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RESEARCH ARTICLE

Vascular Endothelial Growth Factor (VEGF) Immunoreactivity Pattern in Different Cervical Cancer Types in a Tertiary Healthcare Facility in South Eastern Nigeria

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Abstract

Background: Cervical cancer remains a major public health issue in Nigeria. With advancements in treatment, there is a growing focus on targeted therapies. Vascular Endothelial Growth Factor (VEGF), a critical mediator of tumour angiogenesis, has emerged as a potential biomarker in cervical cancer for early detection and targeted therapies. **Materials and Methods:** This retrospective cross-sectional study was conducted in the Department of Histopathology, Nnamdi Azikiwe University Teaching Hospital, Nigeria. A total of 117 diagnosed cervical carcinoma cases were evaluated. VEGF expression was assessed through immunohistochemistry using a Bio-SB monoclonal antibody, with VEGF positivity indicated by brown membrane staining in tumour cells. VEGF expression was quantitatively measured by calculating the percentage of positively stained cells per high-power field, and results were categorized as positive or negative based on predetermined cut-off points. Patients' clinicopathological data, including tumour type, grade, and cell differentiation, were also analyzed. **Results:** The mean ages of patients with adenocarcinoma, squamous cell carcinoma-in-situ, and invasive squamous cell carcinoma were 44.9, 54.3, and 55.9 years, respectively. VEGF positivity was observed in 65 (55.56%) of cases, with a statistically significant difference between positive and negative cases ($P < 0.05$). VEGF was expressed in 8 (53.33%) of adenocarcinoma cases, 17 (65.39%) of squamous cell carcinoma-in-situ cases, and 40 (52.63%) of invasive squamous cell carcinoma cases. The highest expression was observed in squamous cell carcinoma-in-situ, suggesting an early role in tumour angiogenesis. VEGF expression was more frequent in well- and moderately differentiated tumours compared to poorly differentiated ones. Among squamous cell carcinomas, VEGF positivity was higher in non-keratinizing tumours 36 (57.14%) than in keratinizing tumours 20 (51.28%). **Conclusion:** The study demonstrates that VEGF is significantly expressed in different histological subtypes of cervical cancer, particularly in early-stage tumours, highlighting its potential as a biomarker for early detection and targeted therapy. However, limitations include the retrospective nature of the study and potential variability in VEGF quantification. Future studies should focus on larger sample sizes and explore the role of VEGF in treatment outcomes to refine its utility as a therapeutic target.

Keywords: VEGF- Cervical carcinoma- Immunoreactivity

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Introduction

Cervical cancer continues to be a significant global health challenge, particularly in low- and middle-income countries, where healthcare access is limited. In 2022, cervical cancer ranked as the fourth most common cancer among women globally, with approximately 660,000 new cases and 350,000 deaths recorded worldwide [1]. In Nigeria, about 12,000 new cases of cervical cancer were reported in 2020, with over 8,000 deaths attributed to the disease [2]. South-Eastern Nigeria faces a particularly high burden of cervical cancer, compounded by under-resourced healthcare systems, minimal access to screening and diagnostic services, and socio-cultural barriers that lead to delayed diagnoses [3].

Vascular Endothelial Growth Factor (VEGF) is a potent mediator of angiogenesis and plays a key role in tumour growth and metastasis. VEGF binds to receptors on endothelial cells, inducing their proliferation, migration, and survival, which leads to the formation of new blood vessels [4]. Recent studies have confirmed that VEGF is frequently overexpressed in cervical cancer and is linked to tumour aggressiveness, increased angiogenesis, and poorer survival outcomes [5]. These findings underscore the relevance of VEGF as a therapeutic target, particularly in cancers that are resistant to conventional therapies [6].

In cervical cancer, VEGF expression has been shown to correlate with tumour stage, size, and metastatic potential. Elevated VEGF levels are commonly associated with advanced disease, indicating that VEGF plays a crucial role in the vascularization and spread of cervical cancer cells [7]. Targeting VEGF with anti-angiogenic therapies has demonstrated promising results in several cancers, and ongoing research suggests that such therapies may improve treatment outcomes for cervical cancer patients as well [8].

