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Programmed death-ligand 1 (PD-L1) expression in malignant and benign cervical and breast cancers

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Abstract

Background: Programmed death-ligand 1 (PD-L1) expression has become a valuable biomarker for guiding immunotherapy selection in various cancers, including breast and cervical malignancies.

Objective: This study aimed to investigate the immunohistochemical expression of PD-L1 in malignant and benign breast and cervical cancers.

Methods: This retrospective study involved the analysis of 40 formalin-fixed paraffin-embedded tissue blocks, with 20 blocks from breast cancer patients and 20 from cervical cancer patients. Immunohistochemical analysis was performed via the avidin-biotin immunoperoxidase method to detect PD-L1 expression. The expression was assessed using a semi-quantitative method, grading the staining intensity and the percentage of stained cells per field. The stained sections were observed under a Leica microscope (Leica DM750, Switzerland) connected to a digital camera (Leica ICC50).

Results: PD-L1 expression was greater in cervical cancer than in breast cancer. In breast cancer, benign cases mostly presented negative PD-L1 expression, with a mean percentage reactivity (MPR) of 14.8%, whereas malignant cases presented mild expression, with an MPR of 46.4%. In cervical cancer, benign cases were mainly negative, with an MPR of 18.4%, whereas malignant cases displayed mild to moderate PD-L1 expression, with an MPR of 71.3%.

Conclusion: PD-L1 expression was more pronounced in cervical cancer than in breast cancer. The elevated levels of PD-L1 in cervical cancer suggest that this type of cancer may be more responsive to immunotherapeutic interventions targeting the PD-L1 pathway compared to breast cancer. Recognising these differences is crucial for tailoring treatment plans and implementing personalised medicine strategies for each specific cancer type.

Keywords: Cervical cancer, breast cancer, PD-L1, immunotherapy, HPV.

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INTRODUCTION

Breast cancer mostly affects breast tissue in women and is less prevalent among men. It is the most common type of cancer among women worldwide and is characterised by the uncontrolled growth and spread of abnormal epithelial cells lining the ducts or lobules of the breast tissue [1]. Triple-negative breast cancer (TNBC) is a subgroup of breast cancer that tests negative for human epidermal growth factor receptor 2 (HER2), progesterone receptor (PR), and oestrogen receptor (ER) on the basis of immunohistochemistry (IHC) [2]. TNBC has distinct metastatic patterns, an aggressive nature, and a specific molecular profile but lacks targeted therapy. Worldwide, there are an estimated 170,000 cases of breast cancer, with TNBC accounting for 10–20% of invasive breast cancers [3]. Epidemiological data show that premenopausal women under 40 years of age make up 15–20% of all breast cancer cases, with TNBC primarily affecting these women [4]. Cervical cancer originates in the cervix [5] and remains a significant cause of morbidity and mortality worldwide among women. High-risk HPV infections (HPV 16 and 18) and an inflammatory tumour microenvironment are associated with cervical cancer and can be targeted by

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immunotherapy [6]. Approximately 95% of cervical cancers are caused by untreated persistent HPV infections of the cervix. With an estimated 570,000 new cases each year, cervical cancer is the fourth most common cancer in women worldwide, with 85% of cases occurring in developing countries [7]. Immunotherapy using immune checkpoint inhibitors (ICIs) has emerged as an effective therapeutic option. The immune checkpoint programmed death-receptor 1 (PD-1) negatively regulates T-cell immunological function. Programmed death-ligand 1 (PD-L1) on tumour cells interacts with PD-1, which is produced by T lymphocytes, to inhibit the growth and cytotoxic potential of T cells. Inhibiting the function of checkpoint inhibitors can enhance the immune response against cancer cells [8].

While the use of immunotherapy in breast cancer treatment is increasing, the impact of immune checkpoint inhibitor response biomarkers on prognosis remains unclear. A study by Parvathareddy et al. [9] revealed a correlation between PD-L1 expression and poor clinical and pathological characteristics in patients with breast cancer, including younger age, higher grade, and TNBC subtype. PD-L1 expression in cervical cancer has also been linked to a poorer prognosis and a reduced response to immunotherapy [10]. Research suggests that high PD-L1 expression is associated with decreased overall survival rates in cancer patients and accelerated tumour growth [11]. PD-L1 has indeed been proven to be a relevant diagnostic biomarker for various indeed been proven to be relevant, but further clinical studies are needed on its expression in breast and cervical malignancies. This study aimed to determine the immunohistochemical expression of PD-L1 in breast and cervical cancer.

