OncoTargets and Therapy

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ORIGINAL RESEARCH

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

This article was published in the following Dove Press journal:
OncoTargets and Therapy
4 March 2016
Number of times this article has been viewed

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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, $P_{heterogeneity}$=0.067), and ovarian cancer in the recessive model (MM vs ML/LL: OR =1.526, 95% CI =1.110–2.097, $P_{heterogeneity}$=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

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http://dx.doi.org/10.2147/OTT.S96990

related to the PON1-55L allele than to PON1-55M,[5,6] and a decreased stability of the PON1-55M protein may lead to a lower activity of PON1.[7] In addition, the association between the polymorphism and risk of different cancers, such as prostate cancer[8] and breast cancer,[9] was identified by case–control studies, whereas no significant association was identified between the polymorphism and cancer risk in renal cell carcinoma[10] and ovarian cancer.[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 (MM vs LL), recessive (MM vs ML/LL), and dominant (ML/MM vs LL). Between-study heterogeneity was assessed by χ^2-test-based Q-statistic test,[12] and quantified by I^2 values, as well as P-values.[13] No significant heterogeneity was observed when $I^2<50\%$ and $P>0.10$, and ORs were pooled by a fixed-effects model. Otherwise, the random-effects model was used.[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.[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).[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[16] and Ahmed et al,[21] 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, $P_{heterogeneity}=0.000$),

Table 1 Characteristics of the eligible case–control studies enrolled in the meta-analysis

First author	Year	Ethnicity	Genotyping method	Control source	Cancer type	Case			Control			Y or N (HWE)
						MM	LM	LL	MM	LM	LL	
Antognelli et al[8]	2005	Caucasian	PCR-RFLP	H-B	Prostate cancer	67	197	120	43	169	148	Y
Van Der Logt et al[18]	2005	Caucasian	PCR-RFLP	P-B	Colorectal cancer	59	166	139	50	162	140	Y
Stevens et al[32]	2006	Caucasian	PCR-RFLP	P-B	Breast cancer	77	230	176	58	223	202	Y
Stevens et al[19]	2008	Mixed	TaqMan	P-B	Prostate cancer	165	609	481	189	575	498	Y
Lurie et al[17]	2008	Mixed	TaqMan	P-B	Ovarian cancer	192	65	14	276	145	24	Y
Arpaci et al[11]	2009	Caucasian	PCR-RFLP	H-B	Ovarian cancer	5	19	27	2	27	25	Y
Antognelli et al[16]	2009	Caucasian	PCR-RFLP	P-B	Breast cancer	325	115	107	231	125	188	N
Martinez et al[31]	2010	Caucasian	TaqMan	H-B	Brain tumor	30	32	11	88	94	38	Y
Naidu et al[23]	2010	Asian	PCR-RFLP	P-B	Breast cancer	50	178	159	17	109	126	Y
Uyar et al[10]	2011	Caucasian	PCR-RFLP	P-B	Renal cell carcinoma	6	25	29	10	29	21	Y
Ergen et al[28]	2011	Caucasian	PCR-RFLP	P-B	Osteosarcoma	3	23	24	9	20	21	Y
Aksoy-Sagirli et al[26]	2011	Caucasian	PCR-RFLP	H-B	Lung cancer	10	94	119	14	102	118	Y
Hussein et al[9]	2011	Caucasian	PCR-RFLP	P-B	Breast cancer	60	21	19	6	23	35	Y
Vecka et al[27]	2012	Caucasian	PCR-RFLP	H-B	Pancreatic cancer	10	39	24	8	37	28	Y
Kokouva et al[30]	2013	Caucasian	PCR-RFLP	H-B	Lymphohematopoietic cancers	60	139	117	50	159	142	Y
de Aguiar Goncalves et al[25]	2012	Mixed	TaqMan	H-B	Acute leukemia	34	99	104	19	75	131	Y
Wang et al[20]	2012	Asian	PCR-RFLP	P-B	Lung cancer	2	47	307	0	18	166	Y
Akkiz et al[22]	2013	Caucasian	PCR-RFLP	P-B	Hepatocellular carcinoma	31	81	105	27	89	101	Y
Antognelli et al[24]	2013	Caucasian	PCR-RFLP	H-B	Prostate cancer	100	291	180	131	540	497	Y
Vasconcelos et al[29]	2014	Mixed	TaqMan	P-B	Embryonal tumor	15	56	85	25	134	177	Y
Ahmed et al[21]	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.

homozygote (MM vs LL: OR =1.463, 95% CI =1.123–1.905, $P_{heterogeneity}$=0.000), heterozygote comparison (ML vs LL: OR =1.161, 95% CI =1.069–1.261, $P_{heterogeneity}$=0.162), recessive (MM vs ML/LL: OR =1.381, 95% CI =1.107–1.724, $P_{heterogeneity}$=0.000), and dominant (MM/ML vs LL: OR =1.218, 95% CI =1.054–1.407, $P_{heterogeneity}$=0.000) models (Table 2, Figure 2).

