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ORIGINAL RESEARCH

Causal Analysis of Platelet Indices and Breast Cancer, Including Estrogen Receptor-Specific Subtypes: A Mendelian Randomization Study

Yuhao Zhu[1], Jundong Wu[1,2]

[1]Breast Center, Cancer Hospital of Shantou University Medical College, Shantou, Guangdong, People's Republic of China; [2]Shantou Key Laboratory of Precision Diagnosis and Treatment in Women's Cancer, Cancer Hospital of Shantou University Medical College, Shantou, Guangdong, People's Republic of China

Correspondence: Jundong Wu, Breast Center, Cancer Hospital of Shantou University Medical College, 7 Raoping Road, Shantou, Guangdong, 515041, People's Republic of China, Tel +86-13829663428, Email wujun-dong@163.com

Background: Changes in platelet indices are associated with breast cancer. But the causal relationship between them remains unclear.

Methods: Genetic variation data of platelet indices, including platelet count (PLT), mean platelet volume (MPV), platelet distribution width (PDW), and plateletcrit (PCT), were collected as instrumental variables (IVs). We assessed their impact on the risk of overall breast cancer and its estrogen receptor (ER)+ and ER- subtypes through Mendelian randomization (MR) analysis, including IVs selection, multiple corrections, causality assessment, and sensitivity analysis. Additionally, the findings were validated using an independent dataset and extended the validation to East Asian populations.

Results: Our results found that PCT was significantly associated with an increased risk of overall breast cancer (OR, 1.0693 [95% CI, 1.0281–1.1121]; P = 0.0008) and its ER+ subtype (OR, 1.0691 [95% CI, 1.0233–1.1169]; P = 0.0028), while they were suggestive evidence of a causal relationship after excluding the outliers determined by MR-PRESSO test. After removing the outliers, the suggestive evidence of a causal relationship between PLT and the increased risk of overall breast cancer (OR, 1.0351 [95% CI, 1.0003–1.0711]; P = 0.0483) disappeared, whereas MPV was suggestively associated with an increased risk of overall breast cancer (P = 0.0291). PDW was suggestively associated with a lower risk of overall breast cancer (OR, 0.9597 [95% CI, 0.9236–0.9971]; P = 0.035) and ER+ (OR, 0.9528 [95% CI, 0.9118–0.9957]; P = 0.0315), ER- (OR, 0.9199 [95% CI, 0.8644–0.979]; P = 0.0085) subtypes, whose outlier-corrected results were consistent with raw causal estimates. These findings were replicated in an independent dataset but did not generalize to the East Asian population.

Conclusion: This study reveals suggestive evidence of a causal relationship between platelet indices, specifically PCT, MPV, and PDW, and the risk of breast cancer and its subtypes.

Keywords: Mendelian randomization, platelet indices, breast cancer, subtypes, causal relationship

Introduction

Breast cancer is one of the most common malignant tumors among women in the world, with high morbidity and mortality, which brings a heavy burden to women's health.[1,2] The occurrence of breast cancer is related to many factors, including heredity, endocrine, lifestyle, and environmental factors.[3,4] Especially, estrogen receptor (ER) status is of great significance for the treatment and prognosis of breast cancer.[5] According to ER status, breast cancer can be divided into ER positive (ER+) and ER negative (ER-) subtypes, with significant differences in biological behavior, treatment response, and prognosis.[6–8] Although significant progress has been made in the diagnosis and treatment of breast cancer and its subtypes, estimating risk remains critical for prevention and treatment strategies.

Platelets, as an important component of blood circulation, have been proven to be associated with the development and progression of tumors such as breast cancer, surpassing their traditional coagulation function.[9,10] It was reported that platelet-secreted factors, such as vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF), could promote angiogenesis by stimulating endothelial cell proliferation and migration, a key process for tumor growth.[11]

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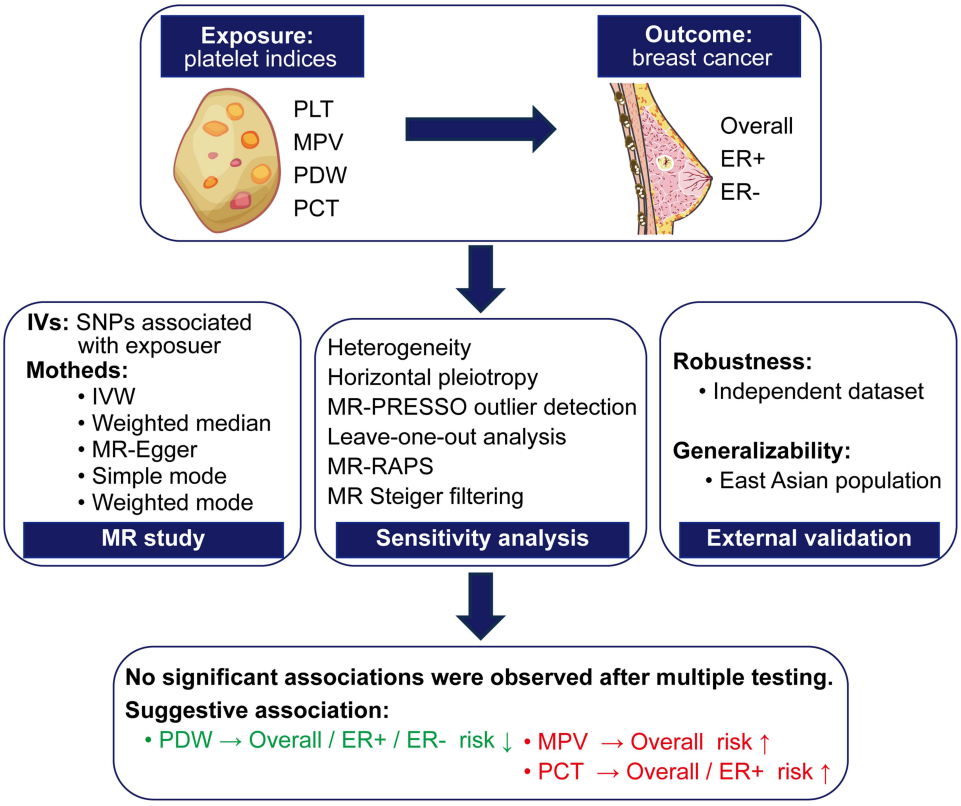
Graphical Abstract