MATERIALS AND METHODS

Tissue sample selection

In this retrospective study, a total of 40 formalin-fixed paraffin-embedded tissue blocks comprising 20 blocks from cervical cancer patients (10 benign and 10 malignant) and 20 blocks from breast cancer patients (10 benign and 10 malignant) were retrieved from the Pathological Archives of University College Hospital (UCH) Ibadan, Oyo State, Nigeria. All analyses were carried out in the Molecular Laboratory at the University of Ibadan, Oyo State, Nigeria.

Immunohistochemical analysis

The expression of the PD-L1 biomarker was demonstrated immunohistochemically using the avidin-biotin immunoperoxidase method. Sections on adhesive-coated glass slides were deparaffinised in xylene and rehydrated using different gradients of ethanol. The sections were pretreated in a pressure cooker for antigen retrieval, using antigen retrieval buffer at 95°C for 30 minutes, 90°C for 10 seconds and 10°C for 10 minutes. Endogenous peroxidase activity was blocked by immersion in a 3% hydrogen peroxidase solution for 5 minutes. Nonspecific binding was blocked by a blocking buffer (or nonimmune serum) for 15 minutes. Two hundred microliters of diluted primary antibody (BioGenex mouse monoclonal primary antibody) for PD-L1 were added to the slides, which were subsequently incubated at room temperature for 80 minutes. The slides were then incubated with biotinylated rabbit anti-mouse secondary immunoglobulins for 15 minutes at room temperature. They were subsequently incubated with the avidin-biotin peroxidase complex. 3,3'-Diaminobenzidine was used as a chromogen. The sections were counterstained with hematoxylin [12].

Immunostaining assessment

The expression of PD-L1 was determined through a semi-quantitative method. The immunoreactivity of the biomarker was determined by assessing the staining intensity and percentage of stained cells per field. The staining intensity was graded as mild, moderate or severe. The percentages of positive cells were graded as follows:
0.1–10% stained = negative (-), grade 0.
10.1–39% stained = positive (+), grade 1.
40.0–79% stained = positive (++), grade 2.
80.0–100% stained = positive (+++), grade 3 [12].

Photomicrography

The stained sections were examined under a Leica research microscope (Leica DM750, Switzerland) interfaced with a digital camera (Leica ICC50). Digital photomicrographs of the stained sections for histomorphology and immunohistochemistry of the organs studied were taken at various magnifications and reported for morphological changes.

Data analysis

The results are presented in figures, tables and pictures (micrographs). PD-L1 staining was evaluated using light microscopy at x100 and x400. The values are presented as simple frequencies and percentages. Statistical analysis was performed using Stata (Version 14.0, StataCorp, College Station, Texas).

RESULTS

Figure 1 is an H&E-stained micrograph of benign breast tissue sections at x100 and x400 magnification, showing the general tissue structure with purple nuclei and pink cytoplasm with well-defined structures. The tissue exhibited a uniform glandular pattern characteristic of normal breast tissue, with fibrous and fatty tissues supporting the lobules and ducts. The basement membrane separating the epithelium and stroma is present, along with connective tissues and fibroblasts. Figure 2 is an H&E-stained micrograph of malignant breast tissue sections at x100 and x400 magnification, showing stained nuclei, severe dysplasia, and hyperchromasia. The cells displayed a disorganised tissue structure and a high nuclear-cytoplasmic ratio. Figure 3 shows a micrograph of immunohistochemically stained PD-L1 in benign breast tissue sections at x100 and x400 magnification. The section