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,

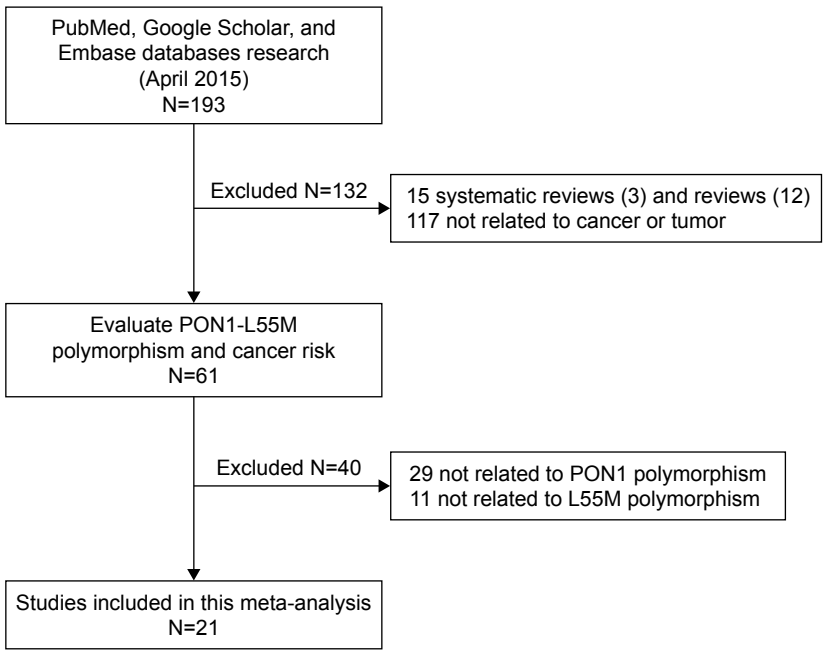

Figure 1 Flow chart presenting the publication selection process.