Jiang et al found that platelet-released VEGF stimulated breast cancer cell proliferation through VEGF receptor 2-integrin synergistic signaling.[12] Platelet-derived PDGFB participated in tumor progression by promoting the recruitment of cancer-associated fibroblasts in the tumor microenvironment (TME).[13] Additionally, platelets could inhibit T-cell activity and enhance pro-tumorigenic functions of myeloid cells (neutrophils, classical monocytes) via surface-overexpressed immune checkpoint molecules, thereby shaping the immunosuppressive TME in breast cancer.[14]

Platelet indices, including platelet count (PLT), mean platelet volume (MPV), platelet distribution width (PDW), and plateletcrit (PCT), are important parameters for evaluating platelet function and quantity.[15] In recent years, an increasing number of studies have shown that the change of platelet indices is related to the occurrence, metastasis, and prognosis of tumors such as colorectal cancer, liver cancer, endometrial cancer, and lung cancer.[16–19] For breast cancer, a retrospective cohort study found that PCT predicted clinical outcome and prognosis.[20] High levels of MPV, PDW, and PLT were associated with poor prognosis of breast cancer.[21–23] For instance, elevated MPV, indicating platelet activation, was associated with distant metastasis, primary tumor size, and tumor-lymph node metastasis stage of breast cancer.[24] The mechanism may be that activated platelets aggregate and wrap around tumor cells to form microthrombi, helping tumor cells evade immune attacks (such as NK cells, macrophages, etc.), thereby promoting metastasis and progression.[25] Although these studies may find an association between platelet indices and breast cancer, the causal relationship between platelet indices and the risk of breast cancer and its ER+ and ER- subtypes has not been thoroughly investigated.

Mendelian randomization (MR) analysis is a widely used method in epidemiological research to infer causal relationships between exposures and outcomes.[26] Using genetic variations as instrumental variables (IVs) can effectively overcome the confounders and reverse causality problems in traditional observational studies.[27] Previous MR analyses have demonstrated a causal relationship between platelet indices, such as PLT, and liver and lung cancer,[28,29] but have

not been reported in relation to breast cancer. This study aims to infer the causal relationship between the genetic variation closely related to four platelet indices and breast cancer and its ER+ and ER- subtypes through MR analysis, which is expected to bring new breakthroughs and opportunities for the prevention and treatment of breast cancer.

Material and Methods

Data Source

The genetic tools related to the four platelet indices (PLT, MPV, PDW, and PCT) were selected from a genome-wide association study (GWAS), which comprised 408,112 European participants in the UK Biobank.[30] The Breast Cancer Association Consortium (BCAC) provided summary data of overall breast cancer (122,977 cases), ER+ subtype (69,501 cases), ER− subtype (21,468 cases), and control (no breast cancer, 105,974 cases).[31] All cases and controls were female. The dataset information was shown in Table 1.

Selection of IVs

Single nucleotide polymorphisms (SNPs) that significantly correlated with four platelet indices ($P < 5.0\times10^{-8}$) were selected as IVs. To eliminate the influence of linkage disequilibrium (LD) and obtain independent and reliable SNPs, we set specific parameters: $r^2 < 0.001$ and clumping distance = 10,000 kb. SNPs associated with exposure were extracted from the GWAS dataset of the outcome variables, which were recorded as IVs, containing information such as effect allele, allele effect size (β), standard error, and P value. SNP harmonization was conducted to ensure consistency in the direction of effect alleles between exposure and outcome datasets, with the following steps: First, the input data containing SNP ID, effect allele, β, and effect allele frequency (EAF) were validated, and then exposure and outcome data were combined through SNP ID. Next, for non-palindromic SNPs (non-A /T or C/G allele combinations), if effect alleles of the exposure and outcome were inconsistent, directional correction was applied to outcome's effect allele (β were multiplied by −1, EAF were converted to 1-EAF, and effect and non-effect allele labels were exchanged), and SNPs that remain inconsistent after correction were removed. For palindromic SNPs (A/T or C/G) with inconsistent effect alleles, further judgment was based on EAF; SNPs with an EAF within 0.42–0.58 were retained, while those outside this range underwent directional alignment by reversing the outcome's β (synchronously exchanging allele labels). Ultimately, SNPs missing in the outcome data or remaining unmatchable after the above steps were excluded. The strength of each IV was assessed by F-statistic, calculated as follows: $R^2= 2\times MAF\times(1\text{-}MAF)\times\beta^2$, $F = R^2(N-2)/(1-R^2)$, where R^2 represented the variation proportion of exposure factors explained by each variation coefficient, MAF represented minor allele frequency, β represented the effect size of SNP on exposure, N represented the sample size of the exposure dataset.[32] When F > 10, there was no weak IVs bias.