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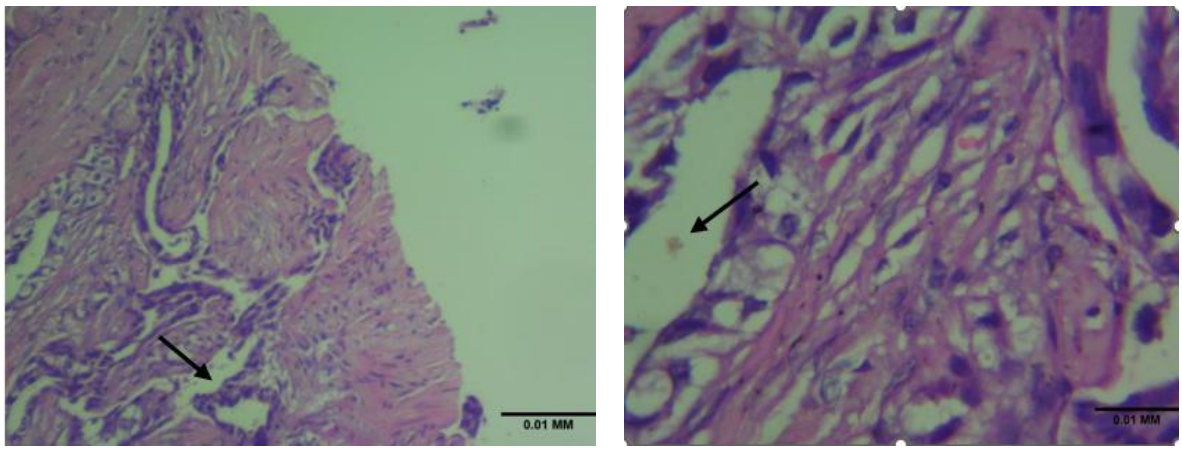
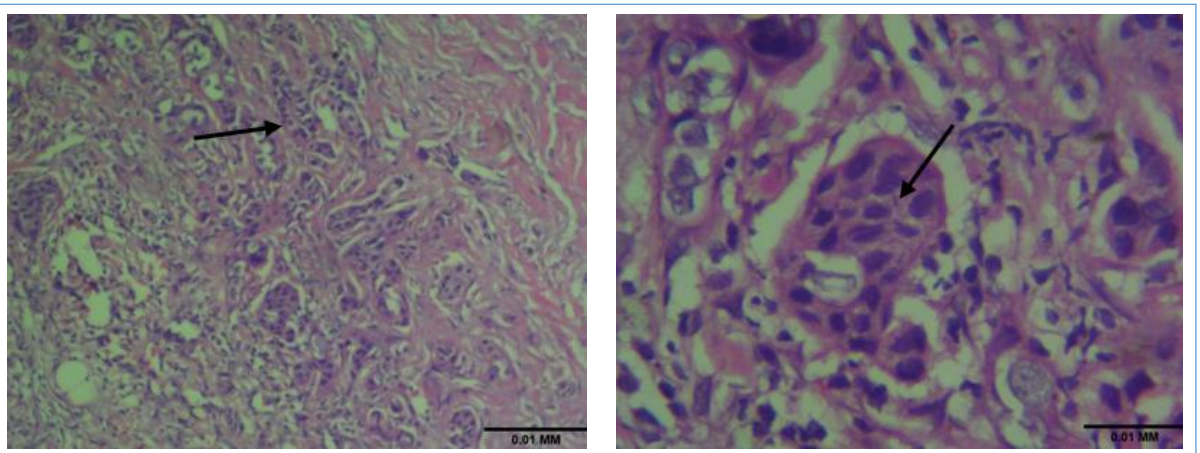


X100 X400

Figure 1. H&E-stained micrographs of a benign breast tissue section at ×100 and ×400 magnifications. The arrows indicate normal or hyperplastic epithelial cells lining the ducts and lobules.

