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Interaction Between Agricultural Environmental Exposure and Inflammatory Biomarkers in Breast Cancer Risk

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Abstract: Breast cancer remains the most common malignancy among women worldwide, and environmental exposures may contribute to breast carcinogenesis through inflammatory pathways such as NLR, PLR, and interferon-γ. This study aimed to examine the association between agricultural environmental exposure, represented by rice field area, and inflammatory biomarkers including the Neutrophil-to-Lymphocyte Ratio, Platelet-to-Lymphocyte Ratio, and Interferon-γ in breast cancer. A case–control method was applied to 128 histopathologically confirmed samples consisting of 100 malignant (Invasive Carcinoma NST) and 28 benign (Fibroadenoma Mammae) breast tumors; hematologic indices were derived from preoperative blood tests, IFN-γ expression was analyzed immunohistochemically, and rice field proportions near participants' residences were obtained from national statistics, with data analyzed using Chi-square and multivariate logistic regression. The results showed that agricultural exposure (rice field ≥60%) was not significantly associated with breast cancer ($p = 0.703$), whereas elevated NLR (OR = 4.89, $p = 0.014$), PLR (OR = 12.13, $p = 0.017$), and IFN-γ expression ≥20% (aOR = 23.94, $p = 0.049$) were significantly associated with malignancy. In conclusion, although agricultural land area was not a direct risk factor, inflammatory and immune biomarkers—particularly IFN-γ—served as strong predictors of breast cancer, indicating their potential utility in risk stratification for agrarian populations.
Keywords: Breast cancer; interferon-γ; neutrophil-to-lymphocyte; platelet-to-lymphocyte ratio; rice fields.

INTRODUCTION

Breast cancer incidence has exhibited the most significant global increase over the past four decades. Between 2010 and 2019, the incidence rose by 0.5% per year (Giaquinto et al., 2022). It currently represents the most common cancer among the eight major cancer types, with approximately 2.3 million new cases annually. Breast cancer accounts for one-quarter of all cancer types among women (Arnold et al., 2022). Compared to Singapore, Malaysia, the Philippines, Sri Lanka, Taiwan, and Japan, Indonesia has the highest incidence of breast cancer, reaching 59.9 per 100,000 population, with a mortality rate of 18.6 per 100,000 population (Widiana & Irawan, 2020). In 2013, breast cancer became the second most prevalent cancer in Indonesia, with approximately 70% of cases diagnosed at an advanced stage. The

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provinces of East Java and Central Java report the highest number of breast and cervical cancer cases in the country (Kurniati & Romadhon, 2021). Risk factors for breast cancer include alcohol abuse, aging, obesity, a family history of breast cancer, exposure to harmful radiation, and reproductive factors (Zafar et al., 2022). Additionally, lifestyle changes, demographic structure shifts, and environmental exposures—including air pollution and radiation—contribute to the increasing incidence of breast cancer (Momenimovahed & Salehiniya, 2019).

Among the environmental risk factors is the presence of anthropogenic pollutants, which are defined as contaminants produced by human activity, including industrial, domestic, and agricultural sources, and which pose significant health hazards, including carcinogenic effects (Domingo-Relloso et al., 2019; Nakata et al., 2018). Several studies have shown that airborne and groundwater pollutants may enter the body and increase cancer risk through the promotion of reactive oxygen species (ROS) production and inflammation (Chen et al., 2019; Kim et al., 2019; Ma et al., 2020). The concentration of anthropogenic pollutants in areas such as coastal zones with rivers that pass through industrial areas, rice field regions, and densely populated settlements is referred to as domestic pollutant accumulation (Andara & Suryanto, 2014; Damaianto et al., 2014; Darmawan et al., 2014; Ondang et al., 2019). A 60–70% increase in agricultural production is required to meet food security demands (Beckman & Countryman, 2021; Pawlak & Kołodziejczak, 2020).

Currently, about 45% of the Earth's land surface is used for agriculture (Alston & Pardey, 2014; Ritchie & Roser, 2024). Modern agriculture, however, relies heavily on chemical inputs such as fertilizers and pesticides to sustain productivity (Alalaf, 2020; Bauddh et al., 2020; Butu et al., 2020; Meena & Mishra, 2020; Nes et al., 2018; Safdar et al., 2022). Several classes of insecticides, fungicides, and herbicides have been linked to an increased risk of breast cancer (Yang et al., 2020), potentially through endocrine disruption, genotoxicity, and epigenetic modulation (Panis & Lemos, 2024). The impact of pesticide exposure on breast cancer is ideally evaluated through direct biomonitoring of blood pesticide levels, as demonstrated in a California study (Go et al., 2023). Alternatively, Brazilian studies have compared breast cancer incidence and inflammatory marker expression across regions with differing pesticide expenditures (M. I. G. da Silva et al., 2024; R. G. S. da Silva et al., 2023). Supporting this approach, previous evidence shows that agricultural workers have higher blood levels of pesticide residues and heavy metals than non-agricultural populations, reflecting increased environmental exposure in intensive farming areas. In this study, rice-field coverage was used as a proxy indicator for anthropogenic pollutant accumulation, based on the assumption that paddy fields serve as sinks for pesticides and heavy metals.

