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Association Between *Paraoxonase1* (*Q192R* and *L55M*) Gene Polymorphisms and Risk of Breast Cancer: A Meta-analysis of 12 Studies

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Abstract

Background: The *paraoxonase1* gene (*PON1*) is part of the *paraoxonase* family of multifactorial antioxidants (EC 3.1.1.2). The functional single-nucleotide polymorphisms *L55M* and *Q192R* are located in the coding site of this gene. The association between these polymorphisms and breast cancer risk has been investigated, with contradictory results.

Objectives: A meta-analysis was done to find the association between *PON1* (*L55M* and *Q192R*) gene polymorphisms and breast cancer risk.

Methods: We searched Embase, Pubmed, and Web of Science for related articles. Twelve eligible studies before December 2021 were selected. Statistical analysis was done by STATA 14.0.

Result: We summarized 12 studies of *L55M* and *Q192R* polymorphisms and breast cancer risk, involving 5,769 subjects (2,519 controls and 3,250 patients). In all genetic models, *PON1-L55M* polymorphisms were significantly associated with breast cancer risk. Besides, *PON1-Q192R* polymorphisms decreased breast cancer risk. The *PON1-Q192R* allele reduced the cancer risk, particularly breast cancer (OR (R vs. Q): 0.7932). However, an association was found between the *PON1-L55M* allele and increased breast cancer risk (OR (M vs. L): 1.6041).

Discussion: The results of 11 out of 12 studies were consistent with our results. In a non-conforming study, this was probably due to errors in conducting experiments. Nonetheless, well-designed studies with more samples are needed to confirm our findings at protein levels.

Keywords: Polymorphism, *Paraoxonase1*, *Q192R*, *L55M*, Meta-analysis, Breast Cancer

1. Background

Breast cancer (BC) is the second most prevalent cancer in females (1). This cancer is the second cause of mortality in developing countries and the most significant cause in developed countries (2). Many factors may be responsible for susceptibility to BC, such as estrogen, diet, lifestyle, environmental chemicals, oxidative stress, and carbon dioxide, which are involved in the progression and pathogenesis of BC (3). Oxygen-free radicals (OFR) are oxidative stress agents found in cells subjected to an aerobic environment in pathological and physiological conditions in breast tissues (1). A balance is found between antioxidant defense and free radicals at normal cellular levels. The polymorphisms of enzyme-releasing genes possibly contribute to the elimination of free radicals, affecting the sensitivity of individuals to BC. Various antioxidant systems, including *PON1* (*paraoxonase1*), are available against oxidative stress (4). The *PON1* enzyme is produced in the human liver and then transmitted to the bloodstream, where it is linked to high-density lipoprotein (HDL) (4). Besides, *PON1* is an HDL-dependent enzyme that maintains the function and integrity of HDL with an antioxidant action for Low-density Lipoprotein (LDL) antioxidants, which are more sensitive against oxidation (5, 6). The *PON1* gene is one of the multifactorial enzymes of the family of *paraoxonase* gene antioxidants (EC.3.1.1.2) (4, 7). With the advancement of genetic studies of *PON1*, *PON1-L55M*, and *PON1-Q192R*, as the commonest functional genetic polymorphisms in *PON1*, are found at positions 55 and 192 (8). The *PON1-Q192R* polymorphism (rs662A>G) is due to the substitution of glutamine (Q genotype) for arginine (R genotype) 192 of the gene 6 exons of the *PON1* gene (9). Besides, *PON1-L55M* (rs854560) is caused by replacing 55 leucine (L genotype) with methionine (M genotype) at third exon 55 (9). Also, *Q192R* and *L55M*,

as two functional SNPs, are linked to the risk of different tumors (9).

Due to the importance of *PON1* to develop tumors and the relationship between phenotypes and genotypes, it was speculated that the *PON1* gene *Q192R* variation and *L55M* could be associated with tumor vulnerability. Several studies have been conducted in the last two decade to examine the relationship between *PON1* polymorphism and BC risk (3, 7, 10-19).

2. Objectives

This study conducted a comprehensive meta-analysis to determine the relationship between *L55M* and *Q192R* polymorphisms and BC risk. We performed a more comprehensive analysis by examining all data obtained from studies before December 2021.

3. Methods

3.1. Search Strategy

PubMed, Embase, Google Scholar, and Web of Science databases were searched for all related articles before December 2021 using the keywords *paraoxonase1* or *PON1*, *Q192R*, *L55M*, and BC. We also manually searched references for further articles or studies on this topic. All the studies were limited to humans.

3.1.1. Inclusion and Exclusion Criteria

We selected articles based on the following criteria: (1) Reports evaluating the relationship between *PON1-Q192R* or *PON1-L55M* polymorphisms and BC risk, (2) studies on patients and controls, and (3) studies controlling the frequency of specific genotypes in cases and controls (from the text of the article). In addition, we did not include (1) reports that only surveyed patient samples, (2) no specific genotypic studies of *PON1-L55M* or *PON1-Q192R* polymorphisms, (3) animal studies, (4) repeated studies, (5) case reports, and (6) review studies.

3.2. Data Extraction

All papers were double-checked, and data were extracted by a standard form. For each report, the following information was collected: (1) First author name, (2) publication year, (3) country, (4) ethnicity, (5) genotypic methods, (6) source of controls, (7) the number of patients, (8) the number of genotypes for three polymorphisms in controls and patients, and (9) P-value for Hardy-Weinberg equilibrium (HWE) in controls.

3.3. Statistical Analysis

Odds ratio (OR) and confidence intervals (95% CIs) were applied to assess the relationship between *PON1-L55M* or *PON1-Q192R* polymorphisms and BC risk in five genetic models: allele contrast (R vs. Q; L vs. M), homozygote (RR vs. QQ; MM vs. LL), heterozygote (QR vs. QQ; LM vs. LL), recessive (RR vs. QR/QQ; MM vs. LM/LL), and dominant (QQ vs. RR/QR; LL vs. MM/LM). We also conducted subgroup analyses based on ethnicity and genotyping methods. We calculated the heterogeneity of the studies by Cochran's QQ statistical test (chi-square test) (20). The heterogeneity was determined by calculating the P-values (21), and a $P > 0.10$ indicated the lack of significant heterogeneity. Besides, ORs were pooled using the fixed-effects model; otherwise, we used the random-effects model (22). Also, sensitivity analysis was used for estimating the data stability. Data analysis was done with STATA 14.0 software, and a $P < 0.05$ was regarded as significant.

For each control group in the studies, the observed frequency of the *PON1-L55M* or *PON1-Q192R* polymorphism for HWE was evaluated using χ^2 statistics (23). The control group agreed with the HWE if the P-value was < 0.05. We used this website to calculate the data and obtain CI, OR, P-value, and Q-statistic.

