cancer      | 30 (16, 4)       | 24 (36, 24)         | 0.76 | 0.38 Y   |
| Akkiz et al.       | 2013 | Caucasian | PCR-RFLP          | Colorectal Cancer      | 109 (95, 13)     | 115 (88, 14)        | 0.27 | 0.6 Y    |
| Naidu et al.       | 2010 | Asian     | PCR-RFLP          | Breast Cancer          | 200 (158, 29)   | 115 (115, 22)       | 0.81 | 0.37 Y   |
| Antognelli et al.  | 2013 | Caucasian | PCR-RFLP          | Breast Cancer          | 291 (250, 30)   | 217 (258, 203)      | 0.24 | 0.01 N   |
| Eom et al.         | 2015 | Asian     | PCR-RFLP          | Lung Cancer            | 37 (170, 209)   | 188 (180, 0.011)    | 0.92 |          |
| Uyar et al.        | 2011 | Caucasian | PCR-RFLP          | Renal Cell             | 38 (21, 1)      | 27 (27, 6)          | 0.03 | 0.84 Y   |
| de Aguiar Goncalves et al. | 2012 | Mixed | TaqMan | H-B | Acute Leukemia | 96 (102, 40) | 74 (106, 54) | 1.79 | 0.18 Y   |
| Ergen et al.       | 2010 | Caucasian | PCR-RFLP          | Lung Cancer            | 93 (111, 19)    | 121 (93, 20)        | 0.13 | 0.72 Y   |
| Stevens et al.     | 2006 | Caucasian | PCR-RFLP          | Breast Cancer          | 259 (182, 42)   | 238 (198, 47)       | 0.38 | 0.54 Y   |
| Agachan et al.     | 2006 | Caucasian | PCR-RFLP          | Breast Cancer          | 17 (4, 12)      | 6 (29, 17)          | 1.46 | 0.23 Y   |
| Gallicchio et al.  | 2007 | Caucasian | PCR-RFLP          | Breast Cancer          | 38 (15, 5)      | 463 (353, 82)       | 1.73 | 0.19 Y   |
| Antognelli et al.  | 2009 | Caucasian | PCR-RFLP          | Breast Cancer          | 484 (50, 13)    | 1340 (52, 27)       | 0.29 |          |
| Hussein et al.     | 2011 | Caucasian | PCR-RFLP          | Breast Cancer          | 51 (41, 8)      | 46 (42, 12)         | 0.25 | 0.62 Y   |
| Vecka et al.       | 2012 | Caucasian | PCR-RFLP          | Pancreatic Cancer      | 40 (28, 5)      | 40 (20, 13)         | 9.74 | 0.0018 N |
| Conesa-Zamora et al. | 2013 | Caucasian | TaqMan            | Renal Cell             | 83 (99, 33)     | 100 (104, 10)       | 0.07 | 0.0001 N |
| Vasconcelos et al. | 2014 | Mixed     | TaqMan            | Embryonal Tumour       | 36 (85, 41)     | 160 (14, 72)        | 0.51 | 0.48 Y   |
| Kokouva et al.     | 2012 | Caucasian | PCR-RFLP          | Acute Leukemia         | 213 (88, 15)    | 181 (141, 29)       | 0.008 |          |
| Martinez et al.    | 2010 | Caucasian | TaqMan            | Brain Tumor            | 31 (33, 9)      | 22 (89, 109)        | 0.37 | 0.54 Y   |
| Ozturk et al.      | 2009 | Caucasian | PCR-RFLP          | Bladder Tumor          | 8 (53, 15)      | 37 (84, 14)         | 1.07 | 0.0011 N |
| Kerridge et al.    | 2002 | Caucasian | PCR-RFLP          | Lymphoma               | 73 (50, 30)     | 103 (74, 22)        | 2.35 | 0.13 Y   |
| Antognelli et al.  | 2005 | Caucasian | PCR-RFLP          | Prostate Cancer        | 197 (168, 20)   | 212 (85, 64)        | 67.98 |          |
| Lurie et al.       | 2008 | Mixed     | TaqMan            | Ovarian Cancer         | 66 (120, 86)    | 122 (211, 111)      | 1.065 | 0.3 Y    |
| Arpaci et al.      | 2009 | Caucasian | PCR-RFLP          | Ovarian Cancer         | 38 (6, 6)       | 17 (29, 6)          | 1.46 | 0.23 Y   |
| Van Der Logt et al.| 2005 | Caucasian | PCR-RFLP          | Colorectal Cancer180   | 150 (24, 158)   | 120 (17, 0.87)      | 0.35 |          |
| Rajaraman et al.   | 2008 | Mixed     | TaqMan            | Brain Tumor            | 266 (207, 39)   | 244 (165, 44)       | 0.043 |          |
| Stevens et al.     | 2008 | Mixed     | TaqMan            | Prostate Cancer        | 624 (537, 95)   | 487 (121, 4.74)     | 0.029 |          |
| Searles Nielsen et al. | 2005 | Mixed | TaqMan | H-B | Brain Tumor | 32 (28, 6) | 100 (105, 31) | 0.17 | 0.68 Y   |
| Lincz et al.       | 2004 | Caucasian | PCR-RFLP          | Multiple Myeloma       | 33 (41, 16)     | 103 (74, 22)        | 2.35 | 0.13 Y   |
| Kafadar et al.     | 2006 | Caucasian | PCR-RFLP          | Brain Tumor            | 43 (26, 15)     | 24 (18, 8)          | 1.96 | 0.16 Y   |

*PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism; HWE: Hardy-Weinberg equilibrium; Y: polymorphisms conformed to HWE in the control group; N: polymorphisms didn’t conform to HWE in the control group; H-B: hospital based; P-B: population based
Table 2. Results of Meta-analysis for PON1 Q192R Polymorphism and Cancer Risk

| Variables          | Case/Control | R vs. Q        | OR (95% CI) | P       | RR vs. QQ | OR (95% CI) | P       | RQ vs. QQ | OR (95% CI) | P       | RR+RQ vs. QQ | OR (95% CI) | P       |
|--------------------|--------------|----------------|-------------|---------|-----------|-------------|---------|-----------|-------------|---------|----------------|-------------|---------|
| Total              |              |                |             |         |           |             |         |           |             |         |                 |             |         |
| Prostate cancer    | 8121/8735/773 | 0.437 (0.354-0.543) | 0.966 | 0.377 | 0.928 (0.791-1.081) | 0.267 | 0.912 (0.757-1.101) | 0.283 | 0.984 (0.803-1.200) | 0.768 | 0.888 (0.726-1.088) | 0.206 |
| Breast cancer      | 7243/7735/773 | 0.440 (0.357-0.544) | 0.981 | 0.380 | 0.942 (0.799-1.107) | 0.304 | 0.997 (0.840-1.175) | 0.875 | 0.900 (0.746-1.080) | 0.283 | 0.873 (0.724-1.056) | 0.131 |
| Lymphoma           | 4032/4032/4032 | 0.446 (0.357-0.546) | 0.981 | 0.380 | 0.942 (0.799-1.107) | 0.304 | 0.997 (0.840-1.175) | 0.875 | 0.900 (0.746-1.080) | 0.283 | 0.873 (0.724-1.056) | 0.131 |
| Colorectal cancer  | 7172/7172/7172 | 0.446 (0.357-0.546) | 0.981 | 0.380 | 0.942 (0.799-1.107) | 0.304 | 0.997 (0.840-1.175) | 0.875 | 0.900 (0.746-1.080) | 0.283 | 0.873 (0.724-1.056) | 0.131 |
| Mixed              | 5626/5626/5626 | 0.446 (0.357-0.546) | 0.981 | 0.380 | 0.942 (0.799-1.107) | 0.304 | 0.997 (0.840-1.175) | 0.875 | 0.900 (0.746-1.080) | 0.283 | 0.873 (0.724-1.056) | 0.131 |
| Population based   | 5095/5095/5095 | 0.446 (0.357-0.546) | 0.981 | 0.380 | 0.942 (0.799-1.107) | 0.304 | 0.997 (0.840-1.175) | 0.875 | 0.900 (0.746-1.080) | 0.283 | 0.873 (0.724-1.056) | 0.131 |
| Hospital based     | 6350/6350/6350 | 0.446 (0.357-0.546) | 0.981 | 0.380 | 0.942 (0.799-1.107) | 0.304 | 0.997 (0.840-1.175) | 0.875 | 0.900 (0.746-1.080) | 0.283 | 0.873 (0.724-1.056) | 0.131 |

HWE: Hardy-Weinberg equilibrium; Y: I2, P = 0.026; and RR vs RQ+QQ: OR=2.934, 95% CI=1.869-4.605, P = 0.043) and prostate cancer under heterozygote comparison (RR vs QQ: OR=1.782, 95% CI=1.077-2.950, P = 0.000) and dominant models (RR+RQ vs QQ: OR=1.281, 95% CI=1.044-1.573, P = 0.056). Nevertheless, a decreased risk was identified in breast cancer (R vs Q: OR=0.605, 95% CI=0.378-0.907, P = 0.000; RR vs QQ: OR=0.494, 95% CI=0.275-0.888, P = 0.000; R vs QQ: OR=0.465, 95% CI=0.259-0.835, P = 0.000; and RR+RQ vs QQ: OR=0.485, 95% CI=0.274-0.857, P = 0.000), and prostate cancer in homozygote and recessive models (RR vs QQ: OR=0.475, 95% CI=0.251-0.897, P = 0.001 and RR vs RQ+QQ: OR=0.379, 95% CI=0.169-0.853, P = 0.000).