Based on this approach, this study uses the percentage of rice field area as a proxy indicator of high pesticide contamination in a region. This approach is further supported by findings from several rice-producing regions in Indonesia, which have consistently shown high levels of pesticide and metabolite contamination in soil, irrigation water, and agricultural products sold in the market (Cahyaningrum et al., 2018; Hasmayani, 2019; Puspitasari et al., 2021; Putranto & Susanto, 2019; Sumarya et al., 2020; Supriyanto et al., 2021).

Chronic inflammation is recognized as a key driver in the development of various cancers, including breast cancer. It contributes to malignant transformation and is an important component of breast carcinogenesis. However, the precise role of chronic inflammation in the initiation and progression of malignancy in previously normal breast tissue remains unclear and warrants further investigation (Danforth, 2021). Multiple studies have demonstrated the important role of the systemic inflammatory response in the progression and development of breast cancer (Lee & Min, 2020; Qi et al., 2023), with inflammation identified as a significant prognostic factor (Kou et al., 2023). One widely studied inflammatory biomarker is the neutrophil-to-lymphocyte ratio (NLR), which has been used as a prognostic marker in both chronic and acute infectious diseases, as well as autoimmune disorders (Shojaan et al., 2023; J. Zhao et al., 2024). This ratio is calculated by dividing the neutrophil count by the lymphocyte count based on routine blood examinations. Although its use in breast cancer is still emerging, a study in a Jewish population found that elevated NLR values were associated with more advanced cancer stages and complications (Williams et al., 2014). A study by Huzno and Kolosza found that elevated NLR and platelet-to-lymphocyte ratio (PLR) values were associated with poorer survival rates among breast cancer patients. The study concluded that these markers could be used as prognostic factors in breast cancer (Huszno & Kolosza, 2019; Romadhon et al., 2024). Other studies have shown that high PLR values are associated with worse prognosis and a higher risk of lymphatic and distant metastasis (Gong et al., 2022; Huszno & Kolosza, 2019). PLR, calculated as the ratio between platelet count and lymphocyte count, has been employed as a prognostic indicator in various cancers, including gastric, colorectal, liver, ovarian, non-small cell lung, pancreatic, prostate, and kidney cancers (Huszno & Kolosza, 2019). Interferon-gamma (IFN-γ) is a pro-inflammatory cytokine secreted by tumor-infiltrating lymphocytes (Dick et al., 2022). In the context of cancer, IFN-γ exhibits antiproliferative, antiangiogenic, and pro-apoptotic effects, which support its role in antitumor activity (Heimes et al., 2020; M. Li et al., 2014). In non–small-cell lung cancer and melanoma, studies have shown that high IFN-γ expression, often accompanied by elevated PD-L1 (programmed death-ligand 1) expression, is associated with tumor differentiation, metastasis, and poor prognosis (Mendoza-Valderrey et al., 2024; Prelaj et al., 2019).

One study suggested that activation of the IFN-γ signaling pathway may lead to CD8+ T cell dysfunction, contributing to tumor progression (Yamashita et al., 2021). However, the precise role of IFN-γ in the progression of breast cancer remains unclear. Some studies have identified it as a marker of chemosensitivity, while others have reported the opposite (Tecalco-Cruz et al., 2021; Todorović-Raković et al., 2022). A study in Iraq that assessed plasma IFN-γ levels in breast cancer patients found that higher levels correlated with more aggressive malignancy (Yousif, 2023). In contrast, a study in Brazil found lower IFN-γ plasma levels in breast cancer patients compared to healthy controls (de Sousa Pereira et al., 2023). These conflicting results highlight existing research gaps that warrant further investigation.

Although inflammatory markers and agricultural environmental exposure have been extensively investigated in cancer research, integrative analyses that combine these two domains remain scarce. In particular, studies linking inflammatory biomarkers such as the neutrophil-to-lymphocyte ratio (NLR) or platelet-to-lymphocyte ratio (PLR) with geospatial variables—such as agricultural environments—are still limited. Most existing research focuses on clinical or individual-level parameters, while geographic studies tend to emphasize environmental exposure and regional health disparities. However, integrative analyses combining inflammatory marker data with spatial epidemiology remain rare. This gap underscores the need for interdisciplinary research that bridges clinical and environmental data to enhance understanding of breast cancer risk factors and inform more targeted public health interventions.