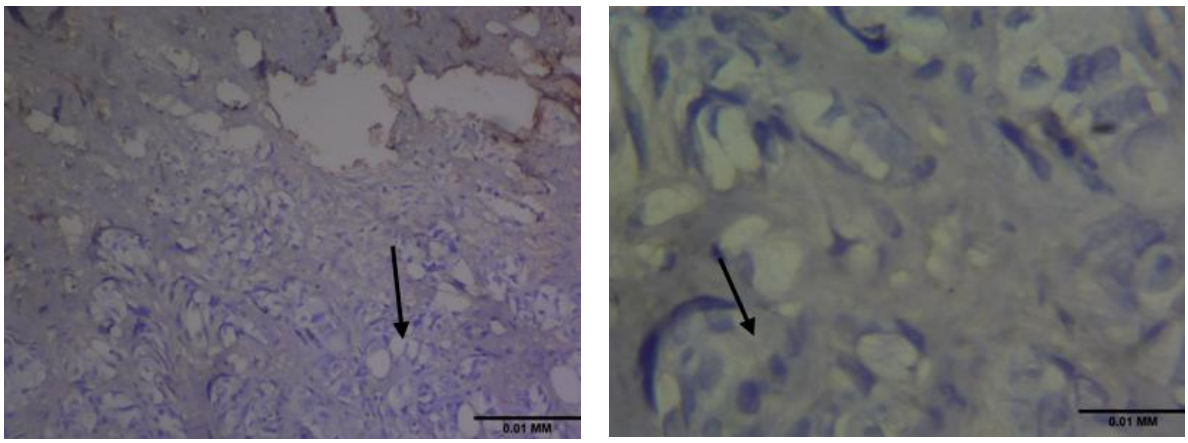


X100 X400

Figure 2. H&E-stained micrographs of malignant breast tissue sections at ×100 and ×400 magnifications. The arrows point to malignant epithelial cells showing features such as nuclear pleomorphism and disrupted tissue architecture.

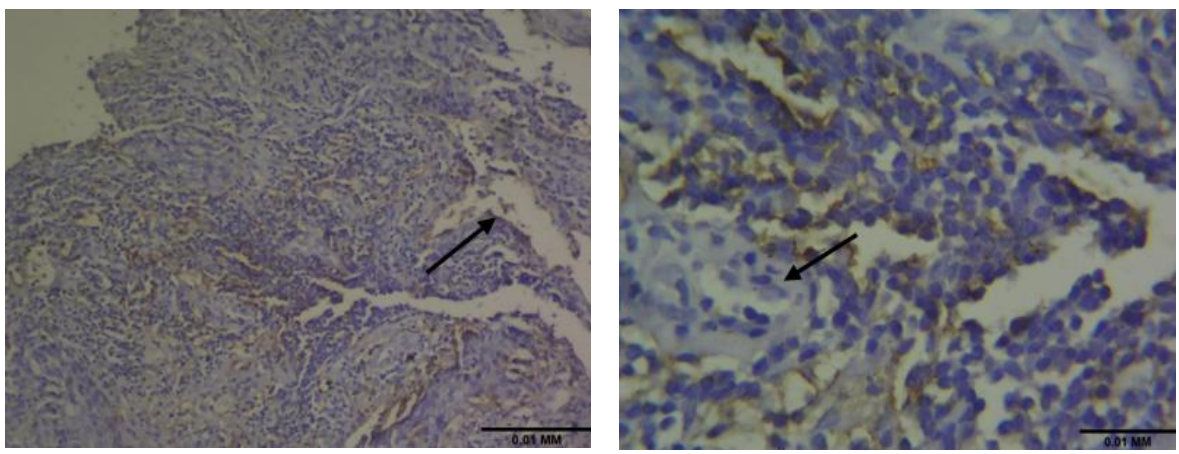
shows negative staining for PD-L1 in the majority of tumour cells, with only scattered cells exhibiting faint cytoplasmic staining (mild expression). Figure 4 shows a micrograph of immunohistochemically stained PD-L1 in malignant breast tissue sections at x100 and x400 magnifications. The section exhibits moderate staining intensity with mild dysplasia, which is indicative of hyperchromasia.

Figure 5 is an H&E-stained micrograph of benign cervical cancer tissue sections at x100 and x400 magnification, showing the general tissue structure with purple nuclei and pink cytoplasm, with well-defined structures. The basal layer, composed of small, cuboidal, or columnar cells, is observed at the bottom of the epithelium. The basement membrane separating the epithelium and stroma is present, as are the koilocytes. Figure 6 is an H&E-stained micrograph of malignant cervical cancer tissue sections at x100 and x400 magnification, showing severe dysplasia, hyperchromasia, and invasion of cells beyond the epithelium, indicating carcinoma in situ. Figure 7 shows a micrograph of immunohistochemically stained PD-L1 in benign cervical cancer tissue sections at x100 and x400 magnifications. The section shows mild staining intensity, suggesting the upregulation of PD-L1 expression in the tissue. Figure 8 shows a micrograph of immunohistochemically stained PD-L1 in malignant cervical tissue sections at x100 and x400 magnifications. The section displays moderate staining intensity with mild dysplasia and multiple tumours.