4. Results

4.1. Study Characteristics

Twelve case-control publications, including 2,519 cases and 3,250 controls, met the inclusion criteria (Tables 1 and 2) (3, 7, 10-19). Figure 1 shows the flow chart of the articles' screening process. Also, 10 studies with 3,000 controls and 2,286 cases were done on the *PON1-Q192R* polymorphism (Table 1), and eight articles including 2,159 controls and 2,259 cases were found on the *PON1-L55M* polymorphism (Table 2).

Moreover, regarding the *PON1-Q192R* polymorphism, three studies were done in Asians and seven studies in Caucasians. Also, we found two studies utilizing the TaqMan assay, whereas eight studies used PCR-RFLP. Regarding the *PON1-L55M* polymorphism, four studies were done on each of Asians and Caucasians. In addition, one study utilized the TaqMan assay, and seven studies used PCR-RFLP.

4.2. Meta-analysis

4.2.1. Association Between PON1-Q192R and Breast Cancer Susceptibility

In the allele contrast model, there was a relationship between the *PON1-Q192R* allele and decreased BC risk (Table 3): R vs. Q: OR = 0.793, 95%CI = 0.726 - 0.866; RR vs. QQ: OR = 0.756, 95%CI = 0.623 - 0.918; QR vs. QQ: OR = 0.721, 95%CI =

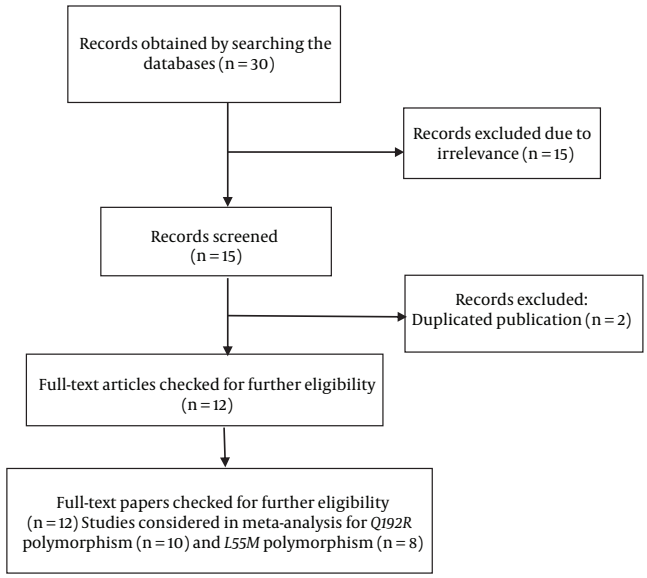

Figure 1. Flow chart of meta-analysis for inclusion and exclusion of articles

Table 1. Studies Assessed in the Meta-analysis for *Q192R* Polymorphism

Study	Year	Controls/Cases	Genotyping Method	Country (Ethnicity)	Source of Controls	Genotypes of Controls				Genotypes of Cases		
						QQ	QR	RR	HWE [a] < 3.84	QQ	QR	RR
Wu et al. (15)	2017	378/365	TaqMan	China (East Asian)	H-B [b]	167	156	55	3.42	155	156	54
Kaya et al. (14)	2016	35/32	TaqMan	Turkey (Caucasian)	H-B	5	13	17	0.88	10	11	11
Bayati (12)	2016	100/83	PCR-RFLP	Iran (Iranian)	H-B	8	83	9	43.6 [c]	2	62	19
Rinaldi (11)	2014	152/144	PCR-RFLP	Europe (Southern Italy)	H-B	143	7	2	14.62 [c]	110	30	4
Hussein et al. (10)	2011	100/100	PCR-RFLP	Egypt (Caucasian)	P-B [d]	46	42	12	0.25	51	41	8
Naidu et al. (7)	2010	252/387	PCR-RFLP	Malaysia (East Asian)	P-B	115	115	22	0.81	200	158	29
Antognelli et al. (3)	2009	544/547	PCR-RFLP	Italy (Caucasian)	P-B	340	152	52	27.19 [c]	484	50	13
Gallicchio et al. (19)	2007	904/58	PCR-RFLP	USA (Caucasian)	P-B	469	353	82	1.93	38	15	5
Ağaçhan et al. (18)	2006	52/87	PCR-RFLP	Turkey (Causasian)	P-B	17	29	6	1.461	17	4	12
Stevens et al. (17)	2006	483/483	PCR-RFLP	USA (Causasian)	P-B	238	198	47	0.38	259	182	42

Abbreviations: Y: yes (they are in HWE); N, No (they are not in HWE); Y, polymorphisms according to HWE in controls; N, polymorphisms not according to HWE in controls.
[a] χ^2 for testing HWE.
[b] Hospital-based.
[c] $P < 0.001$.
[d] Population-based.

0.640 - 0.812; and RR+RQ vs. QQ: OR = 0.728, 95%CI = 0.652 - 0.813.

Also, based on race, a decreased cancer risk was detected in the recession model (RR+RQ vs. RR: OR = 0.5404, 95%CI = 0.4673 - 0.6248) in Caucasians (Figure 2). Consistently, in the stratification assessment of the control group, the overall risk of BC reduced in the heterozygote comparison and dominant model (RQ vs. QQ: OR = 0.5911, 95%CI = 0.5138 - 0.6801; RR+RQ vs. QQ: OR = 0.5881, 95%CI = 0.5159 - 0.6703) in the population-based group (Figure 2). Besides, risk factors were found in the subgroup analysis based on the genotyping method. Figure 2 shows the Forest plot of the meta-analysis of the relationship between cancer risk and *PON1-Q192R* polymorphism.

4.2.2. Association Between PON1-L55M and Breast Cancer

The *PON1-L55M* polymorphism showed a significant association with increased BC risk in all genetic models (Table 4): M vs. L: OR = 1.6041, 95%CI = 1.4712 - 1.7490; MM vs. LL: OR = 2.0198, 95%CI = 1.7249 - 2.3650; ML vs. LL: OR = 1.6142, 95%CI = 1.4103 - 1.8476; MM vs. ML+LL: OR = 1.6391, 95%CI = 1.4161 - 1.8972; and ML+MM vs. LL: OR = 1.7587, 95%CI = 1.5602 - 1.9823. Figure 3 shows the Forest plot of the meta-analysis of the association between BC risk and *PON1-L55M* polymor-