MATERIALS AND METHODS

Study Design

This research was an analytical observational study with a case–control design. The study aimed to analyze the relationship between the percentage of rice field area and the values of Neutrophil–Lymphocyte Ratio (NLR), Platelet–Lymphocyte Ratio (PLR), and Interferon-γ expression in breast cancer. The sampling technique employed total sampling, resulting in 128 specimens consisting of 28 cases of benign breast tumors (Fibroadenoma Mammae) as the control group and 100 cases of breast cancer (Invasive Carcinoma of No Special Type / NST) as the case group. The study was conducted at the Anatomical Pathology Laboratory of PKU Muhammadiyah Hospital and the Anatomical Pathology Laboratory, Faculty of Medicine, Universitas Sebelas Maret, Surakarta, Indonesia.

Population and sample

The study population consisted of female patients who underwent biopsy or mastectomy procedures due to breast tumors and were histopathological diagnosed with either fibroadenoma mammae (FAM) or invasive carcinoma of no special type (NST). Sampling was conducted using a total sampling technique based on predetermined inclusion and exclusion criteria. Inclusion criteria included: (1) female patients with a confirmed histopathological diagnosis of FAM or NST; (2) availability of complete hematologic data (neutrophils, lymphocytes, platelets, hemoglobin); and (3) residence for environmental analysis. Exclusion criteria included: (1) patients with a history of autoimmune disease, severe infections, or other conditions affecting the immune system; and (2) patients with incomplete data or tissue samples that were unsuitable for evaluation.

Agricultural environment

Rice field area is defined as the proportion of rice field area in a village where the respondent lives. The data source comes from the official publication of the Central Statistics Agency (BPS), which provides annual information on rice field area and village administrative area. The percentage of rice field area is calculated by dividing the total rice field area recorded in BPS by the total village area according to BPS for the village where the respondent lives in 2021. This value represents the percentage of the village area used for rice field activities as a unit of analysis at the village level.

Breast tumor type

The classification of breast tumor types was based on the histopathological diagnosis stated in the final report by the anatomical pathology specialist. Benign breast tumors were identified as Fibroadenoma Mammae (FAM), whereas malignant breast tumors were classified as Invasive Carcinoma of No Special Type (NST).

According to the WHO classification (2012), Breast cancer is broadly classified into in situ and invasive types. Most invasive cases are categorized as No Special Type (NST), accounting for 40–75% of all cases. Fibroadenoma Mammae (FAM) is the most common benign breast tumor, representing typical features of benign lesions (Kurniati & Khonsa, 2021; WHO, 2012).

Neutrophil-to-lymphocyte ratio (NLR) and Platelet-to-lymphocyte ratio (PLR)

The leukocyte differential count was performed using blood samples obtained from breast tumor and breast cancer patients prior to mastectomy. The neutrophil-to-lymphocyte ratio (NLR) was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count, while the platelet-to-lymphocyte ratio (PLR) was determined by dividing the platelet count by the lymphocyte count. The laboratory results for all samples produced continuous data, which were subsequently transformed into categorical variables for both NLR and PLR using the 75th percentile cut-off point, as described in a previous study (Rodríguez-Rodríguez et al., 2022). In this study, the 75th percentile value for NLR was 3.5, resulting in two groups: NLR ≥ 3.5 and NLR < 3.5. Similarly, the 75th percentile value for PLR was 17.4, creating two categories: PLR ≥ 17.4 and PLR < 17.4.

Interferon-γ expression

The results of the reading of Interferon-γ expression obtained from immunohistochemical examination of breast cancer tissue are expressed in percentage values (ratio scale). Interferon-γ expression is the primary data resulting from the calculation of the score of positively stained tumor cells. A positive result is if the cell cytoplasm is brown, which is scored semi-quantitatively (percentage) (Prastyo et al., 2018) . The reading was carried out by two pathologists, using an Olympus Optilab electron microscope. The staining intensity per unit surface area of the slide was measured in 5 fields, using a 20x objective lens (García-Tuñón et al., 2007).

An inter-observer reliability test was used in this study to assess IFN-γ expression. Inter-observer reliability measures the consistency of assessments between observers of the same phenomenon. Since IFN-γ expression data is continuous, the Intraclass Correlation Coefficient (ICC) was used as the reliability test.

Immunohistochemistry Interferon-γ Procedure

The IHC procedure consisted of sample preparation, staining, and result interpretation. Samples were obtained from paraffin-embedded blocks of breast cancer tissue that met the inclusion criteria. Tissue sections of 4–5 µm thickness were placed on poly-L-lysine–coated slides and incubated at 37°C overnight. Deparaffinization was carried out using xylene, followed by graded rehydration with alcohol solutions.