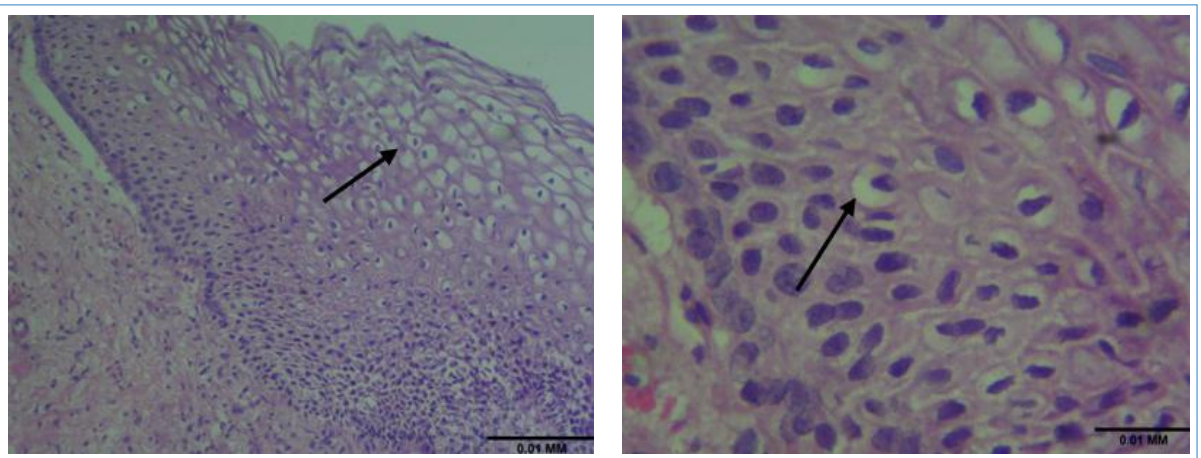
X100 X400

Figure 3. Immunohistochemically stained micrographs of a benign breast tissue section at ×100 and ×400 magnifications, showing PD-L1 expression. The arrows indicate weak or absent PD-L1 staining in the epithelial cells.



X100 X400

Figure 4. Immunohistochemically stained micrographs of malignant breast tissue sections at ×100 and ×400 magnifications. The arrows highlight malignant epithelial cells exhibiting positive PD-L1 expression.



X100 X400

Figure 5. H&E-stained micrographs of a benign cervical tissue section at ×100 and ×400 magnifications. The arrows highlight normal, non-dysplastic epithelial cells with uniform nuclei and organized tissue architecture.

