Original Article

Analysis of the Histopathological Characteristics and Expression of RIPK1 and NF- κB in Cervical Cancer in Kumasi, Ghana

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Received: 08-Aug-2024;
Revision: 05-Feb-2025;
Accepted: 25-Feb-2025;
Published: 26-Apr-2025

ABSTRACT

Background: Cervical cancer is the second most common cancer in Kumasi, Ghana. The fact that survival rates are low, despite the advances made in clinical management necessitates exploration of alternatives to improve survival. **Aim:** This study reviews the histopathological and molecular characteristics of cervical cancer in relation to Receptor Interacting Protein Kinase 1 (RIPK1) and Nuclear Factor kappa B (NF-κB), which are involved in the regulation of inflammation, cell death and cell survival. **Materials and Methods:** The study reviewed 135 consecutive cases diagnosed from January 2015 to December 2016 in our centre. Clinicodemographic data were abstracted and suitable formalin fixed paraffin embedded (FFPE) tissue blocks were selected for tissue microarray construction and subsequent immunohistochemical assessment of RIPK1 and NF-κB expression. A statistical analysis of the data was done using SPSS version 26. **Results:** The mean age of the cases was 58.93 years with a standard deviation of 17.88. The histological type of most (96.3%) of the cases was the Squamous cell carcinoma (SCC). Majority (49.63%) of the cases were of histological grade 3, followed by grade 2 with 33.32% and grade 1 with 17.04% of cases. Both RIPK1 and NF-κB were highly expressed (56.6% and 69.3%, respectively) among the case. RIPK1 expression was significantly associated with NF-κB expression ($P = 0.001$). **Conclusion:** The significant co-expression of RIPK1 and NF-κB in the high-grade carcinomas suggest they are active in signalling pathways that supress apoptosis and enhance survival and/or proliferation.

KEYWORDS: *Cervical carcinoma, clinicopathologic features, immunohistochemistry*

INTRODUCTION

Cervical cancer is the second most common cancer in Kumasi, Ghana.[1] It has been an important health challenge for women over the decades, ranking as the fourth most diagnosed cancer, and fourth leading cause of cancer-related deaths in women on the global front. The 2020 Global Cancer Statistics indicates that there were an estimated 604,000 new cervical cancer cases globally, with an accompanying mortality of 342,000 women (2). Countries in Sub-Saharan Africa, as well as other low-and middle-income countries bear the highest share of the global cervical cancer burden. Sub-Saharan Africa currently has the highest rates of incidence and mortality, with figures on incidence up to 10 times that of high-income countries, and mortality rates as high as 18 times that of high-income countries.[2]

While perhaps, poverty, and the persistence of notable risk factors including infection with high-risk human papilloma virus (HPV) may account for the higher rates of incidence and mortality in low-income countries,[3] administration of effective cervical screening and vaccination programs have proven to be critically important in the fight toward the elimination of cervical

Access this article online

Quick Response Code:

Website: www.njcponline.com

DOI: 10.4103/njcp.njcp_520_24

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How to cite this article: Duduyemi BM, Addae EK, Bedu-Addo K, Atta Manu E, Ngongou FR. Analysis of the histopathological characteristics and expression of RIPK1 and NF- κB in cervical cancer in Kumasi, Ghana. Niger J Clin Pract 2025;28:496-501.

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cancer. This became apparent from the dynamics in incidence and mortality observed in most parts of Europe, the Americas, Oceania and Asia.[2,4-6] Despite the glaring importance of screening and vaccination, it is sad to note that national screening and vaccination programs are either non-existent or has a woefully low coverage in Ghana and other low- and middle-income countries.[4,7]

Consequent to the low screening, women especially from these low-and-middle income countries are predominantly diagnosed with cervical cancer at a later stage.[8] Consistent with this, a study on cases from the two national oncology centres in Ghana revealed that the majority (47.5%) of cases presented with a stage III disease at diagnosis.[9] In accordance with the National Comprehensive Cancer Network guidelines, treatment/management of majority of these cases would therefore be effected with concurrent chemoradiotherapy, using platinum-based chemotherapeutics.[10] Despite the success realized in the use of concurrent chemoradiotherapy, cervical cancer is still regarded as a relatively chemoresistant form of cancer. Response is usually variable and short-lived, with as much as 40% of patients experiencing relapses.[11]

This gap in treatment success has necessitated the need to explore alternative treatment modalities, through a thorough understanding of the biological characteristics. This would lead to the elucidation of altered signalling pathways, which could be of prognostic or targeted therapeutic importance. Already, a number of studies have been conducted in this regard, with the identification of some potential markers, leading to some clinical trials.[12,13] Indeed, the potential of targeted therapy, stemming from an improved understanding of the molecular alterations of cervical cancer has been reaffirmed, following the accelerated approval of an immunotherapeutic which is based on the programmed-death ligand 1 (PDL1) expression.[14] Conspicuously missing from the efforts in advancing knowledge and identification of important markers are cases from underrepresented groups in low- and middle-income countries, who bear the greatest share of the global cervical cancer burden.