Antigen retrieval was performed using Tris–EDTA buffer (pH 9) at 90°C, followed by inactivation of endogenous peroxidase with 3% H_2O_2 methanol solution. After serum blocking, slides were incubated with the primary polyclonal antibody IFN-γ Rabbit pAb (ABclonal, Gene ID 3458) at 4°C for 18 hours. Detection was carried out using the Trekkie Universal Link and TrekAvidin-HRP Label system. The reaction was visualized with DAB substrate, producing a brown color in positive cells. Counterstaining was performed using hematoxylin before mounting. The expression of Interferon-γ was obtained as primary data from the scoring of tumor cells showing positive staining. A result was considered positive when the cytoplasm of the cells appeared brown, and the scoring was performed semi-quantitatively based on the percentage of positive cells (García-Tuñón et al., 2007; Prastyo et al., 2018). The readings were independently conducted by two pathologists using an Olympus Optilab electron microscope. The staining intensity per unit area of the slide was assessed in five representative fields using a 20× objective lens.

In this study, several confounding variables were considered to minimize potential bias in the analysis. These variables included patient age, hemoglobin level, and location of residence. Age was categorized into two groups: ≤45 years and >45 years, to reflect potential differences in hormonal status and breast cancer risk profiles. Anemia was classified as a blood level below 12 g/dL.

Data analysis

Data analysis was conducted in two stages. Bivariate analysis employed odds ratio (OR) to compare the likelihood of outcomes between exposed and unexposed groups, were assessed using the Chi-square test (McHugh, 2009; Thompson & Zeni, 2011). Multivariate analysis was performed using logistic regression to obtain adjusted odds ratio (aOR), indicating independent associations among variables (Ali et al., 2018; B. Li, 2006; McNutt et al., 2003; Tchetgen Tchetgen, 2013). Model adequacy was assessed using the Hosmer–Lemeshow goodness-of-fit test (Ali et al., 2018; Sarkar & Midi, 2010). The Nagelkerke R^2 value was used to evaluate the model's predictive capacity, where higher values indicate better explanatory power of the outcome variation (Gómez-Benito et al., 2009; J. Li et al., 2017; Lumley, 2017).

Ethical statement

This study was approved by the Ethics Committee of PKU Muhammadiyah Hospital, Surakarta, with ethical clearance number: 03/KEPK/RS.PKU/VI/2025.

RESULTS AND DISCUSSION

Data analysis was conducted in two stages. Bivariate analysis employed odds ratio (OR) to compare the likelihood of outcomes between exposed and unexposed groups, were assessed using the Chi-square test (McHugh, 2009; Thompson & Zeni, 2011). Multivariate analysis was performed using logistic regression to obtain adjusted odds ratio (aOR), indicating independent associations among variables (Ali et al., 2018; B. Li, 2006; McNutt et al., 2003; Tchetgen Tchetgen, 2013). Model adequacy was assessed using the Hosmer–Lemeshow goodness-of-fit test (Ali et al., 2018; Sarkar & Midi, 2010). The Nagelkerke R^2 value was used to evaluate the model's predictive capacity, where higher values indicate better explanatory power of the outcome variation (Gómez-Benito et al., 2009; J. Li et al., 2017; Lumley, 2017).

Table 1. Respondent Characteristics (n=128)

Variable	Category	Frequency	Percentage
Tumor Type	Benign	28	21.9
	Malignant	100	79.1
Age	< 45 y.o	49	38.3
	≥ 45 y.o	79	61.7
Rice Field Area	< 60%	96	75.0
	≥ 60%	32	25.0
Hemoglobin Level	Normal	102	79.7
	Anemia	26	20.3
NLR	< 3.5	91	71.1
	≥ 3.5	37	28.9
PLR	< 17.4	94	73.4
	≥ 17.4	34	26.6
IFN-γ Expression	< 20 %	4	3.1
	≥ 20 %	124	96.9

A total of 128 respondents were analyzed in this study, with the majority (79.1%) diagnosed with malignant breast cancer, while 21.9% had benign breast tumors (Fibroadenoma Mammae). Most participants were ≥ 45 years old (61.7%) and resided in areas where rice fields covered < 60% of the village area (75.0%). The majority exhibited normal hemoglobin levels (79.7%), NLR < 3.5 (71.1%), PLR < 17.4 (73.4%), and Interferon-γ expression ≥ 20% (96.9%). These findings indicate that most breast cancer patients were middle-aged or older, with relatively normal hematologic profiles and high immune activity.