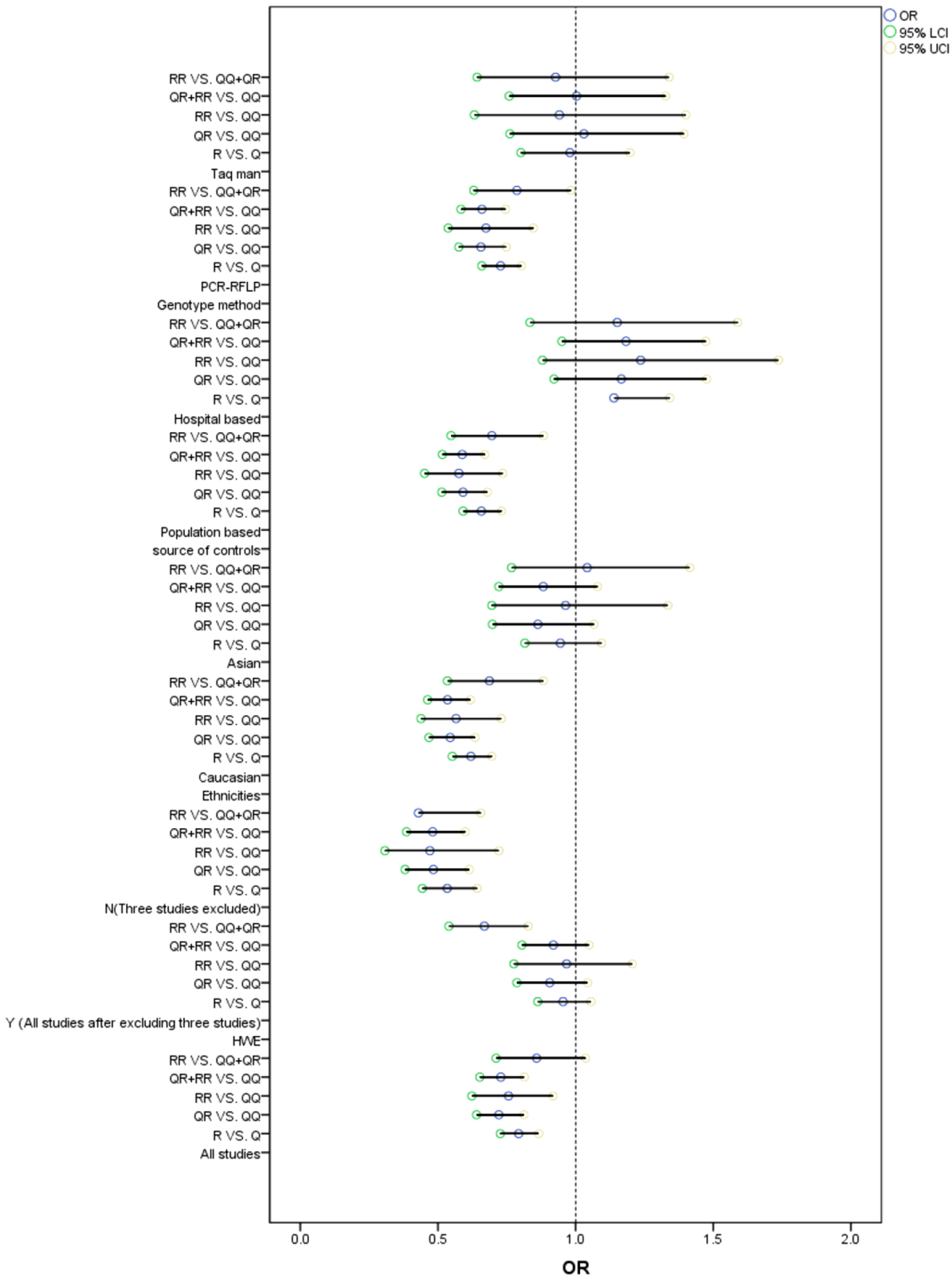

Figure 2. Forest plot of the meta-analysis of the relationship between *PON1-Q192R* polymorphism and breast cancer risk. OR, odds ratio; CI, confidence interval.

Table 2. Studies Assessed in the Meta-analysis for *L55M* Polymorphism

Study	Year	Controls/Cases	Genotyping Method	Country (Ethnicity)	Source of Controls	Genotypes of Controls				Genotypes of Cases		
						LL	LM	MM	HWE [a] < 3.84	LL	LM	MM
Ramzanpour et al. (16)	2020	150/150	PCR-RELP	Iran (Iranian)	H-B	66	59	25	3.41 (Y)	47	65	38
Wu et al. (15)	2017	378/365	TaqMan	China (East Asian)	H-B [b]	346	30	2	3.24 (Y)	284	72	9
Hamta et al. (13)	2016	100/83	PCR-RELP	Iran (Iranian)	H-B	4	81	15	40.93 [c] (N)	2	69	12
Rinaldi (11)	2014	152/144	PCR-RELP	Europe (Southern Italy)	H-B	130	7	15	95.69 [c]	70	58	16
Hussein et al. (10)	2011	100/100	PCR-RELP	Egypt (Caucasian)	P-B [d]	35	23	6	0.58 (y)	19	21	60
Naidu et al. (7)	2010	252/387	PCR-RFLP	Malaysia (East Asian)	H-B	126	109	17	1.04 (Y)	159	178	50
Antognelli et al. (3)	2009	544/547	PCR-RFLP	Italy (Caucasian)	P-B	188	125	231	157.2 [c] (N)	107	155	325
Stevens et al. (17)	2006	483/483	PCR-RFLP	USA (Caucasian)	P-B	202	233	58	0.88 (Y)	176	230	77

Abbreviations: Y, yes (they are in HWE); N, No (they are not in HWE); Y, polymorphisms according to HWE in controls; N, polymorphisms not according to HWE in controls.
[a] χ^2 for testing HWE.
[b] Hospital-based.
[c] $P < 0.001$.
[d] Population-based

phism. Consistently, there was an increased risk in the five genetic models in Caucasians: M vs. L: OR = 2.2304, 95% CI = 2.0017 - 2.4852; MM vs. LL: OR = 2.3005, 95% CI = 1.8946 - 2.7933; ML vs. LL: OR = 1.7842, 95% CI = 1.4781 - 2.1537; MM vs. ML+LL: OR = 1.7393, 95%CI = 1.4665 - 2.0628; and ML+MM vs. LL: OR = 2.0135, 95%CI = 1.7093 - 2.3718, Asians: M vs. L: OR = 1.5108, 95% CI = 1.3040 - 1.7505; MM vs. LL: OR = 2.0352, 95% CI = 1.4493 - 2.8579; ML vs. LL: OR = 1.5162, 95% CI = 1.2455 - 1.8457; MM vs. ML+LL:OR = 1.7315, 95%CI = 1.2438 - 2.4103; and ML+MM vs. LL: OR = 1.6068, 95%CI = 1.3360 - 1.9324 (Table 4), hospital - based groups: M vs. L: OR = 0.6667, 95%CI = 0.5649 - 0.7869; MM vs. LL: OR = 2.198, 95%CI = 1.4836 - 2.7499; ML vs. LL: OR = 1.8479, 95%CI = 1.5340 - 2.2262; MM vs. ML+LL: OR = 1.6118, 95%CI = 1.1931 - 2.1774; and ML+MM vs. LL: OR = 1.8833, 95%CI = 1.5838 - 2.2394, and population - based groups: M vs. L: OR = 1.6781, 95%CI = 1.4922 - 1.8872; MM vs. LL: OR = 2.204, 95%CI = 1.7908 - 2.7124; ML vs. LL:OR = 1.4996, 95%CI = 1.2238 - 1.8376; MM vs. ML+LL: OR = 1.7829, 95%CI = 1.4928 - 2.1293; and ML+MM vs. LL:OR = 1.807, 95%CI = 1.5116 - 2.1601. Also, an increased risk was detected based on the genotyping method.