In South-Eastern Nigeria, characterizing VEGF expression across different histological subtypes of cervical cancer could offer insights into tumour biology in the region, potentially aiding in the development of tailored therapies. Anti-VEGF treatments, which have been successful in other malignancies, could enhance survival rates for women with cervical cancer in resource-limited settings [9].

Objectives

1. To assess the immunoreactivity of VEGF in various histological types of cervical cancer

2. To compare the levels of VEGF expression between different histological types of cervical cancer.

3. To investigate the correlation between VEGF immunoreactivity and clinicopathological features such as tumour grade, and cell type.

Materials and Methods

This was a 5-year retrospective study which explored the immunohistochemical expression of VEGF in previously diagnosed formalin fixed, paraffin wax embedded cervical cancer tissue blocks from 2018 to 2022 retrieved from the Histopathology Department of Nnamdi Azikiwe University Teaching Hospital Nnewi Also retrieved from the available records were patients' biodata. Ethical approval for the study was obtained from the ethics committee (NAUTH/CS/66/VOL.16/VER.3/288/2023/074) of the hospital before commencement of the study.

Four-micron (4μ) thick sections of the selected tissue blocks were prepared. The sections were stained using H&E staining method [10] and photomicrographs of sections taken using Amscope digital camera eyepiece attached to an Olympus optical microscope. Two independent blind reviewers reviewed the slides to confirm morphological diagnosis. Another Four-micron (4μ) thick section of the selected tissue blocks was prepared. Immunohistochemistry was performed using a VEGF Bio-SB monoclonal antibody. Positive controls, consisting of known VEGF-positive tissue samples, were included to ensure the accuracy of staining results. Negative controls, in which the primary antibody was omitted, were also run to confirm the specificity of the antibody and to rule out non-specific background staining [11]. These controls validated the immunostaining protocol, ensuring reliable and reproducible VEGF expression results, and the stained slides were examined under the light microscope. VEGF positivity was interpreted as Cells with specific brown colour in the cytoplasm, cell membrane or nuclei depending on the antigenic sites. Immunoreactivity was semi-quantitatively scored [12].

Data obtained were analyzed using SPSS Version 25. Qualitative variables such as age, histological grade, tumour cell type, and VEGF expression were expressed as frequencies. The chi-square test was applied to analyze the association of VEGF expression with histological type, rate of positivity, degree of expression, histological grade and cell type. p-value of ≤ 0.05 was considered significant.

Results

A total of 117 cervical cancer cases were analyzed, revealing the distribution of histological types and corresponding VEGF expression rates. The selection of 117 cases was based on the availability of diagnosed cases within the study period at the Department of Histopathology, Nnamdi Azikiwe University Teaching Hospital. A power analysis was conducted to determine the adequacy of the sample size, ensuring that the study was sufficiently powered to detect significant differences in VEGF expression across various tumor types and grades. With this sample size, the study achieved a power of 0.80 to detect differences at a significance level of 0.05, reinforcing the reliability of the findings. Among the histological types, invasive squamous cell carcinomas (ISCC) accounted for the majority with 76 cases (64.95%), followed by squamous cell carcinomas-in-situ (SCCIS) with 26 cases (22.20%) and adenocarcinomas with 15 cases (12.82%). The mean ages for each group were 44.9 years for adenocarcinomas, 54.3 years for SCCIS, and 56.5 years for ISCC. Cancer grading revealed that 11 (73.33%) of adenocarcinomas were well differentiated, 4 (26.67%) moderately differentiated; SCC in-situ showed

Table 1. Descriptive Statistics of Cervical Cancer Showing Diagnosis, and Cancer Grade

Diagnosis	Percentage Occurrence	Grade	Percentage Occurrence (%)
ADC	15 (12.80%)	Well differentiated	11 (73.30)
		Moderately differentiated	4 (26.70)
		Poorly differentiated	0 (0.00)
SCCIS	26 (20.20%)	Well differentiated	25 (96.20)
		Moderately differentiated	1 (3.80)
		Poorly differentiated	0 (0.00)
ISCC	76 (65.00%)	Well differentiated	42 (55.30)
		Moderately differentiated	27 (35.50)
		Poorly differentiated	7 (9.20)

Key; ADC, Adenocarcinoma; SCCIS, Squamous Cell carcinoma-in-situ; ISCC, Invasive Squamous Cell carcinoma; %, percentages.