Tabel 2. Bivariate Analysis

Variable	Category	Benign (n=28) Σ (%)	Malignant (n=100) Σ (%)	OR	p	95% CI
Rice Field Area	< 60%	20 (21.1)	75 (78.9)	0.833	0.703	0.327 – 2.126
	≥ 60%	8 (24.2)	25 (75.8)			
NLR	< 3.5	25 (28.4)	63 (71.6)	4.894	0.014	1.382 – 17.332
	≥ 3.5	3 (7.5)	37 (92.5)			
PLR	< 17.4	27 (28.1)	69 (71.9)	12.130	0.017	1.577 – 93.330
	≥ 17.4	1 (3.1)	31 (96.9)			
IFN-γ Expression	< 20%	3 (75.0)	1 (25.0)	11.880	0.035	1.185 – 119.123
	≥ 20%	25 (20.2)	99 (79.8)			

The percentage of rice field area was obtained from BPS-Central Statistics Agency in Indonesia-data, calculated as the ratio of rice field area to total village area. The cut-off point was set at the 75th percentile, referring to previous studies that reported agricultural exposure above the 75th percentile correlated with increased cancer risks (Barrón Cuenca et al., 2019; Camille et al., 2017; VoPham et al., 2015). The analysis revealed no significant association between rice field area ≥60% and breast cancer occurrence (OR = 0.833; 95% CI: 0.327–2.126; p = 0.703), suggesting that this variable did not significantly influence tumor malignancy.

The cut-off point for NLR was set at the 75th percentile (3.5), following Rodríguez-Rodríguez et al. (2022). Results showed that the proportion of respondents with NLR ≥3.5 was higher in the malignant breast cancer group compared to benign tumors (OR = 4.894; 95% CI: 1.382–17.332; p = 0.014). This indicates that systemic inflammation, as reflected by elevated NLR, is significantly associated with the risk of malignancy. Using the same categorization approach, PLR ≥17.4 was found more frequently among malignant breast cancer cases (OR = 12.130; 95% CI: 1.577–93.330; p = 0.017). This finding reinforces that an increased PLR may serve as an inflammatory indicator contributing to breast cancer development (Rodríguez-Rodríguez et al., 2022).

Interferon-γ expression was evaluated using immunohistochemistry, based on the percentage of tumor cells exhibiting positive brown cytoplasmic staining. A cut-off of ≥20% was used, by analogy with Ki-67 expression thresholds in breast cancer (Muftah et al., 2017; Vrânceanu et al., 2014). The results demonstrated that Interferon-γ expression ≥20% was significantly more common in breast cancer cases (OR = 11.880; 95% CI: 1.185–119.123; p = 0.035). Inter-observer reliability testing revealed excellent agreement between the two pathologists evaluating Interferon-γ expression, with ICC (single measures) = 0.928 (95% CI: 0.896–0.950; p < 0.001) and ICC (average measures) = 0.963 (95% CI: 0.945–0.974; p < 0.001). An ICC value above 0.90 indicates very high reliability, validating the data for further analysis. An example of the results of reading the expression of Interferon-y is as shown in figure 1 (Koo & Li, 2016; Trevethan, 2017; Ventura et al., 1980; Zaki et al., 2013).