4.2.3. Publication Bias and Sensitivity Analysis

A sensitivity analysis was done to detect individual articles' effect on the whole data by excluding a study from the pooled analysis. No study markedly influenced the pooled OR. Figure 4 shows the plot of the sensitivity analysis to evaluate the relationship between cancer risk and *PON1-Q192R* (RR vs. QQ). Also, we performed Begg's funnel plot and Egger's test to evaluate publication bias (Figure 5). The results did not reveal publication bias concerning the *PON1* (*Q192R* and *L55M*) gene. Therefore, the findings are robust because of no significant publication bias in the meta-analysis.

5. Discussion

As known, *PON1* is one of the xenobiotic-metabolizing enzymes reducing oxidative stress. Genetic polymorphisms affect the enzyme, affecting individual sensitivity to certain pathologies (24). Different variants of *PON1*, such as *L55M* and *Q192R*, are biologically responsible for cancer. The *PON1* (*L55M* and *Q192R*) gene polymorphisms are involved in different cancers, such as BC (15). For example, Ramzanpour et al. (16), Wu et al. (15), Rinaldi (11), Hussein et al. (10), Naidu et al. (7), Antognelli et al. (3), and Stevens et al. (17) showed a significant relationship between the *PON1-L55M* polymorphism and BC risk, which is consistent with our results. However, Hamta et al. (13) showed no significant association between *PON1-L55M* polymorphisms and BC risk.

Also, Wu et al. (15), Kaya et al. (14), Hussein et al. (10), Naidu et al. (7), Antognelli et al. (3), Gallicchio et al. (19), and Stevens et al. (17) indicated no significant relationship between the *PON1-Q192R* polymorphism and BC risk, which is consistent with our results. However, in studies conducted by Bayati (12), Ağaçhan et al. (18), and Rinaldi (11), there was a significant correlation between polymorphisms and BC risk, which was not in line with our results due to several reasons, including the small number of samples and errors in testing.

In our meta-analysis, a significant relationship was observed between the *PON1-L55M* polymorphism and BC risk in all genetic models, whereas no relationship was observed between the *PON1-Q192R* allele and decreased BC risk (except in the recessive model). Therefore, *PON1* (*L55M* and *Q192R*) gene polymorphisms are involved in BC development. Also, genetic factors and other contributors, such as lifestyle and nutrition, have a significant effect on *PON1* enzyme activity, leading to BC risk reduction (25). Besides,

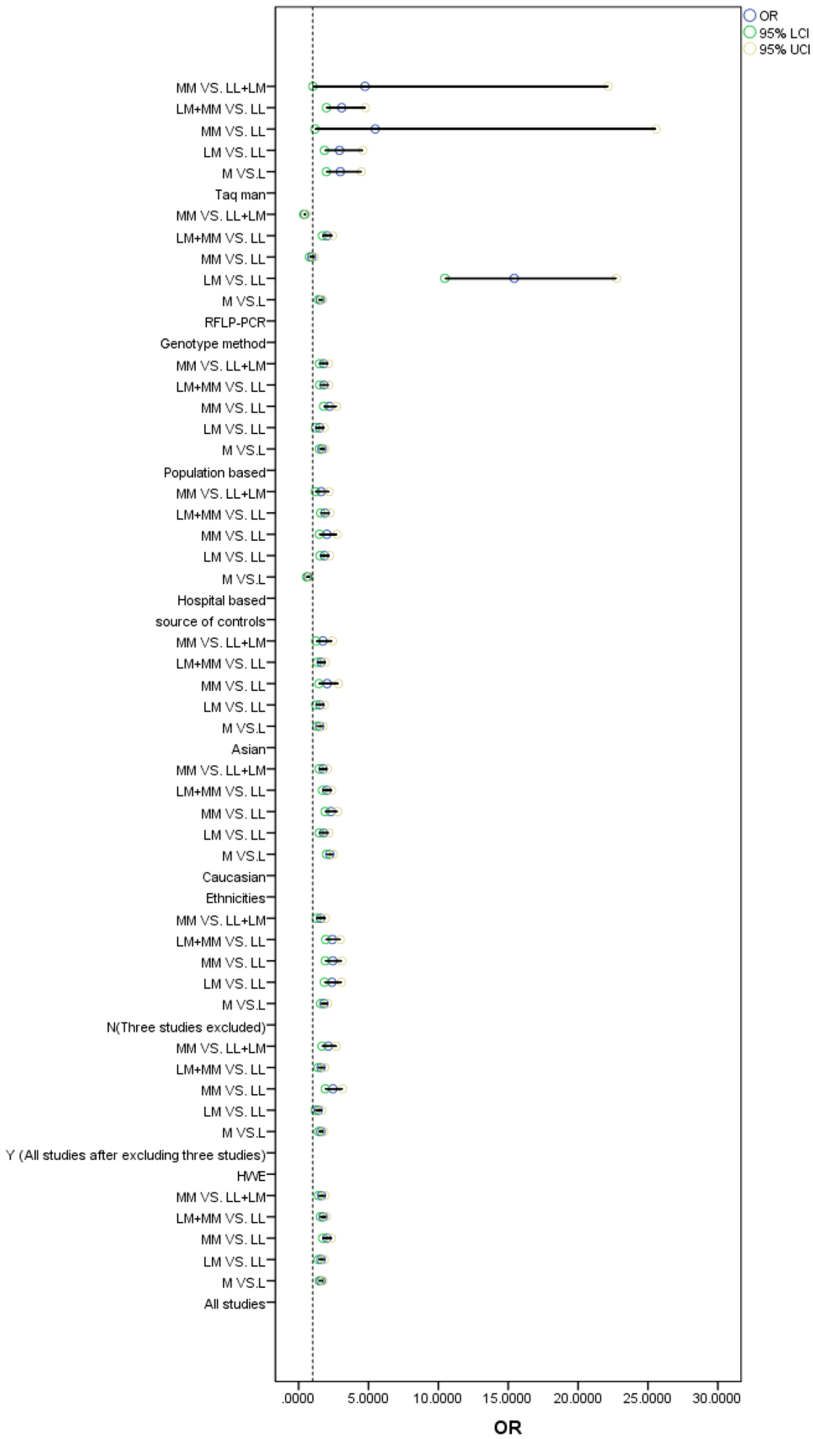

Figure 3. Forest plot of the meta-analysis of the relationship between *PON1-L55M* polymorphism and breast cancer risk. OR, odds ratio; CI, confidence interval.