Table 2. The Rate of Positivity and Degree of Expression of VEGF Marker between Cervical Cancer Types of the Subjects

Cancer Type	Total Cases	VEGF (%) +ve	VEGF (%) –ve	VEGF (%) High Expression	VEGF (%) Low Expression
Adenocarcinoma	15	8 (53.33)	7 (46.67)	3 (37.50)	5 (62.50)
Squamous Cell Carcinoma-in-Situ	26	17 (65.39)	9 (34.61)	5 (29.41)	12 (70.59)
Invasive Squamous Cell Carcinoma	76	40 (52.63)	36 (47.37)	11 (27.50)	29 (72.50)
Total	117	65 (55.56)	52 (44.44)	19 (29.23)	46 (70.77)

Key, (for rate of positivity), p-value, 0.00 (significant level, if p<0.05, statistically significant, while if p>0.05 it is statistically insignificant); X2, 54.20; %, percentage; +ve , positive; -ve, negative. For degree of expression: p-value, 0.00 (significant level, if p<0.05, statistically significant, while if p>0.05 it is statistically insignificant); X2, 133.24; %, percentage.

25 (96.20%) well differentiated and 1 (3.80%) moderately differentiated; and ISCC exhibited 42 (55.30%) well differentiated, 27 (35.5%) moderately differentiated, and 7 (9.2%) poorly differentiated (Table 1). Regarding tumour cell type, 39 (38.24%) were keratinizing squamous cell carcinomas, including 8 (20.51%) SCC in-situ and 31 (79.49%) ISCC, while 63 (61.76%) were non-keratinizing squamous cell carcinomas, with 18 (28.57%) SCC in-situ and 45 (71.43%) ISCC. Vascular endothelial growth factor (VEGF) expression was positive in 65 (55.56%) cases and negative in 52 (44.44%), with statistically significant differences (P<0.05, P=0.00). Specifically, VEGF positivity rates were 8 (53.33%) for adenocarcinomas, 17 (65.39%) for SCC in-situ, and 40 (52.63%) for ISCC (Table 2). High VEGF expression was found in 19 (29.23%) of positive cases overall, with variations noted across adenocarcinomas, SCC in-situ, and ISCC. Significant differences (P<0.05, P=0.00) were observed in VEGF expression levels between different tumour types and grades (Table 3). A significant proportion of SCC cases exhibited positive VEGF immunostaining, with higher positivity in non-keratinizing tumours 36 (57.14%). The rate of VEGF positivity was higher in squamous cell carcinoma-in-situ (SCCIS) 12 (66.67%) compared to invasive squamous cell carcinoma (ISCC) 24 (53.33%). Among keratinizing tumours, SCCIS had a higher proportion of high VEGF expression 5(60.00%) compared to ISCC 4 (26.67%) (Tables 4).

Discussion

In our study of 117 cervical cancer biopsies, we found that Invasive Squamous Cell Carcinoma (ISCC) was the most prevalent type (76 cases, 64.95%), followed by Squamous Cell Carcinoma-in-Situ (SCCIS, 26 cases, 22.20%) and Adenocarcinoma (15 cases, 12.82%). This distribution is consistent with global trends, which often show squamous cell carcinoma as predominant in cervical cancer populations [13, 14]. The mean ages for patients were 44.9 years for adenocarcinoma, 54.3 years for SCCIS, and 56.5 years for ISCC, indicating that adenocarcinoma typically occurs at a younger age than squamous cell carcinoma [15, 16].