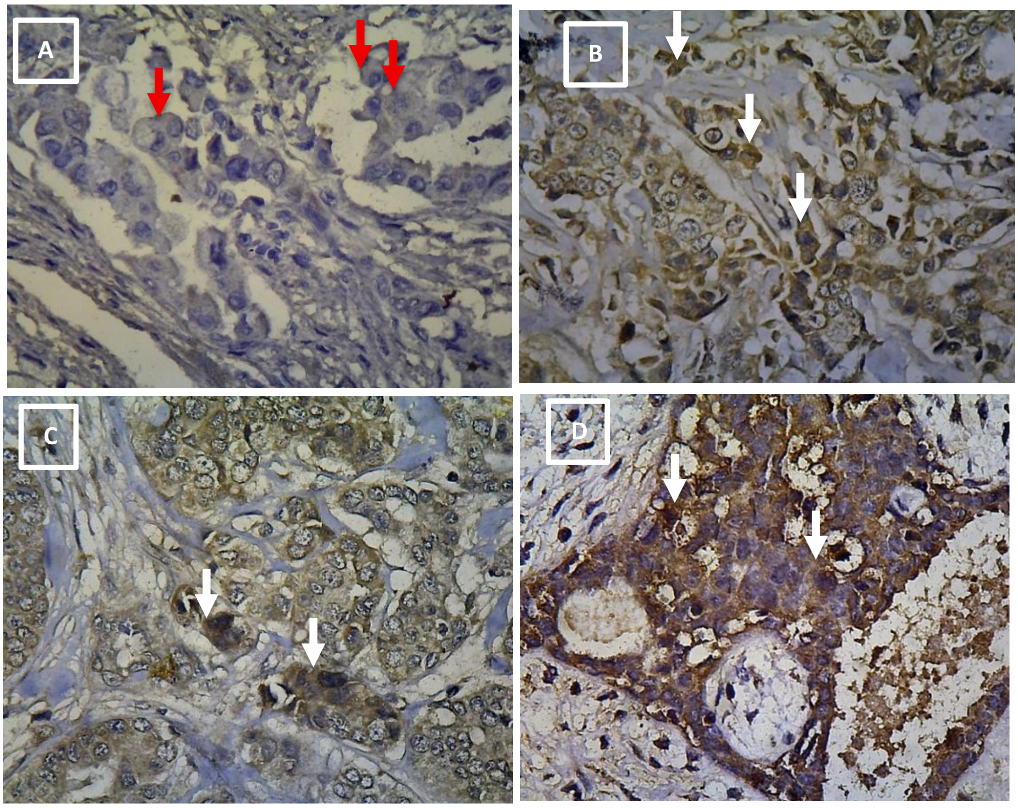

Figure 1. Interferon-γ expression in NST breast cancer specimens with a 20x objective lens. Cancer cells with positive results are shown in the white arrows, while negative results are shown in the red arrows. A. Positive percentage <10%, B. Positive percentage 20-50%, C. Positive percentage >50-75%, and D. Positive percentage >75%.

Table 3. Multivariate Analysis

Variable	Category	Benign (n=28) Σ (%)	Malignant (n=100) Σ (%)	aOR	p	95% CI
Rice Field Area	< 60%	20 (21.1)	75 (78.9)	0.608	0.362	0.209 – 1.773
	≥ 60%	8 (24.2)	25 (75.8)			
NLR	< 3.5	25 (28.4)	63 (71.6)	8.309	0.109	0.622 – 110.926
	≥ 3.5	3 (7.5)	37 (92.5)			
PLR	< 17.4	27 (28.1)	69 (71.9)	4.564	0.252	0.340 – 61.200
	≥ 17.4	1 (3.1)	31 (96.9)			
IFN-γ Expression	< 20%	3 (75.0)	1 (25.0)	23.935	0.049	1.019 – 562.432
	≥ 20%	25 (20.2)	99 (79.8)			

Table 4. Hosmer and Lemeshow Test

Step	Chi-square	df	p (Sig.)
1	6.869	4	0.143

Table 4. Model Summary

Step	-2 Log Likelihood	Cox & Snell R^2	Nagelkerke R^2
1	111.324[a]	0.166	0.255

Multivariate logistic regression was performed to assess the simultaneous effects of predictor variables on breast cancer risk. The results indicated that only Interferon-γ expression ≥ 20% remained statistically significant (aOR = 23.935; 95% CI: 1.019–562.432; p = 0.049). The variables of rice field area, NLR, and PLR were not significant after mutual adjustment. The logistic regression results were interpreted using a 95% confidence interval. Interferon-γ expression levels greater than 20% were associated with a 23.935-fold increased risk of developing breast cancer. The NLR variable with a value greater than 3.5 indicated an 8.309-fold higher risk, while a PLR value above 17.4 was associated with a 4.564-fold increased likelihood of breast cancer occurrence. Conversely, respondents residing in areas with rice field coverage exceeding 60 km^2 exhibited a lower risk (OR = 0.608) of developing breast cancer. Therefore, the extent of rice field area was not identified as a significant factor (p = 0.362), suggesting no substantial difference in breast cancer risk between respondents living in regions with larger versus smaller agricultural land areas.

The Hosmer–Lemeshow test yielded p = 0.143, indicating a good model fit (Ali et al., 2018; Sarkar & Midi, 2010). The Cox & Snell R^2 = 0.166 and Nagelkerke R^2 = 0.255 suggested that the model explained approximately 16–26% of the variation in malignancy risk among breast cancer patients (J. Li et al., 2017; Qu et al., 2017).

Overall, this analysis suggests that high Interferon-γ expression potentially represents the strongest independent factor associated with breast cancer occurrence, compared to systemic inflammatory markers (NLR and PLR) and geographic characteristics (rice field area).