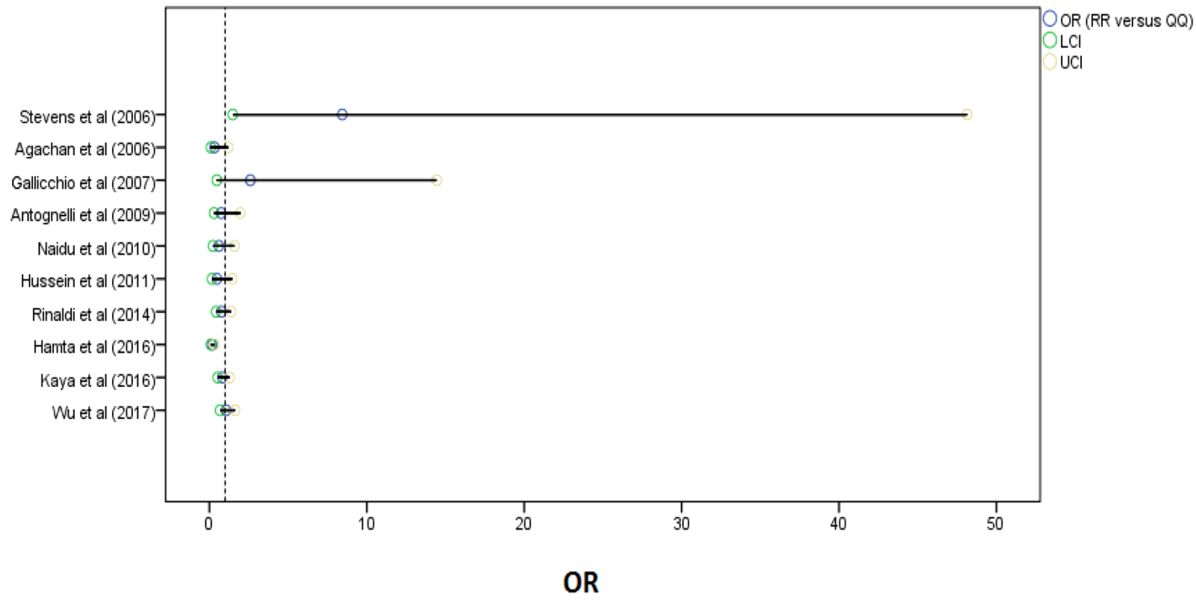

Figure 4. Sensitivity analysis of *PON1-Q192R* in overall OR coefficients (RR vs. QQ). CI, confidence interval; OR, odds ratio. Sequentially calculated findings of each paper are omitted. Both broken line ends indicate 95% CI.

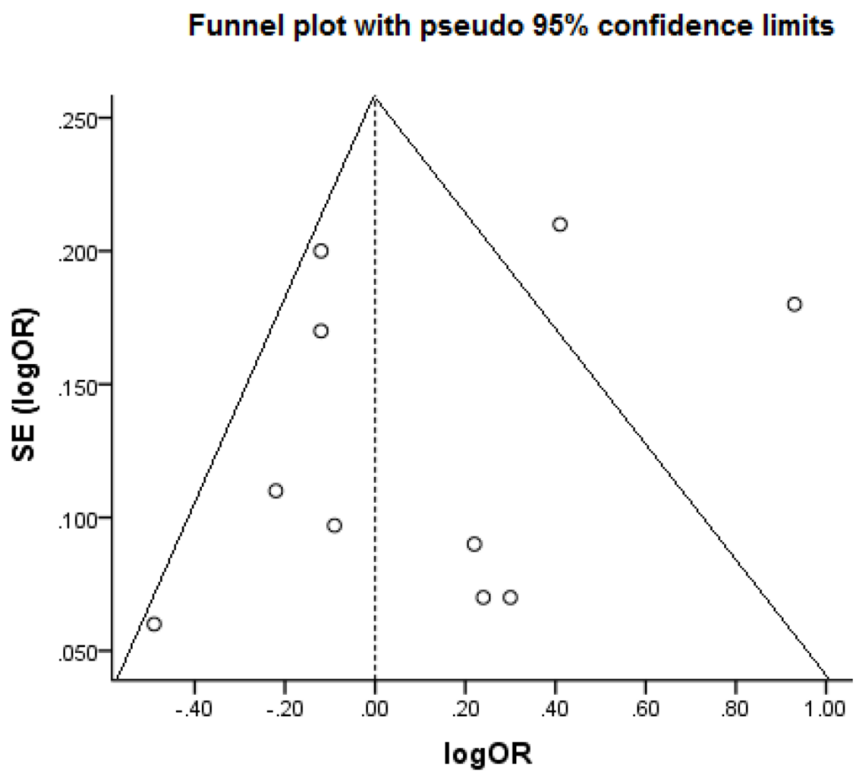

Figure 5. Funnel plot of *PON1-Q192R* in overall OR coefficients (RR vs. QQ). SE, standard error; OR, odds ratio

PON1 belongs to lipid peroxidation scavenging systems affecting BC progression (26). In the ethnographic analysis, ethnic groups showed different findings, possibly because of the living environment, genetic factors, and ethnic living habits. Earlier meta-analyses declared an association between *PON1* polymorphism and breast cancer risk (9, 27-33).

For the first time, we assessed the *PON1* typical functional polymorphisms in all published case-control studies in a comprehensive meta-analysis. In comparison with earlier studies, we did a more detailed analysis for demonstrating our results. The data were up-to-date and qualified studies were included, enabling us to accurately assess the relationship between *PON1* gene SNPs and BC risk. Despite the relationship between *PON1* (*L55M* and *Q192R*) gene polymorphism and BC risk, some limitations should be mentioned. The number of publications was limited, and Caucasians accounted for most of the registered publications.

5.1. Conclusions

PON1- Q192R can significantly decrease BC risk, and the *PON1-L55M* polymorphism is a risk factor for BC. Studies with a larger sample size at protein levels are needed to confirm whether *PON1* polymorphisms are possible genetic markers of tumor prognosis and identify its effect on BC risk.

Footnotes

Conflict of Interests: The authors declare no conflict of interest.

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Ethical Approval: This article is a meta-analysis of previously published articles and does not require ethical endorsement.