Table 1 Genome-Wide Association Study (GWAS) Datasets for MR Analysis

	GWAS ID	Sample	Case	Control	SNP	Population	Author	PMID	Year
Platelet indices									
Platelet count	ebi-a-GCST90002402	408,112	/	/	40299783	European	Vuckovic D	32888494	2020
Platelet distribution width	ebi-a-GCST90002401	408,112	/	/	408112	European	Vuckovic D	32888494	2020
Plateletcrit	ebi-a-GCST90002400	408,112	/	/	40299196	European	Vuckovic D	32888494	2020
Mean platelet volume	ebi-a-GCST90002395	408,112	/	/	40299375	European	Vuckovic D	32888494	2020
Breast cancer									
Breast cancer	ieu-a-1126	228,951	105,974	122,977	10680257	European	Michailidou K	29059683	2017
ER+ Breast cancer	ieu-a-1127	175,475	105,974	69,501	10680257	European	Michailidou K	29059683	2017
ER- Breast cancer	ieu-a-1128	127,442	105,974	21,468	10680257	European	Michailidou K	29059683	2017

Abbreviations: MR, Mendelian randomization; ER+, estrogen receptor-positive; ER-, estrogen receptor-negative; SNP, Single nucleotide polymorphism.

Study Design

To ensure accurate assessment of causal effects in MR analysis, SNPs served as IVs should follow three basic assumptions: firstly, IVs should be significantly correlated with platelet indices (as exposure variable); secondly, IVs must be independent of all potential confounders; finally, IVs can only affect breast cancer (as outcome variable) through platelet indices.

Statistical Analysis

Inverse variance-weighted (IVW), weighted median, MR-Egger regression, simple mode, and weighted mode methods were used to infer causal relationships in MR analysis. Among these methods, IVW was the primary method. It integrated the Wald ratio estimates of the causal effects from different SNPs and provided a consistent estimate of the causal effect of the exposure on the outcome when each genetic variation was applicable to the IV assumptions.[33] The results of IVW method were the most dependable when IVs did not have horizontal pleiotropy.[34] Weighted median can provide a consistent estimate of causal effects when at least half of the SNPs serve as valid IVs.[35] MR Egger regression was applied to evaluate the horizontal pleiotropy of IVs, and its intercept represented the estimated effect of horizontal pleiotropy.[36] When IVs exhibited horizontal pleiotropy, MR Egger regression can still provide unbiased estimates of causal associations. Compared with the MR Egger method, the weighted median method had higher accuracy in the results.[37] Simple mode and weighted mode were used as supplementary analysis.[38]

The heterogeneity test and horizontal pleiotropy assessment of IVs were conducted using the TwoSampleMR package.[39] Specifically, the 'mr_heterogeneity' function was utilized to calculate the Cochran's Q value and its corresponding P-value, which was used to evaluate the consistency of effect estimates among different SNPs. The "mr_egger_regression" function was employed for MR-Egger regression analysis, obtaining the intercept estimate value and its P-value for assessing horizontal pleiotropy. The P-value >0.05 indicated the absence of heterogeneity or horizontal pleiotropy. Additionally, the MR-Pleiotropy RESidual Sum and Outlier (MR-PRESSO) test was used to detect and correct for horizontal pleiotropy by removing outliers.[40] It was performed via the "mr_presso()" function in the MR-PRESSO package[41] with the following parameter settings: OUTLIERtest = TRUE, DISTORTIONtest = TRUE, NbDistribution = 1000, and SignifThreshold = 0.05. Furthermore, the MR-robust adjusted profile score (RAPS) method was used to correct for biases caused by both heterogeneous and systemic pleiotropy ($P < 0.05$), which provided reliable causal association estimates even in the presence of multiple weak IVs.[42] We also employed MR Steiger filtering to eliminate SNPs with higher variability in the outcome than exposure and assessed the causal directionality of the retained SNPs with exposure/outcome, which was crucial for avoiding reverse causality bias or pleiotropy risk.[43] A direction of "TRUE" and $P < 0.05$ was statistically significant.

Additionally, we repeatedly analyzed using an independent dataset from the UK Biobank to verify the results' robustness and assessed their generalizability based on the East Asian population dataset. The relevant dataset information was shown in Supplementary Table 1. Bonferroni correction was used to identify false-positive results generated by multiple tests. $P < 0.004$ [0.05/(4 exposures × 3 outcomes)] was considered statistically significant, and $0.004 < P < 0.05$ was considered suggestive evidence of a potential association. All statistical analyses were performed using R software (version 4.4.0).

Results

Selection of IVs

IVs ($P < 5\times10^{-8}$) significantly correlated with platelet indices were extracted from GWAS and SNPs with strong LD ($r^2 < 0.001$, 10,000 kb) were excluded. Subsequently, palindromic SNPs (ie, A/T or G/C) and SNPs not available in the outcome were removed. Finally, 411 SNPs of PLT, 319 SNPs of PDW, 405 SNPs of PCT, and 377 SNPs of MPV were selected for MR analysis of breast cancer. In total, 411 SNPs of PLT, 322 SNPs of PDW, 407 SNPs of PCT, and 379 SNPs of MPV were selected for MR analysis of ER+ breast cancer. In total, 412 SNPs of PLT, 322 SNPs of PDW, 409 SNPs of PCT, and 376 SNPs of MPV were selected for MR analysis of ER− breast cancer. F-statistics >10 for all IVs indicated no weak IV bias.