Association Between Neutrophil-to-Lymphocyte Ratio and Breast Cancer

The significant difference in NLR between benign and malignant tumors reinforces the utility of this biomarker in clinical oncology. NLR reflects the systemic balance between neutrophil-driven inflammation and lymphocyte-mediated immune surveillance. In cancer pathophysiology, elevated neutrophils are known to secrete pro-tumorigenic factors such as vascular endothelial growth factor (VEGF), matrix metalloproteinases (MMPs), and cytokines that promote angiogenesis, tumor invasion, and immune evasion. Conversely, lymphocytes—particularly cytotoxic T cells—serve as key effectors in antitumor immunity. A reduction in lymphocyte count diminishes the host’s ability to detect and destroy neoplastic cells, thus contributing to tumor progression. The resulting high NLR signifies both heightened inflammatory activity and impaired immune response, a combination that is frequently observed in advanced-stage malignancies. This study’s findings are consistent with those of Templeton et al. (2014) and Ethier et al. (2017), who collectively demonstrated that elevated NLR is associated with worse clinical outcomes in breast cancer, including tumor size, grade, and nodal involvement. The reproducibility of these findings across diverse populations supports NLR as a cost-effective, accessible biomarker for breast cancer stratification (Ethier et al., 2017; Templeton et al., 2014).

Association Between Platelet-to-Lymphocyte Ratio and Breast Cancer

Similarly, PLR serves as a surrogate marker of the complex interaction between thrombocytosis and immune suppression in cancer patients. The 75th percentile value of the Platelet-to-Lymphocyte Ratio (PLR) in this study was 17.4. The data showed that a PLR value of 17.4 or higher was more prevalent among patients with breast cancer than among those with benign breast tumors (fibroadenoma), with an odds ratio (OR) of 12.130 and a p-value of 0.017. These findings are consistent with previous research. Most studies reviewed have consistently demonstrated that elevated pre-treatment PLR values are significantly associated with poorer prognosis in patients with breast cancer. This association has been observed across different breast cancer subtypes and treatment modalities.

Activated platelets play a pivotal role in facilitating tumor cell survival in circulation, aiding in their adhesion to endothelial walls, and promoting the establishment of metastatic niches. They also release pro-inflammatory mediators and growth factors, such as platelet-derived growth factor (PDGF) and transforming growth factor-β (TGF-β), which support tumor progression and immune tolerance. The present study found a significantly higher PLR in malignant tumors, supporting the hypothesis that thrombocytosis combined with lymphopenia signals a microenvironment conducive to cancer aggressiveness. Following stimulation of megakaryocytes by inflammatory mediators produced by the tumor or its surrounding environment, such as IL-3, IL-6, and IL-1, platelets can accumulate. These platelets can express several growth factors, including vascular endothelial growth factor (VEGF) and platelet factor 4 (PF4), which promote tumor growth and spread by promoting tumor cell proliferation and adhesion to other cells (Widyaningsih & Rofinda, 2024).

An elevated PLR prior to therapy has been consistently identified as a poor prognostic factor in breast cancer patients. A meta-analysis by Zhao et al. (2025), including 7,557 patients, found that higher PLR was associated with shorter OS (HR = 1.64) and lower DFS (HR = 2.29). Similar findings were reported by Guo et al. (2019) and Zhu et al. (2016). In addition to prognosis, PLR has been linked to neoadjuvant chemotherapy response, where patients with elevated PLR showed lower rates of pathological complete response (pCR) (Guo et al., 2019; Z. Zhao et al., 2025; Zhu et al., 2016). Interestingly, declines in PLR during therapy have been found to better predict treatment success (Dan et al., 2023).

Biologically, elevated PLR reflects an imbalance between pro-tumorigenic platelet activity and anti-tumor lymphocyte function. Platelets secrete growth factors such as VEGF and PDGF, which promote angiogenesis and protect cancer cells, whereas decreased lymphocyte counts indicate immunosuppression (Gong et al., 2022). Thus, PLR represents a simple, cost-effective, and clinically useful hematologic biomarker for monitoring inflammatory status and disease progression.

Association Between Interferon-γ Expression and Breast Cancer

Interferon-gamma (IFN-γ) is a cytokine classically associated with anti-tumor immunity due to its ability to activate macrophages, stimulate antigen presentation, and enhance cytotoxic T lymphocyte (CTL) function. However, in the tumor microenvironment, its role is more nuanced. Chronic exposure to IFN-γ, or its overexpression, may lead to immune exhaustion and the upregulation of immune checkpoint molecules such as PD-L1, which enable tumor cells to escape immune detection (M. R. Zaidi & Merlino, 2011). In this study, reduced expression of IFN-γ in malignant breast tumors may reflect a dysregulated immune microenvironment, where either the production of IFN-γ is impaired, or its downstream signaling is rendered ineffective. Alternatively, the presence of IFN-γ could indicate a failed immune attempt to mount an effective response, particularly if it coexists with immune escape mechanisms. The use of immunohistochemistry to detect IFN-γ expression provides insight into local immune activity at the tumor site, and its inverse relationship with malignancy in this study may warrant further exploration in larger cohorts, particularly with additional markers of immune activation or suppression.