References

1. Halliwell B, Gutteridge JM. [1] Role of free radicals and catalytic metal ions in human disease: An overview. *Oxygen Radicals in Biological Systems Part B: Oxygen Radicals and Antioxidants*. Elsevier; 1990. p. 1–85. doi: 10.1016/0076-6879(90)86093-b.
2. Li WF, Costa LG, Richter RJ, Hagen T, Shih DM, Tward A, et al. Catalytic efficiency determines the in-vivo efficacy of PON1 for detoxifying organophosphorus compounds. *Pharmacogenet Genomics*. 2000;**10**(9):767–79. doi: 10.1097/00008571-200012000-00002. [PubMed: 11191881].
3. Antognelli C, Del Buono C, Ludovini V, Gori S, Talesa VN, Crino L, et al. CYP17, GSTP1, PON1 and GLO1 gene polymorphisms as risk factors for breast cancer: an Italian case-control study. *BMC Cancer*. 2009;**9**:115. doi: 10.1186/1471-2407-9-115. [PubMed: 19379515]. [PubMed Central: PMC2680904].
4. Mackness B, Durrington PN, Mackness MI. Human Serum Paraoxonase. *Gen Pharmacol*. 1998;**31**(3):329–36. doi: 10.1016/s0306-3623(98)00028-7.
5. La Du BN, Adkins S, Kuo C, Lipsig D. Studies on human serum paraoxonase/arylesterase. *Chem Biol Interact*. 1993;**87**(1-3):25–34. doi: 10.1016/0009-2797(93)90022-q.
6. Mackness MI, Mackness B, Durrington PN, Connelly PW, Hegele RA. Paraoxonase: biochemistry, genetics and relationship to plasma lipoproteins. *Curr Opin Lipidol*. 1996;**7**(2):69–76. doi: 10.1097/00041433-199604000-00004. [PubMed: 8743898].
7. Naidu R, Har YC, Taib NAM. Genetic Polymorphisms of Paraoxonase 1 (PON1) Gene: Association Between L55M or Q192R with Breast Cancer Risk and Clinico-Pathological Parameters. *Pathol Oncol Res*. 2010;**16**(4):533–40. doi: 10.1007/s12253-010-9267-5.
8. Eroglu M, Yilmaz N, Yalcinkaya S, Ay N, Aydin O, Sezer C. Enhanced HDL-cholesterol-associated anti-oxidant PON-1 activity in prostate cancer patients. *Kaohsiung J Med Sci*. 2013;**29**(7):368–73. doi: 10.1016/j.kjms.2012.11.004. [PubMed: 23768700].
9. Pan X, Huang L, Li M, Mo D, Liang Y, Liu Z, et al. The Association between PON1 (Q192R and L55M) Gene Polymorphisms and Risk of Cancer: A Meta-Analysis Based on 43 Studies. *Biomed Res Int*. 2019;**2019**:5897505. doi: 10.1155/2019/5897505. [PubMed: 31467900]. [PubMed Central: PMC6699405].
10. Hussein YM, Gharib AF, Etewa RL, ElSawy WH. Association of L55M and Q192R polymorphisms in paraoxonase 1 (PON1) gene with breast cancer risk and their clinical significance. *Mol Cell Biochem*. 2011;**351**(1-2):117–23. doi: 10.1007/s11010-011-0718-4. [PubMed: 21229382].
11. Rinaldi C. PON I and GLO I Gene Polymorphisms and Their Association with Breast Cancer: A Case-Control Study in a Population from Southern Italy. *J Mol Biomark Diagn*. 2014;**5**(2). doi: 10.4172/2155-9929.1000170.
12. Bayati Z. *[Study of the relationship between different genotypes of paraoxonase 1 gene (PON1) in breast cancer patients]*. Arak Univercity; 2015. Persian.
13. Hamta A, Ansari J, Bayati Z. [Lack of the association between single nucleotide polymorphism (L55M) in PON1 gene and susceptibility With Breast Cancer in Markazi Province]. *J Arak Univ Med Sci*. 2016;**19**(7):99–106. Persian.
14. Kaya MO, Sinan S, Guler OO, Arslan O. Is there a relation between genetic susceptibility with cancer? A study about paraoxanase (PON1) enzyme activity in breast cancer cases. *J Enzyme Inhib Med Chem*. 2016;**31**(6):1349–55. doi: 10.3109/14756366.2015.1134523. [PubMed: 26763308].
15. Wu J, Fang M, Zhou X, Zhu B, Yang Z. Paraoxonase 1 gene polymorphisms are associated with an increased risk of breast cancer in a population of Chinese women. *Oncotarget*. 2017;**8**(15):25362–71. doi: 10.18632/oncotarget.15911. [PubMed: 28445984]. [PubMed Central: PMC5421936].
16. Ramzanpour R, Farmohammadi A, Momeni A, Bahmani B, Ghorbani H. Association of PON1-L55M Genetic Variation and Breast Cancer Risk: A Case-Control Trial. *Asian Pac J Cancer Prev*. 2020;**21**(1):255–8. doi: 10.31557/APJCP.2020.21.1.255. [PubMed: 31983193]. [PubMed Central: PMC7294023].
17. Stevens VL, Rodriguez C, Pavluck AL, Thun MJ, Calle EE. Association of polymorphisms in the paraoxonase 1 gene with breast cancer incidence in the CPS-II Nutrition Cohort. *Cancer Epidemiol Biomarkers Prev*. 2006;**15**(6):1226–8. doi: 10.1158/1055-9965.EPI-05-0930. [PubMed: 16775186].
18. Ağaçhan B, Yaylım İ, Ergen HA, Arıkan S, Küçücük S, Yılmaz H. Is paraoxonase 1 192 BB genotype risk factor for. *Adv Mol Med*. 2006;**2**(1):37–40.
19. Gallicchio L, McSorley MA, Newschaffer CJ, Huang HY, Thuita LW, Hoffman SC, et al. Body mass, polymorphisms in obesity-related genes, and the risk of developing breast cancer among women with benign breast disease. *Cancer Detect Prev*. 2007;**31**(2):95–101. doi: 10.1016/j.cdp.2007.02.004. [PubMed: 17428620].