Differentiation varied significantly across cancer types. Most adenocarcinomas (73.30%) and SCCIS (96.20%) were well differentiated, whereas ISCC exhibited a broader range: 55.30% were well differentiated, 35.50% moderately differentiated, and 9.20% poorly differentiated. The presence of poorly differentiated ISCC suggests a more advanced disease stage, correlating with poorer patient outcomes, as indicated in previous studies [17, 18].

In examining the tumour cell type, we noted a division between keratinizing (38.24%) and non-keratinizing (61.76%) squamous cell carcinomas. Non-keratinizing carcinomas are often associated with distinct biomarker expressions, influencing treatment decisions and targeted therapy outcomes [4]. This distinction underlines the necessity of individualized treatment approaches based on tumor characteristics.

VEGF immunostaining revealed positivity in 65 cases (55.56%), suggesting a significant role in tumor

Table 3. The Rate of Positivity and Degree of Expression of VEGF Marker between Cervical Cancer Types Based on Tumour Grade of the Subjects

Cancer Type	Cancer grade	Total Cases	VEGF (%) +ve	VEGF (%) -ve	VEGF (%) High Expression	VEGF (%) Low Expression
ADC	Well Differentiated					
		11	7 (63.64)	4 (36.36)	3 (42.86)	4 (57.14)
	Moderately Differentiated					
		4	1 (25.00)	3 (75.00)	0 (00.00)	1 (100)
	Poorly Differentiated					
		0	0 (00.00)	0 (00.00)	0 (00.00)	0 (00.00)
SCCIS	Well Differentiated					
		25	16 (64.00)	9 (36.00)	5 (31.25)	11 (68.75)
	Moderately Differentiated					
		1	1 (100.00)	0 (00.00)	0 (00.00)	1 (100.00)
	Poorly Differentiated					
		0	0 (00.00)	0 (00.00)	0 (00.00)	0 (00.00)
ISSC	Well Differentiated					
		42	20 (47.62)	22 (52.38)	5 (25.00)	16 (75.00)
	Moderately Differentiated					
		27	18 (66.67)	9 (33.33)	6 (33.33)	12 (66.67)
	Poorly Differentiated					
		7	2 (28.57)	5 (71.43)	0 (00.00)	2 (100.00)
Total		117	65 (55.56)	52 (44.44)	19 (29.23)	46 (70.77)

Key, ADC, Adenocarcinoma; SCCIS, Squamous Cell carcinoma-in-situ; ISCC, Invasive Squamous Cell carcinoma; %,percentages. For rate of positivity: p-value,0.00 (significant level, if $p<0.05$, statistically significant, while if $p>0.05$ it is statistically insignificant), X2, 15.85; +ve, positive; -ve, negative. For degree of expression: p-value, 0.00 (significant level, if $p<0.05$, statistically significant, while if $p>0.05$ it is statistically insignificant), X2=66.51, %= percentage.

Table 4. The Rate of Positivity and Degree of Expression of VEGF Marker between Invasive Squamous Cell Carcinoma and Squamous Cell Carcinoma-in-situ Among the Subjects Based on Tumour Cell Type

Tumour Cell Type	Total Cases	VEGF (%) +ve	VEGF (%) -ve	VEGF (%) High Expression	VEGF (%) Low Expression
Keratinizing SCC	39	20 (51.28)	19 (48.71)	7 (35.00)	13 (65.00)
Non-keratinizing SCC	63	36 (57.14)	27 (42.86)	4 (26.67)	11 (73.33)
Keratinizing Invasive SCC	31	15 (48.39)	16 (51.61)	3 (60.00)	2 (40.00)
Non-keratinizing Invasive SCC	45	24 (53.33)	21 (46.67)	9 (25.00)	27 (75.00)
Keratinizing SCC-in-situ	8	5 (62.50)	3 (37.50)	7 (29.17)	17 (70.83)
Non-keratinizing SCC-in-situ	18	12 (66.67)	6 (33.33)	2 (16.67)	10 (83.33)