Table 2 Results of meta-analysis for PON1-L55M polymorphism and cancer risk

Variables	Case/control	M vs L			MM vs LL			ML vs LL			ML + MM vs LL			MM vs ML + LL		
		OR (95% CI)	*P*-value[a]	I^2 (%)	OR (95% CI)	*P*-value[a]	I^2	OR (95% CI)	*P*-value[a]	I^2	OR (95% CI)	*P*-value[a]	I^2	OR (95% CI)	*P*-value[a]	I^2
Total	5,627/6,390	1.221 (1.066–1.398)*	0.000	79.5	1.463 (1.123–1.905)*	0.000	72.1	1.161 (1.069–1.261)*	0.162	24.4	1.218 (1.054–1.407)*	0.000	62.9	1.381 (1.107–1.724)*	0.000	69.0
Prostate cancer	2,210/2,790	1.244 (0.949–1.631)	0.000	89.6	1.521 (0.832–2.778)	0.000	90.3	1.258 (1.111–1.423)*	0.067	63.0	1.357 (0.999–1.842)	0.003	83.1	1.293 (0.803–2.082)	0.000	87.0
Breast cancer	970/799	2.120 (1.066–4.218)*	0.000	94.7	3.666 (1.159–11.600)*	0.000	90.3	1.252 (1.020–1.536)*	0.703	0.0	1.887 (1.064–3.349)*	0.001	85.4	3.187 (1.052–9.661)*	0.000	90.7
Ovarian cancer	322/499	1.268 (0.988–1.628)	0.366	0.0	1.305 (0.691–2.465)	0.484	0.0	0.713 (0.418–1.216)	0.764	0.0	0.913 (0.550–1.517)	0.551	0.0	1.523 (1.107–2.094)*	0.464	0.0
Lung cancer	579/418	1.095 (0.666–1.801)	0.104	62.2	0.781 (0.344–1.771)	0.404	0.0	1.047 (0.766–1.433)	0.215	34.8	1.089 (0.670–1.767)	0.146	52.7	0.806 (0.361–1.799)	0.432	0.0
Other cancers	1,182/1,532	1.072 (0.894–1.285)	0.035	53.5	1.249 (0.626–2.492)	0.124	38.3	1.062 (0.896–1.258)	0.268	20.3	1.082 (0.864–1.356)	0.098	42.1	1.219 (0.978–1.519)	0.265	20.7
Cancer type 2																
Solid tumor	5,074/5,814	1.201 (1.035–1.395)*	0.000	80.8	1.420 (1.055–1.911)*	0.000	74.2	1.148 (1.052–1.253)*	0.208	21.1	1.191 (1.017–1.394)*	0.000	63.8	1.356 (1.058–1.739)	0.000	71.7
Hematological tumor	553/576	1.336 (1.123–1.590)*	0.089	65.3	1.717 (1.134–2.600)*	0.262	20.6	1.280 (0.992–1.651)	0.089	65.4	1.419 (0.928–2.168)	0.079	67.6	1.531 (1.092–2.146)*	0.493	0.0
Ethnicity																
Caucasian	2,965/3,686	1.199 (0.993–1.447)	0.000	82.2	1.461 (1.041–2.051)*	0.000	72.9	1.170 (1.050–1.303)*	0.185	25.6	1.199 (0.981–1.466)	0.000	67.7	1.371 (1.025–1.833)	0.000	69.4
Asian	743/436	1.428 (1.143–1.784)*	0.849	0.0	2.344 (1.304–4.214)*	0.925	0.0	1.324 (0.992–1.767)	0.797	0.0	1.443 (1.092–1.907)*	0.938	0.0	2.068 (1.175–3.638)*	0.880	0.0
Mixed	1,919/2,268	1.193 (0.938–1.518)	0.005	76.7	1.252 (0.818–1.916)	0.052	61.1	1.104 (0.842–1.448)	0.093	53.3	1.163 (0.878–1.539)	0.053	60.9	1.265 (0.859–1.861)	0.012	72.7
Control source																
Population-based	3,699/3,705	1.221 (0.989–1.509)	0.000	85.2	1.374 (0.916–2.061)	0.000	78.6	1.082 (0.974–1.203)	0.574	0.0	1.162 (0.953–1.417)	0.001	65.1	1.376 (0.964–1.966)	0.000	79.3
Hospital-based	1,928/2,685	1.303 (1.194–1.423)*	0.062	48.0	1.714 (1.369–2.147)*	0.303	16.2	1.293 (1.134–1.474)*	0.139	36.3	1.314 (1.083–1.594)*	0.059	48.6	1.484 (1.248–1.764)*	0.510	0.0
Genotyping method																
PCR-RFLP	3,635/3,902	1.239 (1.039–1.478)*	0.000	80.9	1.558 (1.119–2.168)*	0.000	71.3	1.188 (1.073–1.316)*	0.208	22.6	1.235 (1.030–1.482)*	0.000	65.7	1.463 (1.097–1.951)	0.000	67.0
TaqMan	1,992/2,488	1.171 (0.956–1.434)	0.012	68.9	1.221 (0.861–1.732)	0.100	48.6	1.112 (0.967–1.279)	0.169	37.9	1.161 (0.912–1.477)	0.103	48.0	1.212 (0.886–1.659)	0.027	63.6

Notes: I^2: 0%–25%, no heterogeneity; 25%–50%, modest heterogeneity; >50%, high heterogeneity; *P*-value[a]: *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.