20. Lau J, Ioannidis JP, Schmid CH. Quantitative synthesis in systematic reviews. *Ann Intern Med*. 1997;**127**(9):820–6. doi: 10.7326/0003-4819-127-9-199711010-00008. [PubMed: 9382404].
21. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;**21**(11):1539–58. doi: 10.1002/sim.1186. [PubMed: 12111919].
22. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;**7**(3):177–88. doi: 10.1016/0197-2456(86)90046-2.
23. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst*. 1959;**22**(4):719–48.
24. Ouerhani S, Ben Bahria I, Rouissi K, Cherni L. Distribution of xenobiotic metabolising enzyme genotypes in different Tunisian populations. *Ann Hum Biol*. 2017;**44**(4):366–72. doi: 10.1080/03014460.2016.1272714. [PubMed: 27978766].
25. Ferre N, Camps J, Fernandez-Ballart J, Arija V, Murphy MM, Ceruelo S, et al. Regulation of serum paraoxonase activity by genetic, nutritional, and lifestyle factors in the general population. *Clin Chem*. 2003;**49**(9):1491–7. doi: 10.1373/49.9.1491. [PubMed: 12928230].
26. Delimaris I, Faviou E, Antonakos G, Stathopoulou E, Zachari A, Dionyssiou-Asteriou A. Oxidized LDL, serum oxidizability and serum lipid levels in patients with breast or ovarian cancer. *Clin Biochem*. 2007;**40**(15):1129–34. doi: 10.1016/j.clinbiochem.2007.06.007. [PubMed: 17673194].
27. Chen L, Lu W, Fang L, Xiong H, Wu X, Zhang M, et al. Association between L55M polymorphism in Paraoxonase 1 and cancer risk: a meta-analysis based on 21 studies. *Onco Targets Ther*. 2016;**9**:1151–8. doi: 10.2147/OTT.S96990. [PubMed: 27019599]. [PubMed Central: PMC4786067].
28. Fang DH, Fan CH, Ji Q, Qi BX, Li J, Wang L. Differential effects of paraoxonase 1 (PON1) polymorphisms on cancer risk: evidence from 25 published studies. *Mol Biol Rep*. 2012;**39**(6):6801–9. doi: 10.1007/s11033-012-1505-3. [PubMed: 22322559].
29. Liu C, Liu L. Polymorphisms in three obesity-related genes (LEP, LEPR, and PON1) and breast cancer risk: a meta-analysis. *Tumour Biol*. 2011;**32**(6):1233–40. doi: 10.1007/s13277-011-0227-9. [PubMed: 21887553].
30. Liu P, Wang Q, Cui Y, Wang J. A meta-analysis of the relationship between paraoxonase 1 polymorphisms and cancer. *Free Radic Res*. 2019;**53**(11-12):1045–50. doi: 10.1080/10715762.2019.1645956. [PubMed: 31762361].
31. Saadat M. Paraoxonase 1 genetic polymorphisms and susceptibility to breast cancer: a meta-analysis. *Cancer Epidemiol*. 2012;**36**(2):e101–3. doi: 10.1016/j.canep.2011.10.015. [PubMed: 22133529].
32. Zhang M, Xiong H, Fang L, Lu W, Wu X, Huang ZS, et al. Paraoxonase 1 (PON1) Q192R Gene Polymorphism and Cancer Risk: A Meta-Analysis Based on 30 Publications. *Asian Pac J Cancer Prev*. 2015;**16**(10):4457–63. doi: 10.7314/apjcp.2015.16.10.4457. [PubMed: 26028114].
33. Wen Y, Huang Z, Zhang X, Gao B, He Y. Correlation between PON1 gene polymorphisms and breast cancer risk: a Meta-analysis. *Int J Clin Exp Med*. 2015;**8**(11):20343.

Table 3. Odds Ratios and 95% Confidence Intervals of the Relationship Between *Q192R* Polymorphism in *PON1* Gene and Breast Cancer Risk [a]

Variables	Cases/Controls	df	Q-statistics	OR	95% CI	P-value [a]
***Q192R* polymorphism**						
All studies	2286/3000					
R vs. Q		9	5.17	0.7932	0.7264 - 0.8660	< 0.0001
QR vs. QQ		9	5.391	0.721	0.6402 - 0.8120	< 0.0001
RR vs. QQ		9	2.824	0.7565	0.6233 - 0.9182	0.0047
QR+RR vs. QQ		9	5.608	0.7284	0.6521 - 0.8137	< 0.0001
RR vs. QQ+QR		9	1.588	0.8585	0.7112 - 1.0364	0.1123
HWE						
Y (three studies excluded)	1512/2204					
R vs. Q		6	0.906	0.9543	0.8623 - 1.0560	0.3648
QR vs. QQ		6	1.369	0.9062	0.7869 - 1.0435	0.1711
RR vs. QQ		6	0.295	0.9673	0.7758 - 1.2061	0.7678
QR+RR vs. QQ		6	1.251	0.919	0.8051 - 1.0491	0.2111
RR vs. QQ+QR		6	3.691	0.6686	0.5399 - 0.8280	0.0002
N (three studies excluded)	774/796					
R vs. Q		2	6.637	0.5336	0.4432 - 0.6423	< 0.0001
QR vs. QQ		2	5.957	0.8434	0.3806 - 0.6140	< 0.0001
RR vs. QQ		2	3.462	0.4708	0.3073 - 0.7212	0.0005
QR+RR vs. QQ		2	6.521	0.4808	0.3858 - 0.5992	< 0.0001
RR vs. QQ+QR		2	3.912	0.429	0.2807 - 0.6555	0.0001
Ethnicities						
Caucasians	1332/2183					
R vs. Q		6	8.125	0.6197	0.5522 - 0.6956	< 0.0001
QR vs. QQ		6	7.791	0.5445	0.4673 - 0.6345	< 0.0001
RR vs. QQ		6	4.376	0.5657	0.4384 - 0.7302	< 0.0001
QR+RR vs. QQ		6	8.484	0.5347	0.4626 - 0.6179	< 0.0001
RR vs. QQ+QR		6	2.937	0.6868	0.5345 - 0.8825	0.0033
Asians	954/817					
R vs. Q		2	0.757	0.9448	0.8158 - 1.0943	0.4489
QR vs. QQ		2	1.362	0.8628	0.6978 - 1.0669	0.1731
RR vs. QQ		2	0.224	0.9635	0.6954 - 1.3349	0.8229
QR+RR vs. QQ		2	1.213	0.8825	0.7211 - 1.0799	0.2249
RR vs. QQ+QR		2	0.264	1.042	0.7675 - 1.4148	0.7919
Source of controls						
Population-based	1662/2335					
R vs. Q		5	7.728	0.6577	0.5914 - 0.7314	< 0.0001
QR vs. QQ		5	7.35	0.5911	0.5138 - 0.6801	< 0.0001
RR vs. QQ		5	4.436	0.576	0.4514 - 0.7350	< 0.0001
QR+RR vs. QQ		5	7.95	0.5881	0.5159 - 0.6703	< 0.0001