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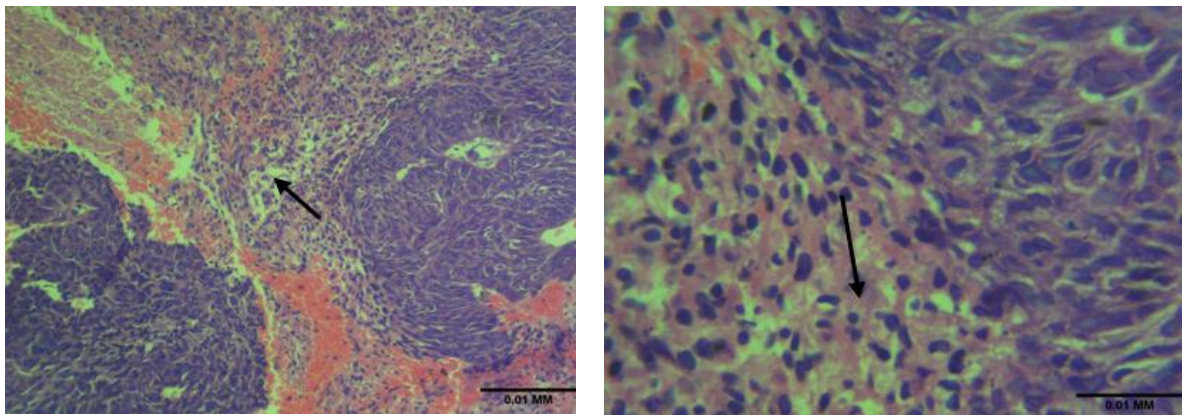
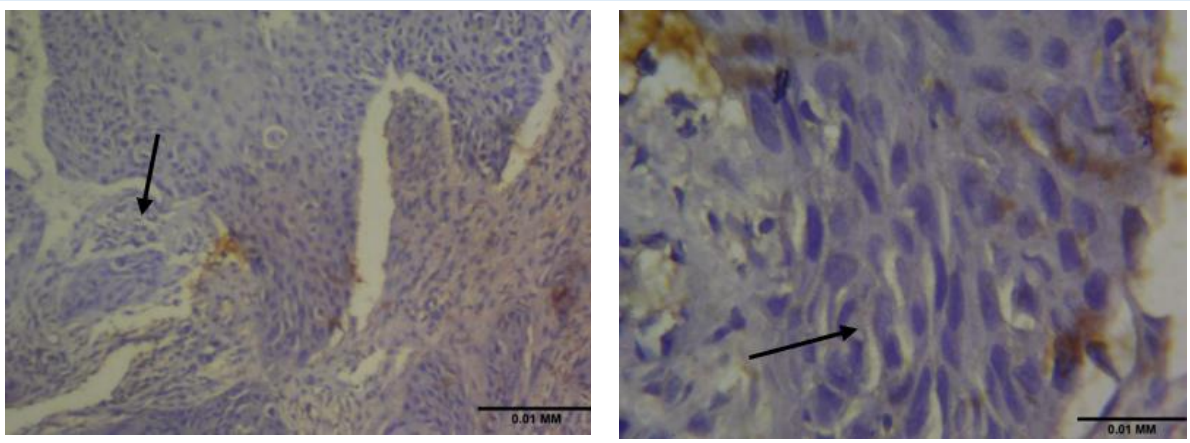


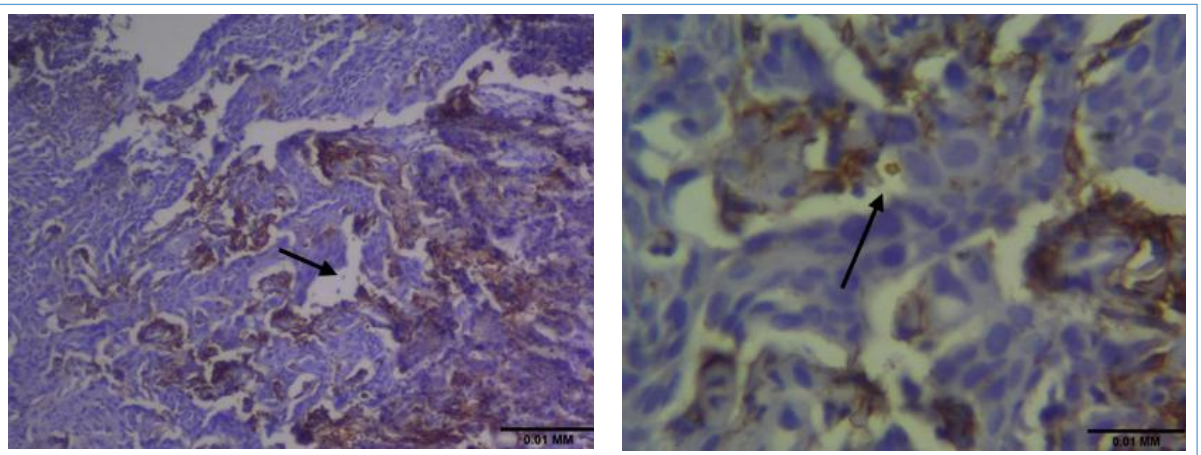
X100 X400

Figure 6. H&E-stained micrographs of malignant cervical tissue sections at ×100 and ×400 magnifications. The arrows highlight malignant epithelial cells characterized by nuclear pleomorphism, hyperchromasia, and disrupted tissue organization.



X100 X400

Figure 7. Micrograph of a benign cervical tissue section immunohistochemically stained with PD-L1 at ×100 and ×400 magnifications. The arrows highlight benign epithelial cells exhibiting weak or focal PD-L1 expression, indicating minimal immunoreactivity.



