

**Research Article**

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**Estrogen Receptor (ER) and Progesterone Receptor (PR) status in breast cancer and its association with histological grade: A case series study****Anastasia Bothou<sup>1\*</sup>; Angeliki Sarella<sup>1</sup>; Georgios Iatrakis<sup>1</sup>; Georgios Tsatsaris<sup>2</sup>; Sonia Kotanidou<sup>2</sup>; Konstantinos Nikolettos<sup>2</sup>; Panagiotis Tsikouras<sup>2</sup>**<sup>1</sup>Department of Midwifery, University of West Attica, Athens, Greece.<sup>2</sup>Department of Obstetrics and Gynecology, Democritus University of Thrace, Greece.**\*Corresponding Author: Anastasia Bothou**

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**Keywords:** Breast cancer; Estrogen Receptor; Progesterone Receptor; ER; PR; Grade.**Abstract****Background:** Tumor type and histological grade are two major morphological factors that impact the classification of Breast Cancer (BC). Markers like the ER and PR can be used in standard clinical laboratories to predict treatment response or drug resistance when using novel medications.**Objective:** The purpose of this study was to investigate if the histology grade in BC is related to ER/PR status.**Methods:** 238 histopathologically confirmed cases of BC were included. For statistical analysis, Pearson's Chi-square test, Spearman's rho Fishers exact test, Mann-Whitney U Test, and correlation coefficient were used. Due to missing data in some factors, to avoid bias, multiple imputation was performed. The level of statistical significance was defined as p-value<0.05.**Results:** 35(14.7%) of the 238 BC patients had DCIS, 152(63.9%) had ductal invasive carcinoma, 37(15.5%) had lobular invasive carcinoma, 5(2.1%) had tubular infiltrative carcinoma, 1(0.4%) had myeloid infiltrative carcinoma, 1(0.4%) had inflammatory carcinoma, and 7(2.9%) had another type of breast cancer. Of the seven patients with different types of carcinoma, five (2.1%) had malignant squamous cell carcinoma, one (0.4%) had papillary infiltrative carcinoma, and one (0.4%) had mucinous infiltrative carcinoma. Of the 238 BC patients, 10(4.2%) had no information available regarding the tumor's grade. Therefore, out of the 228 BC patients for whom grade information was available, grade I was assigned to 36(15.8%), grade II to 102(44.7%), and grade III to 90(39.5%). A histological examination did not reveal the hormone receptor (HR) status for 3 out of the 238 BC patients (1.3%). Out of 235 patients (17.9%) for whom the HR status was known, 193 patients (82.1%) had positive ER, and 42 patients (17.9%) had negative ER. Furthermore, out of the 235 patients for whom HR status information was available, 57 patients (24.3%) had negative PR and 178 patients (75.7%) had positive PR. A link was found between the grade and the ER (p<0.001) and PR (p<0.001) status. Specifically, as the grade increases, ER and PR decrease, and vice versa.**Conclusion:** Our study indicates a statistically significant correlation between ER-PR status and histological grade.

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## Introduction

Over two million women are diagnosed with Breast Cancer (BC) annually, making it the most frequent cancer in women globally [1]. Infiltrating ductal carcinoma is the most common type of invasive breast cancer, accounting for 70-80% of invasive lesions [2]. 60-80% of all instances of BC are invasive ductal carcinoma of no special type Not Otherwise Identified (NOS) [3].

Histologic subtype, grade, sentinel lymph node status [4], Estrogen Receptor (ER)/Progesterone Receptor (PR) status, human epidermal growth factor receptor-2/neu (her-2/neu) status, growth factors, and their receptors, proliferative activity and DNA content, oncogenes, and tumor suppressor genes are characteristics of breast carcinoma that are linked to prognostic significance and survival. Even though ER and PR are codependent variables [3], ER status is now thought to be the most potent prognostic indication in the treatment of BC [5,6].

In the modern day, treating BC with a conservative surgical technique is growing in popularity [7,8]. One important advance in the management of breast carcinoma is the association between the presence of Hormone Receptors (HR) in the tumor and the tumor's responsiveness to hormonal therapy and chemotherapy [3,9]. The purpose of this study was to investigate how the histological grade in BC is related to ER/PR status.

## Materials & methods

### Study design-Patient selection

The present two-year retrospective study included all cases of BC (238 cases) from two breast clinics in Greece. All participants with BC submitted a copy of the result of their histological examination which confirmed the existence of malignancy, while also they completed an anonym questionnaire.

### Statistical analysis

Microsoft Excel (Spreadsheets), version 2010 was used for the initial data recording of this study, and then the statistical package SPSS v. 20.0 was used for statistical analysis.