RR vs. QQ+QR		5	2.98	0.6956	0.5478 - 0.8831	0.0029
Hospital-based	624/665					
R vs. Q		3	1.561	1.1394	0.9672 - 1.3422	0.1186
QR vs. QQ		3	1.279	1.1661	0.9215 - 1.4756	0.2009
RR vs. QQ		3	1.222	1.2363	0.8798 - 1.7372	0.2216
QR+RR vs. QQ		3	1.503	1.1831	0.9502 - 1.4731	0.1328
RR vs. QQ+QR			0.857	1.1512	0.8343 - 1.5886	0.3914
Genotyping method						
PCR-RFLP	1745/1613					
R vs. Q		7	6.295	0.7276	0.6591 - 0.8034	< 0.0001
QR vs. QQ		7	6.313	0.6561	0.5757 - 0.7479	< 0.0001
RR vs. QQ		7	3.395	0.6743	0.5371 - 0.8466	0.0007
QR+RR vs. QQ		7	6.665	0.6596	0.5837 - 0.7455	< 0.0001
RR vs. QQ+QR		7	2.111	0.7868	0.6298 - 0.9830	0.0347
TaqMan	541/1387					
R vs. Q		1	0.203	0.9794	0.8010 - 1.1975	0.8394
QR vs. QQ		1	0.192	1.0301	0.7614 - 1.3936	0.8476
RR vs. QQ		1	0.299	0.9411	0.6323 - 1.4005	0.7646
QR+RR vs. QQ		1	0.024	1.0035	0.7588 - 1.3271	0.9805
RR vs. QQ+QR		1	0.402	0.9273	0.6419 - 1.3395	0.6873

Abbreviations: CI, confidence interval; OR, odds ratio; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; Q allele, Glutamine; R allele, Arginine. Y, polymorphisms according to HWE in controls; N, polymorphisms not according to HWE in controls.

[a] A P-value for heterogeneity based on the Q test is statistically significant ($P < 0.0001$). Hardy-Weinberg equilibrium (HWE < 3.84).

Table 4. Odds Ratios and 95% Confidence Intervals of the Relationship Between *L55M* Polymorphism in *PON1* Gene and Breast Cancer Risk

Variables	Cases/Controls	df	Q-statistics	OR	95% CI	P-Value [a]
***L55M* polymorphism**						
All studies	2286/3000					
M vs. L		7	10.711	1.6041	1.4712 - 1.7490	< 0.0001
LM vs. LL		7	6.95	1.6142	1.4103 - 1.8476	< 0.0001
MM vs. LL		7	8.731	2.0198	1.7249 - 2.3650	< 0.0001
LM+MM vs. LL		7	9.243	1.7587	1.5602 - 1.9823	< 0.0001
MM vs. LL+LM		7	6.624	1.6391	1.4161 - 1.8972	< 0.0001
HWE						
Y (three studies excluded)	1512/2204					
M vs. L		4	7.946	1.5975	1.4232 - 1.7932	< 0.0001
LM vs. LL		4	4.196	1.4105	1.2011 - 1.6563	< 0.0001
MM vs. LL		4	7.027	2.4513	1.9089 - 3.1479	< 0.0001
LM+MM vs. LL		4	6.269	1.6105	1.3876 - 1.8693	< 0.0001
MM vs. LL+LM		4	6.138	2.1286	1.6724 - 2.7092	< 0.0001
N (three studies excluded)	774/796					
M vs. L		2	8.317	1.8123	1.5754 - 2.0849	< 0.0001
LM vs. LL		2	6.669	2.3816	1.8455 - 3.0735	< 0.0001
MM vs. LL		2	7.175	2.4331	1.9083 - 3.1019	< 0.0001
LM+MM vs. LL		2	7.906	2.4099	1.9378 - 2.9971	< 0.0001
MM vs. LL+LM		2	4.358	1.5696	1.2815 - 1.9224	< 0.0001
Ethnicities						
Caucasians	1332/2183					
M vs. L		3	14.533	2.2304	2.0017 - 2.4852	< 0.0001
LM vs. LL		3	6.029	1.7842	1.4781 - 2.1537	< 0.0001
MM vs. LL		3	8.412	2.3005	1.8946 - 2.7933	< 0.0001
LM+MM vs. LL		3	8.374	2.0135	1.7093 - 2.3718	< 0.0001
MM vs. LL+LM		3	6.359	1.7393	1.4665 - 2.0628	< 0.0001
Asians	954/817					
M vs. L		3	5.493	1.5108	1.3040 - 1.7505	< 0.0001
LM vs. LL		3	4.149	1.5162	1.2455 - 1.8457	< 0.0001
MM vs. LL		3	4.103	2.0352	1.4493 - 2.8579	< 0.0001
LM+MM vs. LL		3	5.037	1.6068	1.3360 - 1.9324	< 0.0001
MM vs. LL+LM		3	3.253	1.7315	1.2438 - 2.4103	0.0011
Source of controls						
Population-based	1662/2335					
M vs. L		2	8.64	1.6781	1.4922 - 1.8872	< 0.0001
LM vs. LL		2	3.908	1.4996	1.2238 - 1.8376	< 0.0001
MM vs. LL		2	7.461	2.204	1.7908 - 2.7124	< 0.0001
LM+MM vs. LL		2	6.496	1.807	1.5116 - 2.1601	< 0.0001

MM vs. LL+LM		2	6.383	1.7829	1.4928 - 2.1293	< 0.0001
Hospital-based	624/665					
M vs. L		4	4.793	0.6667	0.5649 - 0.7869	< 0.0001
LM vs. LL		4	6.463	1.8479	1.5340 - 2.2262	< 0.0001
MM vs. LL		4	4.466	2.0198	1.4836 - 2.7499	< 0.0001
LM+MM vs. LL		4	7.163	1.8833	1.5838 - 2.2394	< 0.0001
MM vs. LL+LM		4	3.11	1.6118	1.1931 - 2.1774	0.0019
Genotyping method						
PCR-RFLP	1745/1613					
M vs. L		6	9.445	1.5627	1.4244 - 1.7143	< 0.0001
LM vs. LL		6	13.814	15.431	10.4659 - 22.7509	< 0.0001
MM vs. LL		6	0.655	0.9395	0.7796 - 1.1323	0.5125
LM+MM vs. LL		6	8.006	2.0346	1.7098 - 2.4210	< 0.0001
MM vs. LL+LM		6	9.350	0.4367	0.3671 - 0.5195	< 0.0001
TaqMan	541/1387					
M vs. L		0	5.247	2.9862	1.9845 - 4.4936	< 0.0001
LM vs. LL		0	4.633	2.9239	1.8571 - 4.6036	< 0.0001
MM vs. LL		0	2.165	5.4824	1.1751 - 25.5787	0.0304
LM+MM vs. LL		0	5.036	3.0838	1.9895 - 4.7802	< 0.0001
MM vs. LL+LM		0	1.985	4.7528	1.0199 - 22.1487	0.0471

Abbreviations: PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; CI, confidence interval; OR, odds ratio; M allele, Methionine. L allele, Leucine; Y, polymorphisms according to HWE in controls; N, polymorphisms not according to HWE in controls.

[a] A P-value for heterogeneity based on the Q test is statistically significant (P < 0.0001). Hardy-Weinberg equilibrium (HWE < 3.84).