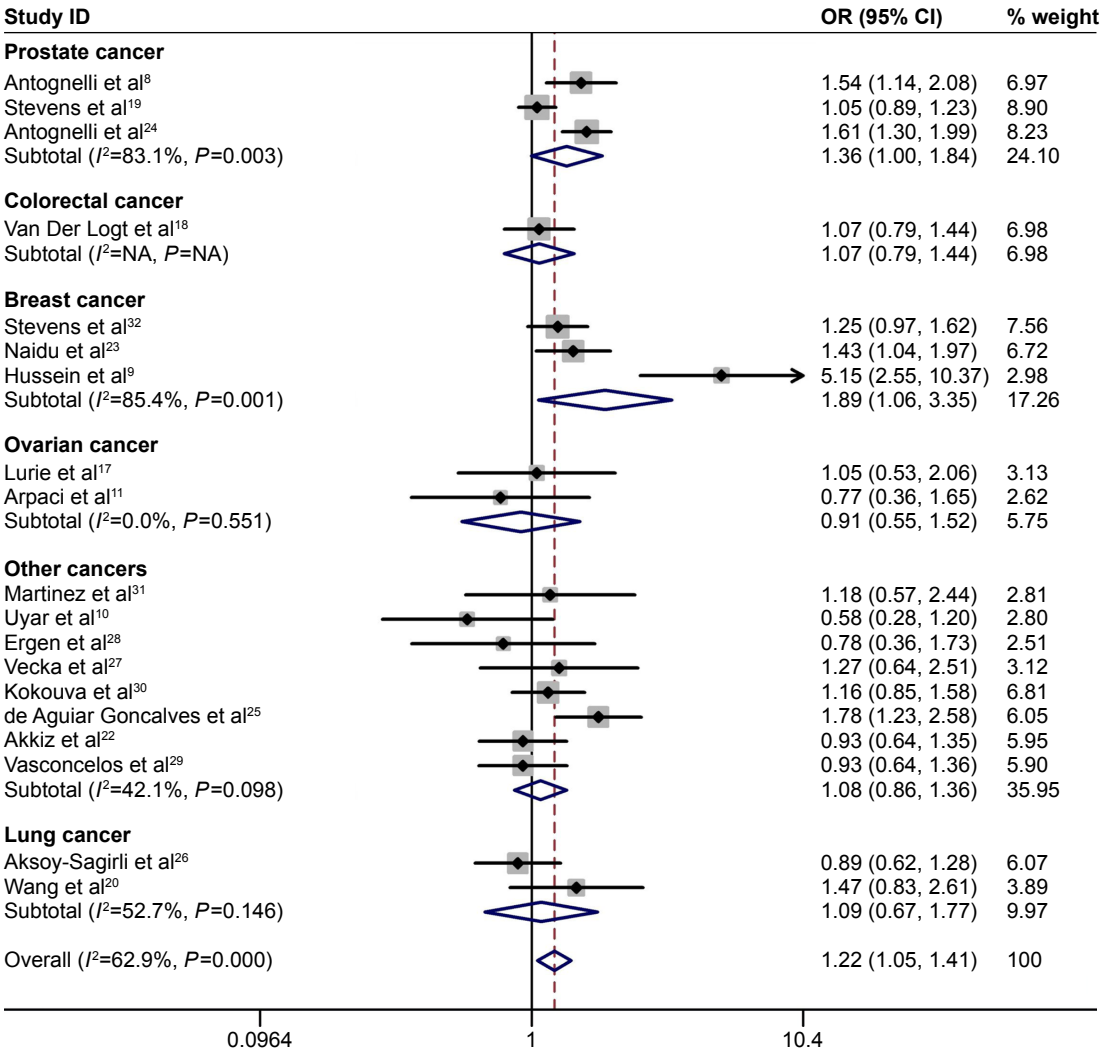

Figure 2 Meta-analysis of the association between PON1-L55M polymorphism and cancer risk in the dominant model (MM/ML vs LL).
Note: Weights are from random effects analysis.
Abbreviations: CI, confidence interval; OR, odds ratio; ID, identification; NA, not available; L allele, leucine; M allele, methionine.

$P_{heterogeneity}$=0.000; homozygote: MM vs LL: OR =3.666, 95% CI =1.159–11.600, $P_{heterogeneity}$=0.000; heterozygote comparison: ML vs LL: OR =1.252, 95% CI =1.020–1.536, $P_{heterogeneity}$=0.703; recessive: MM vs ML/LL: OR =3.187, 95% CI =1.052–9.661, $P_{heterogeneity}$=0.000; and dominant: MM/ML vs LL: OR =1.887, 95% CI =1.064–3.349, $P_{heterogeneity}$=0.001), prostate cancer in the heterozygote comparison model (ML vs LL: OR =1.304, 95% CI =1.049–1.620, $P_{heterogeneity}$=0.067), and ovarian cancer in the recessive model (MM vs ML/LL: OR =1.526, 95% CI =1.110–2.097, $P_{heterogeneity}$=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, $P_{heterogeneity}$=0.000; and heterozygote comparison: ML vs LL: OR =1.170, 95% CI =1.050–1.303, $P_{heterogeneity}$=0.185) and the Asian population (allele contrast: M vs L: OR =1.428, 95% CI =1.143–1.784, $P_{heterogeneity}$=0.849; homozygote: MM vs LL: OR =2.344, 95% CI =1.304–4.214, $P_{heterogeneity}$=0.925; recessive: MM vs ML/LL: OR =2.068, 95% CI =1.175–3.638, $P_{heterogeneity}$=0.880; MM/ML vs LL: OR =1.443, 95% CI =1.092–1.907, $P_{heterogeneity}$=0.938), and hospital-based group (allele contrast: M vs L: OR =1.303, 95% CI =1.194–1.423, $P_{heterogeneity}$=0.062; homozygote: MM vs LL: OR =1.714, 95% CI =1.369–2.147, $P_{heterogeneity}$=0.303; heterozygote comparison: ML vs LL: OR =1.293, 95% CI =1.134–1.474, $P_{heterogeneity}$=0.139; recessive: MM vs ML/LL: OR =1.484, 95% CI =1.248–1.764, $P_{heterogeneity}$=0.510; and dominant: MM/ML vs LL: OR =1.314, 95% CI =1.083–1.594, $P_{heterogeneity}$=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