Statistical data analysis and statistical significance testing were performed using Chi-Square, Fisher's exact test, Mann-Whitney U Test, and correlation coefficient. In the correlations, which involved data from the patient's histology, due to missing data in some factors, multiple imputation was performed using the statistical program to avoid bias. The level of statistical significance was defined as  $p$ -value $<0.05$ .

**Ethical issues:** In all cases (study-control), the principles of the Declaration of Helsinki regarding the rules of privacy, anonymity, and confidentiality governing this research were respected. In fact, before participating in the study, participants were required to read the patient information document provided to them and to sign the informed consent document. There was no conflict of interest about the research protocol.

## Results

The mean age of the patients in the study at the onset of the disease was 58 years. Of the 238 BC patients, 142(59.7%) were diagnosed with BC as they presented symptoms, 2(0.8%) after

screening for another problem, and 94(39.5%) after BC screening. Approximately 20% of women with BC had a palpable mass as a symptom, 4.6% had a change in the breast nipple, and 4.9% had changes in the skin of the breast. An additional 5% had nipple discharge.

Of the 238 BC patients, 35(14.7%) had Ductal Carcinoma In Situ (DCIS), 152(63.9%) had ductal invasive carcinoma, 37 (15.5%) had lobular invasive carcinoma, 5(2.1%) had tubular infiltrative carcinoma, 1(0.4%) had myeloid infiltrative carcinoma, 1(0.4%) had inflammatory carcinoma and 7(2.9%) had other type of breast carcinoma. Of the 7 who had another type of carcinoma, 5(2.1%) had mucinous infiltrative carcinoma, 1(0.4%) had malignant squamous cell carcinoma, and 1(0.4%) had papillary infiltrative carcinoma (Table 1). The mean value of the lesion volume was 1.8 cm; the minimum value of the lesion volume was 0.15 cm, while the maximum value was 15 cm.

For 10 of the 238 BC patients (4.2%), there was no information on the grade of the tumor. Therefore, of the 228 BC patients for whom grade information was available, 36(15.8%) had grade 1, 102 (44.7%) had grade 2, and 90 (39.5%) had grade 3 (Table 2).

For 3 of the 238 BC patients (1.3%), the information about the status of HR was not available on histological examination. Of the 235 (17.9%) patients for whom the information about the status of HR was available, 42 of 235 (17.9%) had negative ER, whereas 193 of 235 (82.1%) had positive ER (Table 3). In addition, 57 of 235 patients (24.3%) for whom information on HR status was available had negative PR, whereas 178 of 235 (75.7%) had positive PR (Table 4).

Following the presentation of the results, a correlation test between some of the most important parameters and the histological characteristics of the cancer was performed. Because, from the histological characteristics some information was not available, the sample was adjusted accordingly. Specifically, it was observed that there is a correlation between grade and estrogen receptors ( $p<0.001$ ). Especially, as grade increases estrogen receptors decrease and vice versa (Table 5). In addition, a correlation was found between grade and progesterone receptors ( $p<0.001$ ). That is, as grade increases progesterone receptors decrease and vice versa (Table 6).

## Discussion

BC affects 1 in 8 women in the United States and is the most common malignancy in developed nations among females [10]. The developing world is not falling behind. In developing nations, the incidence of BC is rising, particularly in urban areas [11].

In our study, the mean age of the patients at the onset of the disease was 58 years. This finding is in line with the already known existing literature, according to which the incidence of BC increases significantly with age, reaching its highest point at the age of menopause [12,13]. Indeed, it has been suggested that this increase is a result of the occurrence of changes in surviving cells and an increase in the likelihood of mutation over time.

The correlation of the expression of ER and PR with each other and to various clinicopathological parameters is very impor-

**Table 1:** Histological type.

Histological Type * Case/Control crosstabulation				
		Count	Case/Control	Total
			Patients	
Histological type	DCIS	Count	35	35
		% within Histological type	100.0%	100.0%
		% within Case/Control	14.7%	14.7%
		% of Total	14.7%	14.7%
	Ductal invasive carcinoma	Count	152	152
		% within Histological type	100.0%	100.0%
		% within Case/Control	63.9%	63.9%
		% of Total	63.9%	63.9%
	Lobular invasive carcinoma	Count	37	37
		% within Histological type	100.0%	100.0%
		% within Case/Control	15.5%	15.5%
		% of Total	15.5%	15.5%
	Tubular infiltrative carcinoma	Count	5	5
		% within Histological type	100.0%	100.0%
		% within Case/Control	2.1%	2.1%
		% of Total	2.1%	2.1%
	Myeloid infiltrative carcinoma	Count	1	1
		% within Histological type	100.0%	100.0%
		% within Case/Control	0.4%	0.4%
		% of Total	0.4%	0.4%
Inflammatory carcinoma	Count	1	1	
	% within Histological type	100.0%	100.0%	
	% within Case/Control	0.4%	0.4%	
	% of Total	0.4%	0.4%	
Another type of breast carcinoma	Count	7	7	
	% within Histological type	100.0%	100.0%	
	% within Case/Control	2.9%	2.9%	
	% of Total	2.9%	2.9%	
Total	Count	238	238	
	% within Histological type	100.0%	100.0%	
	% within Case/Control	100.0%	100.0%	
	% of Total	100.0%	100.0%	