X100 X400

Figure 8. Micrographs of malignant cervical tissue sections subjected to immunohistochemical staining for PD-L1 at ×100 and ×400 magnifications. The arrows highlight malignant epithelial cells with strong, membranous PD-L1 expression, indicating positive immunoreactivity in cancerous regions.

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Table 1. Semiquantitative expression of PD-L1 in breast lesions

Case	No of samples	Neg (-)	Mild (+)	Moderate (++)	Marked (+++)	Mean Percentage Reactivity	p-value
Benign	20	18	2	-	-	14.8%	0.015*
Malignant	20	4	9	7	-	46.4%	

Table 2: Semiquantitative expression of PD-L1 in cervical cancer

Case	No of samples	Neg (-)	Mild (+)	Moderate (++)	Marked (+++)	Mean Percentage Reactivity	p-value
Benign	20	15	5	-	-	18.4%	0.010*
Malignant	20	3	2	13	2	71.3%	

Table 1 shows the semi-quantitative expression of PD-L1 in breast cancer. The results indicate that benign breast cancer has mild (+) PD-L1 expression, whereas malignant breast cancer has mild (+) and moderate (++) PD-L1 expression. The mean percentage reactivity (MPR) of benign and malignant breast cancer was 14.8% and 46.4%, respectively. Table 2 shows the semi-quantitative expression of PD-L1 in cervical cancer. The results revealed that benign cervical cancer had only mild (+) PD-L1 expression, whereas malignant cervical cancer had mild (+), moderate (++) and marked (+++) PD-L1 expression. The mean percentage reactivity (MPR) of benign and malignant cervical cancer was 18.4% and 71.3%, respectively. The MPR was significantly higher in malignant cases compared to benign cases in breast and cervical cancers ($p < 0.05$).

DISCUSSION

In this study, the mean positivity rate of PD-L1 expression was greater in patients with malignant cervical cancer (71.3%) than in those with benign cervical cancer (18.4%). In contrast to this finding, Schellens et al. [13] reported 50% PD-L1 expression in cervical cancer cells, Balar et al. [14] reported 17% and 35% positive PD-L1 expression in cervical adenocarcinoma and squamous cell carcinoma (SCC). Meng et al. [15] reported PD-L1 expression in 68 out of 97 cervical cancer cases (70.1%), and Chen et al. [16] reported PD-L1 expression in 61 out of 95 cases (64.2%). The variations in these results could be attributed to the use of different methods for determining PD-L1 expression (mRNA expression by IHC, tissue microarray, paraffin tissue blocks, and various monoclonal kits used in IHC staining) and variations in scoring systems [17]. Increased expression of PD-L1 on various solid tumours, such as those in cervical cancer, may enable the tumour to evade the immune system. While PD-L1 is rarely observed in normal cervical tissue, at least 50% of cervical cancer cases express PD-L1 [18]. Therefore, targeting PD-L1 in cervical cancer treatment may be crucial for identifying patients who will respond better to immunotherapies that target anti-PD-1/PD-L1.

The semi-qualitative analysis revealed that benign cervical cancer had only mild (+) PD-L1 expression, whereas malignant cervical cancer had mild (+), moderate (++), and marked (+++) PD-L1 expression. Consistent with this study, Saglam et al. [19] reported that PD-L1 expression is higher in inflammatory cells infiltrating tumours than in endometrial and ovarian adenocarcinomas. This may be due to increased PD-L1 expression in the tumour microenvironment through various mechanisms, leading to abnormal activation of the PD-L1/PD-L1 signalling pathway. This, in turn, results in T-cell death and inhibits T-cell proliferation and differentiation through multiple mechanisms, facilitating tumour immune evasion [20]. In addition to acting as a ligand for PD-1, PD-L1 can also function as a receptor for transmitting negative signals, preventing tumour cells from undergoing Fas-FasL-mediated apoptosis and protecting them from being lysed by cytotoxic T lymphocytes [19]. Increased PD-L1 expression in tumour cells is linked to lower disease-free and disease-specific survival rates in patients with squamous cell carcinoma of the cervix [18].