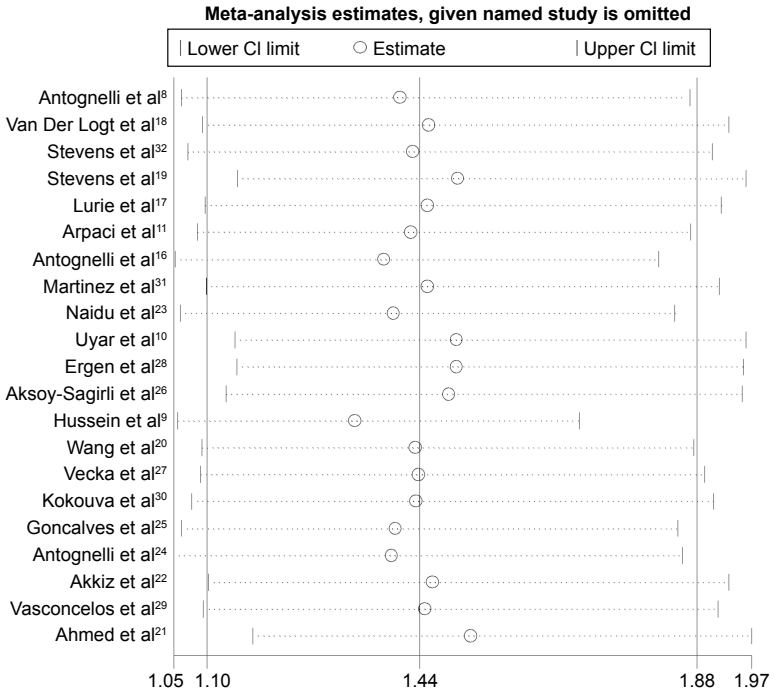

Figure 3 Sensitivity analysis of overall OR coefficients for PON1-L55M (MM vs LL).
Notes: Results were calculated by omitting each study in turn. The two ends of the dotted lines represent the 95% CI.
Abbreviations: CI, confidence interval; OR, odds ratio; L allele, leucine; M allele, methionine.

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.[33–35] There are several enzyme systems in our body that protect against genotoxic damage, either directly or via free-radical detoxification. Moreover, PON1, which is an antioxidant enzyme, may contribute to the disturbance in antioxidant–oxidant balance.[36,37] Decreased expression of PON1 was identified in lung cancer and pancreatic cancer by previous studies.[38,39] 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.[7]

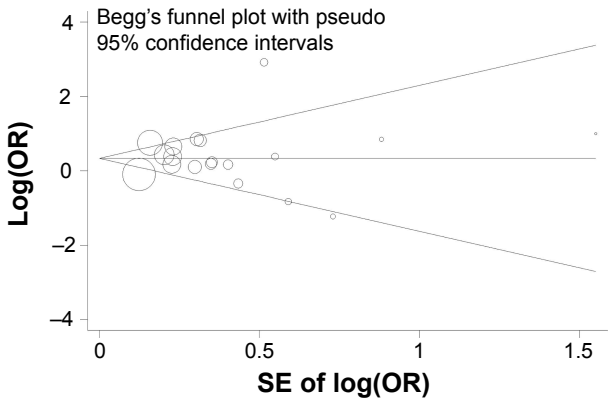

Figure 4 Begg's funnel plot of publication bias (homozygote model: MM vs LL).
Notes: Each point represents a separate study for the indicated association. Log(OR), natural logarithm of OR; horizontal line, mean effect size.
Abbreviations: OR, odds ratio; SE, standard error of the mean; L allele, leucine; M allele, methionine.

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.[40] 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

The work by DY and LC was supported by the Department of Urology, the Second Affiliated Hospital of Anhui Medical University. The authors report no other conflicts of interest in this work.

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