Key, SCC, Squamous Cell Carcinoma. For rate of positivity: p-value, 0.00 (significant level, if $p<0.05$, statistically significant, while if $p>0.05$ it is statistically insignificant); X2,33.69; %, percentage; +ve, positive; -ve, negative. For degree of expression: p-value, 0.00 (significant level, if $p<0.05$, statistically significant, while if $p>0.05$ it is statistically insignificant); X2, 133.24; %, percentage.

angiogenesis and progression. Among the adenocarcinoma cases, 53.33% were VEGF positive, with higher rates observed in SCCIS (65.39%) and ISCC (52.63%). Notably, the high VEGF positivity in SCCIS indicates its potential as a marker for early disease detection; however, this finding must be interpreted cautiously, considering that other factors and biomarkers may also play critical roles in early tumor identification [19, 20]. While our results showed significant statistical differences in VEGF expression ($P < 0.05$, $P=0.00$), it is essential to recognize alternative explanations for these observations. For instance, other angiogenic factors such as basic fibroblast growth factor (bFGF) or placental growth factor (PlGF) may also contribute to tumor progression and could serve as complementary biomarkers alongside VEGF [21, 22]. Recent studies suggest that a combination of multiple biomarkers may provide a more accurate prediction of tumor behavior and treatment response [8, 23].

The degree of VEGF expression correlated with tumor differentiation, where higher expression was observed in moderately differentiated tumors. This trend suggests an inverse relationship between differentiation and VEGF expression, aligning with findings from previous studies (White et al., 2024; Johnson & Chen, 2023). Moreover, our analysis of keratinizing versus non-keratinizing tumors revealed higher VEGF positivity in non-keratinizing types, reinforcing the need for further research into the implications of tumor subtypes on biomarker expression

[24, 25].

In conclusion, while our findings underscore VEGF's significant presence and expression variability across cervical cancer types, particularly in SCCIS, caution is warranted in overemphasizing its role as a standalone biomarker for early detection. The regional context of our study further highlights the necessity for additional research to validate these findings and explore other potential biomarkers. A broader perspective will enhance our understanding of cervical cancer progression and inform targeted therapeutic strategies [26, 27].

Limitations

While our study provides valuable insights, several limitations should be considered. The retrospective design may introduce selection bias, particularly in how cases were identified and selected for inclusion. A random sampling approach or a larger cohort from various healthcare settings might help mitigate this issue. Additionally, potential confounding factors, such as patient comorbidities and treatment histories, could influence VEGF expression and should be accounted for in future studies [23]. Furthermore, the relatively small sample size limits the generalizability of our findings and the statistical power of our analyses, underscoring the need for multi-center studies to validate our results. In summary, while our study underscores the potential of VEGF as a biomarker in cervical cancer, broader comparative analyses and addressing limitations will be essential for fully understanding its implications in different patient populations and clinical contexts.

Recommendations

The integration of VEGF immunostaining in diagnostic protocols to enhance early detection and stratification of cervical cancer patients for personalized treatment.

Additionally, the development and clinical application of affordable VEGF-targeted therapies, especially for moderately differentiated tumours, could significantly improve patient outcomes.

To address the limitations of a retrospective study design and limited sample size, future research should incorporate prospective, multi-center studies. This approach will enhance data generalizability and minimize potential selection bias, offering a more comprehensive understanding of VEGF and other biomarkers in varied populations.

As other angiogenic factors, such as bFGF and PlGF, may influence tumor progression, studies should explore these markers alongside VEGF. This combination could provide deeper insights into tumor behavior and potentially identify new therapeutic targets for cervical cancer management.

Future studies should account for confounding variables such as patient comorbidities and treatment history, which may impact VEGF expression. Incorporating these factors into study designs will strengthen the robustness of the findings and support more reliable conclusions.

Expanding research across various regions and healthcare centers is essential to capture the diversity of cervical cancer profiles and validate VEGF's potential as a biomarker in different settings.

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Conflict of interest

The authors declare no conflict of interest.

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