The results of this study revealed that PD-L1 expression was higher in malignant breast cancer patients (46.4%) than in benign patients (14.8%). Elevated PD-L1 expression in malignant breast cancer indicates its potential role in tumour immune evasion and disease progression. Previous research by Ghebeh et al. [21] revealed PD-L1 expression in 22 (50%) of 44 tumours evaluated, with 15 (34%) showing expression restricted to the tumour epithelium and 18 (41%) in tumour-infiltrating lymphocytes [21]. Another study investigating PD-L1 expression (defined as cell-

surface membrane staining > 5%) in breast cancer revealed higher levels in TNBC patients than in non-TNBC patients ($p < 0.001$) [22]. Soliman et al. [23] demonstrated through flow cytometry that PD-L1 expression was higher in basal-type breast cancer than in luminal-type breast cancer. Ghebeh et al. [24] also reported that PD-L1 expression is associated with tumour characteristics such as high grade, oestrogen receptor negativity, and increased T-regulatory (T-reg) expression. In a study by Morgan et al. [25], PD-L1 expression was found to be higher in tumour cells of medullary-type breast cancer than in those of TNBC. Criscitiello and Curigliano [26] reported no significant association between PD-L1 expression and the response to immunotherapy in breast cancer patients. PD-L1 expression has been observed in a significant proportion of breast cancer cases, ranging from 10–30%, with variability based on tumour stage and molecular subtype [27]. Compared with luminal subtypes, tumours with higher histological grades, including grade 3 tumours, triple-negative breast cancer, and other nonluminal subtypes, have higher PD-L1 expression [28]. Muenst et al. [29] reported positive staining (both membranous and cytoplasmic) for PD-L1 in 152 out of 650 (23.38%) breast cancer patients, with a significant correlation between PD-L1 positivity and several clinicopathological parameters (large tumour size, lymph node involvement, tumour grade, ER negativity, HER2-positive tumours, and high Ki67 index) [29]. Consensus on sampling, staining, and scoring procedures for detecting PD-L1 protein expression using IHC is needed to improve the reproducibility of studies and confirm interstudy results.

The results of this study revealed mild immunoreactivity in breast cancer, indicating low levels of PD-L1 expression. The subtle staining pattern suggests a slight upregulation of PD-L1 expression in the tissue, potentially reflecting an immune response. Mild IHC staining implies a poor response to anti-PD-1/PD-L1 immunotherapies, while the observed PD-L1 expression levels correlate with the aggressiveness of breast cancer [27]. Additionally, PD-L1 expression was greater in malignant cervical samples than in malignant breast samples, suggesting a potentially greater role of the PD-L1 pathway in cervical cancer progression. This finding is consistent with those of previous studies [26,30]. These differences in PD-L1 expression patterns may impact treatment strategies and the development of targeted therapies for each type of cancer. The association of PD-L1 expression with prognosis varies between cervical and breast cancers. The disparity in PD-L1 expression levels between the two types of cancer could indicate variations in immune responses and the tumour microenvironment.

Conclusion

PD-L1 expression was more pronounced in cervical cancer than in breast cancer. The elevated levels of PD-L1 in cervical cancer suggest that this type of cancer may be more responsive to immunotherapeutic interventions targeting the PD-L1 pathway than breast cancer. Recognising these differences is crucial for tailoring treatment plans and implementing personalised medicine strategies for each specific cancer type.

DECLARATIONS

Ethical consideration

Ethical approval for this study was obtained from the Health Research Ethics Committee, College of Medicine and Health Sciences, Afe Babalola University, Ado-Ekiti, Ekiti State, Nigeria. Informed consent was obtained from each participant in the study. All experiments in this study were performed in accordance with the Declaration of Helsinki.

Consent to publish

All authors agreed on the content of the final paper.

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None

Competing Interest

The authors declare no conflict of interest

Author contribution

VOE conceptualised the manuscript. The methodology was developed by CCE, and MAH and VOE conducted formal analyses and visualisations. Resources were contributed by all the authors. EAO wrote the original draft while all the authors reviewed and edited it. Supervision was provided by VOE. EAO was responsible for coordinating with the coauthors and submitting the article. All the authors read and approved the final manuscript.

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None

Availability of data

Data is available upon request to the corresponding author

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