Causal Effect of Platelet Indices on Breast Cancer Risk

After Bonferroni correction, MR analysis supported the causal relationship between PCT and the increased risk of overall breast cancer (OR, 1.0693 [95% CI, 1.0281–1.1121]; P = 0.0008) and ER+ breast cancer (OR, 1.0691 [95% CI, 1.0233–1.1169]; P = 0.0028). There was a suggestive causal relationship between PLT and the overall increased risk of breast cancer (OR, 1.0351 [95% CI, 1.0003–1.0711]; P = 0.0483). PDW may have a suggestive association with a lower risk of overall breast cancer and its two subtypes (0.004 <P < 0.05). Although the MR-Egger results of PDW on ER−breast cancer were contrary to other MR methods, they were not statistically significant, and the accuracy of causality revealed by IVW method was better than that of MR-Egger.[44] In addition, MPV was not associated with breast cancer. The detailed results were shown in Figures 1 and 2.

Sensitivity Analysis

Even though Cochran's Q test results indicated heterogeneity, some heterogeneity was allowed in the primary outcome of the random effects IVW analysis. The MR-Egger intercept (except PDW on ER− breast cancer) indicated no pleiotropy, with P > 0.05. The results were shown in Table 2. In addition, no abnormal IV was found by leave-one-out analysis, which further confirmed the robustness of the results. After global MR-PRESSO testing, it was necessary to exclude some outliers to ensure the effectiveness of the remaining SNPs. MR-PRESSO test results revealed that PCT had a suggestive causal relationship with the increased risk of overall breast cancer and its ER+ subtype in the corrected data. PDW showed a suggestive association with a lower risk of overall breast cancer and its subtypes (ER+ and ER-) in both corrected and uncorrected data. Notably, after outliers were eliminated, the suggestive association between PLT and overall breast cancer disappeared (P = 0.2597), whereas MPV showed a suggestive association with overall breast cancer (P = 0.0291) (Table 3). MR analysis with outliers removed further confirmed the above results, as shown in Table 4. In detail, PCT exhibited a suggestive association with an increased risk of overall and ER+ breast cancer. MPV was also suggestively associated with an increased risk of overall breast cancer. Conversely, PDW demonstrated a suggestive association with a lower risk of overall, ER+, and ER- subtypes. Furthermore, the MR-RAPS test further confirmed the validity of MR causal association (all P < 0.05). The Steiger test revealed that the direction of all MR results was "TRUE" (P < 0.05), indicating no influence from reverse causal effect (Supplementary Table 2).

External Validation Based on Independent Datasets and East Asian Populations

The repeated validation in the independent dataset showed results consistent with the primary analysis, except for PDW on overall and ER+ breast cancer (Supplementary Tables 3 and 4). These results further supported the suggestive associations of PCT on increased overall and ER+ breast cancer risk, MPV on increased overall breast cancer risk, and PDW on reduced ER- breast cancer risk. However, cross-racial validation of the East Asian population did not find a significant causal association between platelet indices and breast cancer risk, suggesting that this effect may be population-specific (Supplementary Tables 5 and 6).

Discussion

This study explored the causal relationship between four platelet indices and the risk of breast cancer and its subtypes (ER+, ER-). We found that suggestive causal relationships exist between PCT and the increased risk of overall breast cancer and ER+, MPV and the increased risk of overall breast cancer, as well as PDW and the lower risk of overall breast cancer and its two subtypes. However, there was no causal relationship between PLT and the risk of breast cancer and its two subtypes, MPV and the risk of ER+, ER- breast cancer, as well as PCT and the risk of ER- breast cancer. The above findings were repeatedly verified in an independent dataset, but they failed to generalize to the East Asian population. These results provide important clues for understanding the role of platelet indices in the development of breast cancer.

The role of platelet in the pathological mechanism of breast cancer is related to its regulation of tumor angiogenesis and vascular integrity, and its influence on TME.[45] A study found that platelet-released VEGF and PDGF may influence the development of breast cancer by promoting angiogenesis and tumor growth.[46] Platelet depletion disrupted vascular integrity in the breast cancer mouse model, causing intratumoral hemorrhage and subsequent cell death.[47] Platelets