**Table 2:** Grade.

		Grade			
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Grade 1	36	15.1	15.8	15.8
	Grade 2	102	42.9	44.7	60.5
	Grade 3	90	37.8	39.5	100.0
	Total	228	95.8	100.0	
Missing		10	4.2		
Total		238	100.0		

**Table 3:** Estrogen receptor status.

		Estrogen receptors			
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Negative	42	17.6	17.9	17.9
	Positive	193	81.1	82.1	100.0
	Total	235	98.7	100.0	
Missing	6	3	1.3		
Total		238	100.0		

**Table 4:** Progesterone receptor status.

Progesterone receptors					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Negative	57	23.9	24.3	24.3
	Positive	178	74.8	75.7	100.0
	Total	235	98.7	100.0	
Missing	6	3	1.3		
Total		238	100.0		

**Table 5:** Grade and estrogen receptor correlation testing.

Grade and estrogen receptor					
Pooled	Spearman's rho	Grade	Correlation Coefficient	1.000	-.347**
			Sig. (2-tailed)		.000
			N	238	238
		ER	Correlation Coefficient	-.347**	1.000
			Sig. (2-tailed)	.000	
			N	238	238
**. Correlation is significant at the 0.01 level (2-tailed).					
*. Corr. is significant at .05 level 1-tail...					
**. Corr. is significant at .01 level 1-tail....					
*. Corr. is significant at .05 level 2-tail...					

**Table 6:** Grade and progesterone receptor correlation testing.

Grade and progesterone receptor					
Pooled	Spearman's rho	Grade	Correlation Coefficient	1.000	-.286**
			Sig. (2-tailed)		.000
			N	238	238
		PR	Correlation Coefficient	-.286**	1.000
			Sig. (2-tailed)	.000	
			N	238	238

tant. ER and PR status are measured by chemical ligand binding assay and are the only prognostic and predictive biomarkers recommended for routine clinical use in BC. Both are relatively weak prognostic factors, but strong predictive factors for response to adjuvant and therapeutic hormonal therapy [14].

In this study, we have included 238 cases of BC. Knowledge of HR and molecular subtypes in a certain population is crucial in implementing BC treatment. We found that 17.9% of patients with BC had ER-negative and 24.3% PR-negative. Our result is remarkably lower compared with the findings from other studies [15,16].

Regarding the histological characteristics, a statistically significant inverse correlation of the degree of aggression (grade) with HR (ER and PR) was demonstrated ( $p < 0.001$ ). Exactly a similar finding was found in the study by Bansal et al in 2017 [17], which underlined that ER and PR expression was found to have a statistically significant correlation with the grade of the tumor ( $p < 0.001$ ). Moreover, similar findings were also confirmed by a study by Sofi et al. in 2012, which indicated that high-grade lesions and larger-size tumors were more likely to be PR and ER-negative [18] and by a study by Siadati et al in 2015, which found a significant correlation between ER and PR-positive status and low-grade tumors [19].

In our study, patients with lower tumor grade were more likely to have ER+/PR+ than patients with higher-grade tumors

when receptor positivity was compared with tumor grade and tumor size. The majority of previous investigations and the study by Dunnwald et al. [20] with sample sizes of 155,175 concurred with these results. However, there are other limited studies, such as a study by Anand et al in 2021, with 72 histopathologically confirmed cases of BC, which concluded that there is no correlation between higher histological grade and ER-PR status [14].

### Conclusion

Based on our research, we recommend that women who have unclear receptor status should be treated with tamoxifen because they are more likely to be ER-positive. This is particularly true for elderly people whose likelihood of having an ER-negative illness is decreased. Our study's findings indicated a favorable association between ER/PR positive status and low-grade tumors. These results demonstrated the significance of the biomarkers since they offer useful prognostic data for selecting the most appropriate course of treatment.

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

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