Furthermore, when subgroup analysis that performed by the control source (hospital based or population based), a decreased risk of the overall cancers was observed in homozygote (RR vs QQ: OR=0.601, 95% CI=0.366-0.907, P = 0.000) and dominant models (RR vs RQ+QQ: OR=0.611, 95% CI=0.384-0.973, P = 0.000) in the hospital based group. Similarly, when stratified by ethnicity, a significantly decreased risks of cancers in Caucasian population (but not Asian) for comparison of R vs Q (OR=0.788, 95% CI=0.626-0.993, P = 0.000, Figure 2b) was uncovered.

Publication bias and sensitivity analysis

Here, we conducted a sensitivity analysis to investigate the impression of individual publications on the integrated data by removing a single report from the pooled analysis each time. And no individual study was revealed influenced the pooled OR (Figure 3). Publication bias was assessed by Egger’s test and Begg’s funnel plot. No apparent publication bias was uncovered by these tests in PON1 Q192R polymorphisms (PON1 Q192R: R vs Q: Begg’s test: z=2.22, P = 0.026; Egger’s test: t=−1.75, P = 0.090).
Upper CI Limit

Discussion

Previous studies suggested that an increased risk of a variety of cancers may relate to oxidative stress and free radicals (Ames, 1983; Sun, 1990). Plenty of endogenous free-radical scavenging systems were existed in our body. PON1, an antioxidant enzyme, may lead to the imbalance of the antioxidant/oxidant system (Karaman et al., 2010), and induce oxidative stress and the ROS formation. Previous studies have revealed a depressed expression of PON1 in lung cancer (Elkiran et al., 2007), pancreatic(Akay et al., 2003a), and gastric cancer(Akay et al., 2003b). Furthermore, publications also showed that Q192R polymorphism increased the risk of bladder cancer(Ozturk et al., 2009) and renal cancer(Uyar et al., 2011), while a lack of association between this polymorphism and brain tumor, colorectal cancer risk was also uncovered(Van Der Logt et al., 2005; Rajaraman et al., 2008). R allele may contribute to the improvement of the detoxification activity of PON1 enzyme confront with latently carcinogenic products of oxidative stress and lipid peroxidation (Cejas et al., 2004).

In our work, we aim to investigate the association between PON1-Q192R polymorphism and cancer risk. We identified that Q192R polymorphism was associated with a decreased risk for cancer development, particularly for breast cancer. In the study conducted by Delimaris et al. (Delimaris et al., 2007), they reported that, during the pathogenesis of breast cancer, oxidative stress may contribute to the cell proliferation and malignant conversion process. Thus, it is fair to predict that PON1, which is a part of the lipid peroxidation scavenging systems, may affect the pathogenesis of breast cancer. In the subgroup analysis by cancer type, the results showed that PON1-192R allele was associated with a decreased risk in breast cancer and prostate cancer (in homozygote and recessive models), indicating that PON1-Q192R polymorphism may work as a protective factor for these two cancer types. Nevertheless, an increased risk was uncovered in lymphoma and prostate cancer (in heterozygote comparison and dominant models), a result consistent with previous studies (Kerridge et al., 2002; Antognelli et al., 2005). Stratifying by control source (hospital based or population based), a decreased risk of the overall cancers was revealed by homozygote and dominant models in hospital based group.

Notably, in the stratified analysis by ethnicity, a significantly reduced risk of the overall cancers under allele contrast model was uncovered in Caucasian. Previous studies indicated that PON1 192Q allele carriers were reported to be lower than that of the R carriers (Davies et al., 1996; Mackness et al., 1997; Li et al., 2000), and a lower PON1 level was regarded as a risk for cancer (Ellidag et al., 2014); notably, allele distributions varied obviously in control groups when stratified by the ethnic group, a result consistent with those reported by the National Center of Biotechnology Information (NCBI) for Caucasian (Q: 0.668) and Asian population (Q: 0.430).

Although we have conducted a comprehensive retrieve for all attainable eligible publications and presented with a landscape of the association between PON1 Q192R polymorphism and cancer risk, there are still existed several limitations that should be interpreted. Firstly, the number of the publications and the sample size of
each reports were relatively small, when a stratification analysis was performed for the cancer type, ethnicity, or the control source, resulting in insufficient capacity which cannot identify slight influence on cancers. Secondly, most of the enrolled publications were Caucasian that might result in the inconspicuousness. Thirdly, there was no data available for Africans. Fourthly, since the lack of raw data from these publications, no further assessment was performed for the potential gene-gene interactions or gene-environment interactions. In conclusion, our study has successfully elaborated that PON1-192R allele was associated with a significantly decreased risk of the overall cancers. More research will be continued in order to refine the investigation on this issue of interest, with larger sample size, detailed original data, especially investigations for African.

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