Exposure	Outcome	SNPs	Method	OR	(95% CI)	Pvalue
			MR Egger	1.0274	0.9678−1.0907	0.376
			Weighted median	1.0524	1.0029−1.1043	0.0379
PLT	Breast cancer	411	Inverse variance weighted	1.0351	1.0003−1.0711	0.0483
			Simple mode	1.0341	0.9132−1.1709	0.5974
			Weighted mode	1.0437	0.9883−1.1022	0.1251
			MR Egger	0.9979	0.9349−1.0652	0.9502
			Weighted median	0.9579	0.9097−1.0086	0.1024
PDW	Breast cancer	319	Inverse variance weighted	0.9597	0.9236−0.9971	0.035
			Simple mode	0.9356	0.8342−1.0493	0.256
			Weighted mode	0.9356	0.8912−0.9822	0.0077
			MR Egger	1.0443	0.9736−1.1202	0.2263
			Weighted median	1.0597	1.0066−1.1155	0.0269
PCT	Breast cancer	405	Inverse variance weighted	1.0693	1.0281−1.1121	0.0008
			Simple mode	1.0666	0.9503−1.1971	0.2744
			Weighted mode	1.0334	0.9835−1.0857	0.1937
			MR Egger	1.0098	0.9612−1.0609	0.6972
			Weighted median	1.0423	1.0016−1.0846	0.0413
MPV	Breast cancer	377	Inverse variance weighted	1.0284	0.9963−1.0616	0.0839
			Simple mode	1.0701	0.9802−1.1683	0.1311
			Weighted mode	1.04	1.0016−1.0798	0.0417
			MR Egger	1.0165	0.9522−1.085	0.6243
			Weighted median	1.0451	0.9892−1.1041	0.1158
PLT	ER+ Breast cancer	411	Inverse variance weighted	1.0283	0.9906−1.0674	0.1432
			Simple mode	0.9936	0.8608−1.1469	0.9299
			Weighted mode	1.0238	0.9661−1.0849	0.4279
			MR Egger	0.9834	0.9121−1.0604	0.6643
			Weighted median	0.9508	0.8947−1.0104	0.104
PDW	ER+ Breast cancer	322	Inverse variance weighted	0.9528	0.9118−0.9957	0.0315
			Simple mode	0.9948	0.8691−1.1386	0.9393
			Weighted mode	0.9391	0.8824−0.9995	0.0491
			MR Egger	1.0442	0.9654−1.1294	0.2804
			Weighted median	1.057	0.9979−1.1195	0.0588
PCT	ER+ Breast cancer	407	Inverse variance weighted	1.0691	1.0233−1.1169	0.0028
			Simple mode	1.0392	0.9056−1.1926	0.5838
			Weighted mode	1.028	0.9718−1.0873	0.3363
			MR Egger	0.9978	0.9458−1.0527	0.9365
			Weighted median	1.022	0.9739−1.0724	0.3766
MPV	ER+ Breast cancer	379	Inverse variance weighted	1.0347	0.9995−1.0711	0.0531
			Simple mode	1.0568	0.9597−1.1637	0.2619
			Weighted mode	1.0248	0.9811−1.0705	0.2705
			MR Egger	1.0885	0.9978−1.1874	0.0567
			Weighted median	1.0616	0.9799−1.1501	0.1435
PLT	ER− Breast cancer	412	Inverse variance weighted	1.0366	0.9862−1.0895	0.1573
			Simple mode	0.9141	0.7596−1.1001	0.3425
			Weighted mode	1.0906	1.0039−1.1847	0.0407
			MR Egger	1.0127	0.9109−1.1259	0.8154
			Weighted median	0.9495	0.8709−1.0352	0.2398
PDW	ER− Breast cancer	322	Inverse variance weighted	0.9199	0.8644−0.979	0.0085
			Simple mode	0.9179	0.764−1.1028	0.3611
			Weighted mode	0.9705	0.8843−1.0651	0.5286
			MR Egger	1.095	0.9863−1.2158	0.0897
			Weighted median	1.0824	0.9941−1.1786	0.0682
PCT	ER− Breast cancer	409	Inverse variance weighted	1.0467	0.9874−1.1096	0.125
			Simple mode	1.0989	0.9083−1.3296	0.3325
			Weighted mode	1.0666	0.9753−1.1665	0.1589
			MR Egger	0.9501	0.885−1.02	0.1583
			Weighted median	0.9567	0.8931−1.0249	0.2075
MPV	ER− Breast cancer	376	Inverse variance weighted	1.0025	0.9575−1.0496	0.916
			Simple mode	0.9193	0.7911−1.0684	0.2732
			Weighted mode	0.9508	0.8878−1.0183	0.1505

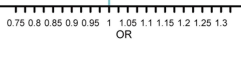


Figure 1 Forest plot of MR analysis for the effect of platelet indices on breast cancer risk.

Abbreviations: MR, Mendelian randomization; SNP, single nucleotide polymorphism; OR, odds ratios; CI, confidence interval; PLT, platelet count; PDW, platelet distribution width; PCT, plateletcrit; MPV, mean platelet volume; ER+, estrogen receptor-positive; ER-, estrogen receptor-negative.