Association Between Rice-Field Area and Breast Cancer

This study demonstrated a non-significant association between the percentage of rice field area and the incidence of breast cancer. Data on rice field coverage were obtained from the Central Bureau of Statistics (BPS), where the calculation was based on the proportion of agricultural land area relative to the total regional area. However, several methodological limitations may have contributed to the lack of statistical significance. First, it was uncertain whether the data used accurately represented the actual conditions of the study year or were derived from previous years. Second, the respondents' residential locations were determined based on the addresses listed on their identification cards (KTP), which may not reflect their actual residence at the time of data collection. Third, this study did not account for the duration of residence in the respective areas, making it difficult to accurately assess environmental exposure. These factors may have affected the validity of the observed association between the agricultural environment variable and breast cancer subtype.

This finding contrasts with the results reported by Nurhadijah (2025) and Zaidi (2025). The relationship between rice field areas and breast cancer is primarily linked to exposure to pesticides and other agricultural chemicals that act as toxic agents and endocrine disruptors. Long-term exposure to pesticides can induce hormonal disruption, DNA damage, oxidative stress, and chronic inflammation, which play key roles in carcinogenesis (Nurhadijah et al., 2025; N. Zaidi et al., 2025). Several studies support this association: Silva et al. (2019) and Tayour et al. (2019) reported a higher risk of breast cancer among individuals residing near agricultural zones (A. M. C. Silva et al., 2019; Tayour et al., 2019). Similarly, Tanha et al. (2020) demonstrated a correlation between serum diazinon levels and breast cancer incidence in intensive rice-farming regions of Iran (Tanha et al., 2020). Comparable findings were reported by Bhoi et al. (2023) in India and by Sombatsawat et al. (2022) and Mohd Nizam et al. (2023) in Southeast Asia (Bhoi et al., 2023; Mohd Nizam et al., 2023; Sombatsawat et al., 2022). In addition to pesticide exposure, heavy metals such as arsenic (As) and cadmium (Cd) can accumulate in rice field ecosystems and exert carcinogenic effects through genotoxic and inflammatory mechanisms (Akram et al., 2018).

Association between rice field area, NLR, PLR and Interferon-γ expression with breast cancer incidence

The logistic regression analysis revealed several key findings. First, Interferon-gamma (IFN-γ) expression levels exceeding 20% were associated with a 23.935-fold increased risk of breast cancer. Second, a Neutrophil-to-Lymphocyte Ratio (NLR) greater than 3.5 was linked to an 8.309-fold higher risk. Third, a Platelet-to-Lymphocyte Ratio (PLR) above 17.4 increased the risk by 4.564 times compared to lower values. The final finding indicated that respondents residing in areas with rice field coverage exceeding 60 km² had a lower risk—approximately 0.608 times—of developing breast cancer. Therefore, rice field area was not identified as a significant factor ($p = 0.362$), suggesting that there was no substantial difference in breast cancer risk between individuals living in regions with either extensive or limited agricultural land coverage.

Chronic exposure to pesticides in agricultural environments can induce oxidative stress and systemic inflammation, which contribute to carcinogenesis (Panis & Lemos, 2024; Ruíz-Arias et al., 2023). Although this study found no direct relationship between agricultural area coverage and breast cancer occurrence, inflammatory biomarkers such as NLR and PLR were higher among malignant cases, suggesting a role of chronic inflammation (Ethier et al., 2017; Huszno & Kolosza, 2019). Furthermore, higher IFN-γ expression in malignant tissues supports the presence of an active immune response that interacts with inflammatory and microenvironmental processes (Kääriö et al., 2016; M. R. Zaidi & Merlino, 2011). Therefore, the combination of agrarian geographic factors and hematologic biomarkers may reflect the complex interplay between environmental exposure, immune regulation, and breast cancer development.

This study has several methodological limitations. The use of proxy exposure measures, such as rice field coverage, may lead to underestimation of risk, as it does not account for meteorological variables, agricultural practices, or wind direction. Additionally, using Google Earth imagery without integrating multi-source satellite data could result in spatial bias due to limited resolution and update frequency. Consequently, pesticide or heavy metal exposure estimates may not fully represent actual conditions.

CONCLUSION

This study demonstrates that the proportion of rice field area was not significantly associated with breast cancer occurrence. In contrast, hematologic parameters such as NLR and PLR showed strong correlations with the disease. Moreover, Interferon-γ expression in tumor tissues exhibited a robust association with breast cancer, and multivariate analysis confirmed that high IFN-γ expression was an independent factor increasing breast cancer risk by approximately 23,935-fold. Future studies should enhance exposure data validity by integrating multi-source satellite imagery, employing advanced spatial modeling, and collecting detailed residential histories of respondents. Such efforts will improve understanding of the interaction between agrarian environmental factors, inflammatory biomarkers, and breast cancer risk.

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CONFLICT OF INTEREST

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

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