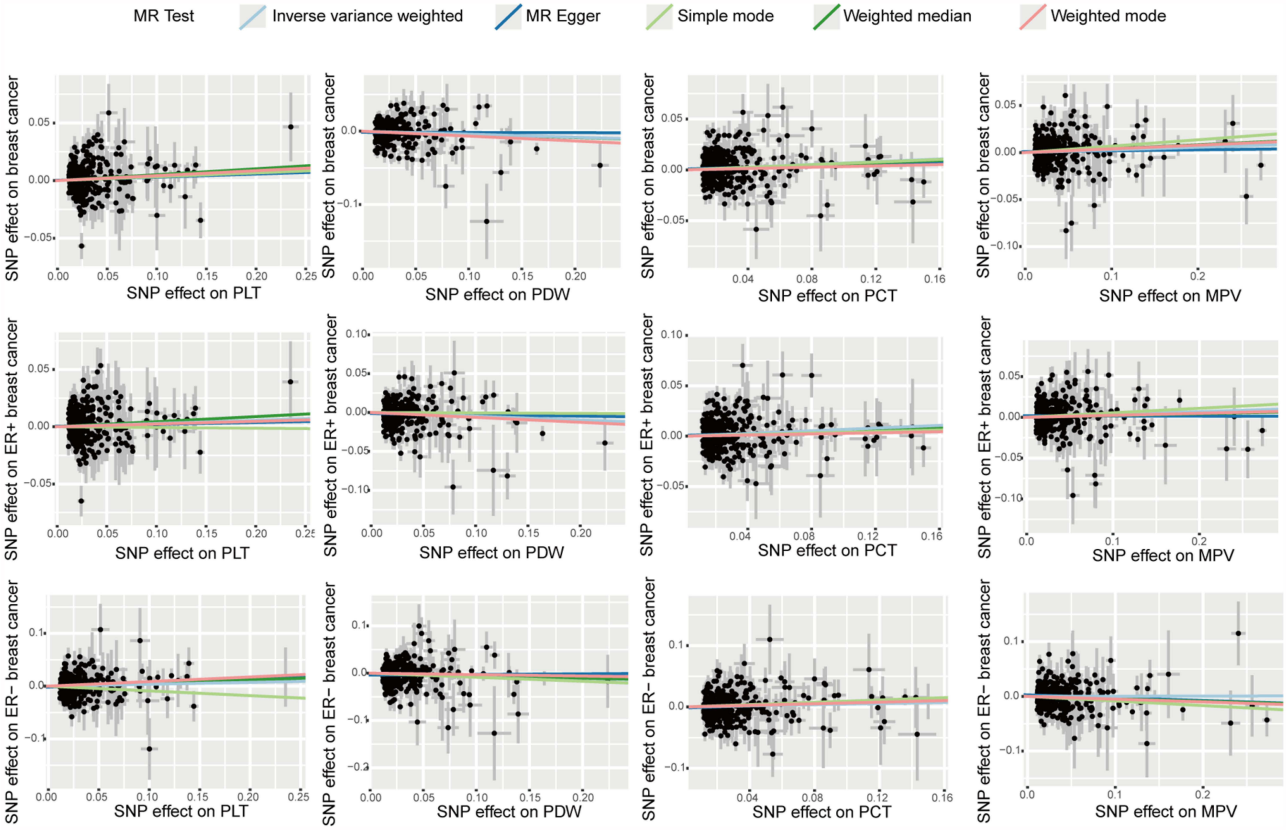


Figure 2 Scatter plots of MR analysis for the effect of platelet indices on breast cancer risk.
Abbreviations: MR, Mendelian randomization; SNP, single nucleotide polymorphism; OR, odds ratios; CI, confidence interval; PLT, platelet count; PDW, platelet distribution width; PCT, plateletcrit; MPV, mean platelet volume; ER+, estrogen receptor-positive; ER-, estrogen receptor-negative.

interacted with myeloid-derived suppressor cells (MDSCs) to suppress the anti-tumor immunity of T and natural killer (NK) cells and form an immunosuppressive microenvironment that promotes lung metastasis of breast cancer.[10] TME in ER+ breast cancer is usually immunosuppressive.[48] Antiangiogenic therapy can reverse the immunosuppressive state of breast cancer microenvironment.[49] As we all know, PCT represents the volume percentage of platelets in the blood. A study showed that it was related to disease-free survival and can be a potential biomarker to predict the clinical results and prognosis of early breast cancer patients.[20] These may indicate that the level of PCT affects the risk of breast cancer and its ER+ subtype through the mechanism of influencing angiogenesis, vascular integrity, and TME. The suggestive causal relationship between PCT and the increased risk of overall and ER+ breast cancer found in our MR results echoed these mechanism studies, further suggesting the potential driving role of platelets in the development and progression of breast cancer.

MPV is the average platelet volume in peripheral blood, which is an indicator of platelet activation status.[50] The interaction between cancer cells and platelets can trigger platelet activation, which enhances the pro-carcinogenic and pro-metastatic functions of platelets.[51] It was reported that the antiplatelet drug Ticagrelor inhibited the metastasis of breast cancer by inhibiting P2Y12-mediated platelet activation.[52] In addition, significantly higher MPV levels were detected in breast cancer patients, which were positively associated with lymph node metastasis and Ki67 proliferation index in preoperative patients.[21] These were consistent with the direction of MR suggestive causality that MPV increased the overall risk of breast cancer in this study.

PDW, a parameter reflecting the variability of platelet volume size, is another marker of platelet activation.[53] Alterations in the balance between pro- and anti-angiogenic factors released by platelets could affect tumor angiogenesis, thereby inhibiting breast cancer growth and metastasis.[54] This implied that a higher PDW may indicate a more active state of platelets, and an imbalance in the proportion of various types of factors released by platelets in this active state

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Table 2 Heterogeneity and Horizontal Pleiotropy Tests of the Impact of Four Platelet Indices on Breast Cancer and Its Subtypes in MR Analysis

Exposure	Outcome	Heterogeneity Test						Horizontal Pleiotropy Test		
		MR Egger			Inverse Variance Weighted			MR Egger		
		Q	Q_df	Q_p-Value	Q	Q_df	Q_p-value	Egger_Intercept	Se	p-Value
PLT	Breast cancer	790.4636075	409	1.43E-26	790.6329552	410	1.92E-26	0.00027329	0.000923239	0.767370662
PDW	Breast cancer	639.9728038	317	5.17E-24	644.2130807	318	2.50E-24	−0.001575756	0.001087284	0.148253811
PCT	Breast cancer	916.1702756	403	5.98E-42	917.6075831	404	6.03E-42	0.000813691	0.00102334	0.427004732
MPV	Breast cancer	827.2220845	375	4.02E-36	829.1988361	376	3.47E-36	0.000913504	0.000965006	0.34443653
PLT	ER+ Breast cancer	663.7124773	409	2.14E-14	664.0040316	410	2.58E-14	0.000427393	0.001008315	0.671884381
PDW	ER+ Breast cancer	604.9820496	320	8.21E-20	606.9239808	321	7.13E-20	−0.001266672	0.001249809	0.311590518
PCT	ER+ Breast cancer	807.690069	405	5.13E-29	808.6977472	406	5.64E-29	0.000811805	0.001142051	0.477598396
MPV	ER+ Breast cancer	689.2978325	377	1.33E-20	694.8277465	378	5.06E-21	0.00181558	0.001043972	0.08283212
PLT	ER- Breast cancer	506.463033	410	0.000792844	508.6899218	411	0.000705536	−0.001802975	0.001342834	0.180123694
PDW	ER- Breast cancer	511.612042	320	5.11E-11	519.2722042	321	1.48E-11	−0.003851798	0.001759705	0.029327228
PCT	ER- Breast cancer	620.7073893	407	4.07E-11	622.289868	408	3.82E-11	−0.001552479	0.001524063	0.308976862
MPV	ER- Breast cancer	511.2916588	374	2.89E-06	516.4267506	375	1.64E-06	0.00268226	0.001383966	0.053363646

Abbreviations: PLT, platelet count; PDW, platelet distribution width; PCT, plateletcrit; MPV, mean platelet volume; ER+, estrogen receptor-positive; ER-, estrogen receptor- negative; MR, Mendelian randomization; Q, heterogeneity statistic Q; df, degrees of freedom; se, standard error.

Table 3 The MR-PRESSO Test's Results

Exposure	Outcome	Raw	Outlier Corrected	Global P	Number of Outliers	Distortion P
PLT	Breast cancer	0.049	0.2597	<0.001	10	0.15
PDW	Breast cancer	0.0357	0.0289	<0.001	6	0.949
PCT	Breast cancer	0.0009	0.0221	<0.001	13	0.063
MPV	Breast cancer	0.0847	0.0291	<0.001	12	0.826
PLT	ER+ Breast cancer	0.144	0.251	<0.001	6	0.528
PDW	ER+ Breast cancer	0.0322	0.0178	<0.001	8	0.973
PCT	ER+ Breast cancer	0.0029	0.0052	<0.001	9	0.606
MPV	ER+ Breast cancer	0.0538	0.078	<0.001	10	0.634
PLT	ER- Breast cancer	0.158	0.2498	<0.001	1	0.697
PDW	ER- Breast cancer	0.0089	0.0178	<0.001	5	0.598
PCT	ER- Breast cancer	0.1258	0.0524	<0.001	5	0.78
MPV	ER- Breast cancer	0.916	0.8737	<0.001	5	0.063

Abbreviations: PLT, platelet count; PDW, platelet distribution width; PCT, plateletcrit; MPV, mean platelet volume; ER+, estrogen receptor-positive; ER-, estrogen receptor-negative.

Table 4 MR Analysis for the Effect of Platelet Indices on Breast Cancer Risk After Excluding Outliers

Exposure	Outcome	SNPs	Method	OR	95% CI	p-Value
PDW	Breast cancer	313	MR Egger	0.9833	0.9256–1.0446	0.5859
PDW	Breast cancer		Weighted median	0.9557	0.9079–1.0060	0.0835
PDW	Breast cancer		Inverse variance weighted	0.9610	0.9276–0.9957	0.0282
PDW	Breast cancer		Simple mode	0.9388	0.8360–1.0543	0.2872
PDW	Breast cancer		Weighted mode	0.9388	0.8931–0.9869	0.0139
PCT	Breast cancer	392	MR Egger	1.0262	0.9637–1.0928	0.4201
PCT	Breast cancer		Weighted median	1.0524	1.0009–1.1065	0.0460
PCT	Breast cancer		Inverse variance weighted	1.0423	1.0061–1.0798	0.0216
PCT	Breast cancer		Simple mode	1.0698	0.9479–1.2074	0.2750
PCT	Breast cancer		Weighted mode	1.0285	0.9791–1.0804	0.2645
MPV	Breast cancer	365	MR Egger	1.0270	0.9827–1.0732	0.2369
MPV	Breast cancer		Weighted median	1.0429	1.0012–1.0864	0.0438
MPV	Breast cancer		Inverse variance weighted	1.0323	1.0034–1.0619	0.0284
MPV	Breast cancer		Simple mode	1.0687	0.9714–1.1757	0.1736
MPV	Breast cancer		Weighted mode	1.0415	1.0023–1.0823	0.0385
PDW	ER+ Breast cancer	314	MR Egger	0.9820	0.9184–1.0501	0.5961
PDW	ER+ Breast cancer		Weighted median	0.9507	0.8973–1.0073	0.0868
PDW	ER+ Breast cancer		Inverse variance weighted	0.9533	0.9165–0.9916	0.0172
PDW	ER+ Breast cancer		Simple mode	0.9952	0.8681–1.1409	0.9449
PDW	ER+ Breast cancer		Weighted mode	0.9383	0.8833–0.9966	0.0393
PCT	ER+ Breast cancer	398	MR Egger	1.0421	0.9695–1.1201	0.2635
PCT	ER+ Breast cancer		Weighted median	1.0564	0.9983–1.1180	0.0574
PCT	ER+ Breast cancer		Inverse variance weighted	1.0597	1.0177–1.1035	0.0050
PCT	ER+ Breast cancer		Simple mode	1.0415	0.8982–1.2075	0.5907
PCT	ER+ Breast cancer		Weighted mode	1.0224	0.9622–1.0864	0.4748
PDW	ER- Breast cancer	317	MR Egger	1.0091	0.9132–1.1151	0.8591
PDW	ER- Breast cancer		Weighted median	0.9634	0.8828–1.0513	0.4023
PDW	ER- Breast cancer		Inverse variance weighted	0.9312	0.8782–0.9875	0.0172
PDW	ER- Breast cancer		Simple mode	0.9143	0.7511–1.1131	0.3729
PDW	ER- Breast cancer		Weighted mode	0.9762	0.8935–1.0665	0.5935

Abbreviations: MR, Mendelian randomization; SNP, single nucleotide polymorphism; OR, odds ratios; CI, confidence interval; PDW, platelet distribution width; PCT, plateletcrit; MPV, mean platelet volume; ER+, estrogen receptor-positive; ER-, estrogen receptor-negative.

might affect breast cancer progression. Notably, the association between PDW and breast cancer risk remains controversial in the literatures.[22,55] Liu et al demonstrated that higher PDW levels were associated with better chemotherapy outcomes in breast cancer patients.[55] Furthermore, Takeuchi et al confirmed that PDW was also associated with ER status.[56] This is consistent with the direction of suggestive causality between PDW and the lower risk of overall breast cancer and its two subtypes in our MR analysis. However, Huang et al reported the opposite results, indicating that elevated PDW may serve as a marker of poor prognosis in breast cancer.[22] These differences may stem from confounders that were difficult to avoid in observational studies. MR analysis overcame these limitations to a certain extent and provided more causal inferential evidence for the relationship between them.

Surprisingly, our study found no causal relationship between PLT and the risk of breast cancer and its two subtypes. However, studies have shown that high PLT are associated with tumor progression, metastasis, and poorer survival in breast cancer patients.[23,57,58] It should be noted that our study may have been limited by sample size, confounding factors, etc., which may have affected the interpretation of the results. Future studies will avoid the above defects to further explore the relationship between them. Collectively, our study revealed suggestive evidence of a causal relationship between platelet indices and breast cancer, providing potential guidance for clinical practice: (i) These platelet indices, as routine items in blood testing, are convenient and low-cost, and are expected to be incorporated into breast cancer risk prediction models as novel biomarkers, especially having potential value for risk stratification in patients with ER subtypes. (ii) Interventions targeting platelet production or functional regulation (such as antiplatelet drugs like aspirin) require subtype-specific evaluation in breast cancer prevention strategies. (iii) The protective association of PDW suggests that platelet heterogeneity may affect the tumor microenvironment through imbalances in the proportions of angiogenic factors.

However, some limitations cannot be ignored. Firstly, this study relied on publicly available GWAS summary data, and although the selected datasets had been applied in other MR studies,[59,60] there may still be potential quality biases. Future studies could further validate the results by incorporating individual-level data. Secondly, the validation in the East Asian population did not replicate the MR results, which might be race-specific or bias caused by insufficient statistical power. Subsequent studies should increase the sample size and validate in diverse populations to enhance the findings' generalizability. Thirdly, the combined effects of long-term chronic inflammatory status, diet, and other environmental factors were not explored in this study, but they were closely related to platelet function and breast cancer in real life. Given the suggestive results and the limitations of this study, subsequent studies will focus on confirming the reliability and generalizability of these findings through prospective clinical cohort studies and large-scale, cross-racial comparisons. Multi-source data, such as clinical data and biomarker data, will be integrated to more comprehensively assess the impact of genetic variations on breast cancer. The clinical intervention studies will be performed to observe the effects of altered platelet indices by drugs or lifestyle modifications on the risk and prognosis of breast cancer, thereby developing new prevention and treatment strategies. Animal experiments will be conducted to deeply explore the molecular mechanisms of PCT, MPV, and PDW on breast cancer development.

Conclusion

Our MR analysis reveals suggestive evidence of a causal relationship between four platelet indices and breast cancer and its subtypes. Genetic prediction suggests that high PCT increases the risk of overall and ER+ breast cancer, high MPV increases the risk of overall breast cancer, and high PDW is related to a low risk of overall breast cancer and its two subtypes. Although the current results provide suggestive evidence of causal relationships, they offer new insights and directions for breast cancer risk prediction, challenge some previous viewpoints based on traditional observational research, and stimulate further exploration of the relationship between platelet indices and breast cancer risk.

Abbreviations

PLT, platelet count; MPV, mean platelet volume; PDW, platelet distribution width; PCT, plateletcrit; IVs, instrumental variables; ER, estrogen receptor; MR, Mendelian randomization; GWAS, genome-wide association study; BCAC, Breast Cancer Association Consortium; SNPs, Single nucleotide polymorphisms; LD, linkage disequilibrium; EAF, effect allele

frequency; IVW, Inverse variance-weighted; MR-PRESSO, MR-Pleiotropy RESidual Sum and Outlier; RAPS, robust adjusted profile score; TME, tumor microenvironment; VEGF, vascular endothelial growth factor; PDGF, platelet-derived growth factor; MDSCs, myeloid-derived suppressor cells; NK, natural killer.

Data Sharing Statement

The datasets presented in this study can be found in the public database.

Ethics Approval and Informed Consent

The publicly available data used in this study were obtained from the UK Biobank and the Breast Cancer Association Consortium, and the corresponding ethical approvals have been received. Given that no human or animal experiments, observations, or interventions were involved in this study, additional ethical approval or informed consent was unnecessary.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no competing interests in this work.

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