Although both proteins have been implicated in cancers, their actual roles and mechanisms of actions have largely been unexplored, and currently no study has assessed their expression profiles and significance in the pathobiology of cervical cancer in Africa. This study therefore aimed to explore both the histologic and molecular characteristics of cervical cancer cases from Ghanaian women, focusing on the expression and probable effects of Receptor Interacting Protein Kinase 1 (RIPK1) and Nuclear Factor kappa B (NF-κB). Under physiological states, RIPK1, acting through NF-κB activation can regulate important cellular process, principal of which include limiting apoptosis or inducing necroptosis in a pro-survival or pro-death state respectively.[15]

Materials and Methods

Ethical considerations and samples

The study involved patient-derived tissues obtained from women visiting the Komfo Anokye Teaching Hospital (KATH), Kumasi, Ghana, and preserved in the form of formalin-fixed paraffin-embedded (FFPE) tissue blocks at the Department of Pathology, KATH. The FFPE blocks were obtained, and corresponding patient clinicodemographic data were abstracted from hospital records at the department of Pathology, KATH, following approval from the research and development unit, KATH. The study was subsequently carried out at the department of Pathology, Kwame Nkrumah University of Science and Technology (KNUST) under the ethical approval (CHRPE/AP/314/20) obtained from the Committee on Human Research Publication and Ethics.

The study assessed all consecutive cervical cases received at the department of Pathology, KATH, within a two-year period, from January 2015 to December 2016. Of the 230 malignant cases diagnosed over the period, 135 cases were selected for tissue microarray (TMA) construction and laboratory analysis based on availability of corresponding FFPE blocks, Haematoxylin and Eosin (HandE) slides and adequate clinicodemographic data. Where necessary, new H and E slides were prepared from available FFPE blocks. Here, 3 μm H and E slides were prepared following standard procedures from microtomy, through deparaffinization in xylene, rehydration in decreasing grades of alcohol solution, incubation in haematoxylin and then eosin, and dehydration in increasing grades of alcohol solution before being mounted for microscopic assessment.

Tissue microarray construction

All H and E slides were subsequently reviewed by a pathologist (BDM) using a Leica DM 200 LED microscope fitted with a digital imaging system, and tumour foci were marked out. Guided by the marked-out regions on the H and E slides, cylindrical tumour cores measuring 1 mm in diameter were obtained from the corresponding FFPE blocks and introduced into predrilled wells in a TMA recipient block using an automated TMA machine (TMA Master by 3DHISTECH).

Immunohistochemistry

Immunohistochemistry was performed according to standard procedures, as previously outlined.[16] Briefly, 3 μm-thick sections were made from the TMA blocks using a semi-automated rotary microtome. The sections were placed on Super Frosted Plus slides and deparaffinized

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using xylene. They were then rehydrated with graded ethanol solutions, using tris buffered saline as diluent, and washed in distilled water. Following rehydration, the TMA sections were incubated in citrus buffer at a pH of 6 in a pressure cooker for 10 minutes for antigen retrieval. Inhibition of background staining and non-specific antibody binding were achieved by incubating the sections in a 3% hydrogen peroxide—methanol solution and casein solution respectively. Next, the sections were incubated in primary antibodies specific for either RIPK1 or NF-κB, according to the manufacturers' specifications. They were then incubated in a secondary antibody conjugated with horseradish peroxidase and developed in 3,3-diaminobenzidine tetrahydrochloride before counterstaining with haematoxylin.

The immunohistochemistry slides were reviewed by a pathologist for positively – and negative stained cores among the sectioned tissue microarray for the antibodies of interest. Positive and negative scores were assigned to individual cases following standard reporting procedures.

Data analysis

Data on the immunohistochemistry scores, along with clinicodemographic details were analysed using SPSS version 26. The Chi-squared test of associations was computed to explore relationships between immunohistochemistry profiles of cases and their corresponding clinicodemographic characteristic. A *P* value less than 0.05 at the 95% confidence level was considered a significant statistic.

Results

A total of 135 suitable cases formed the study population for TMA construction and immunohistochemistry assessment.

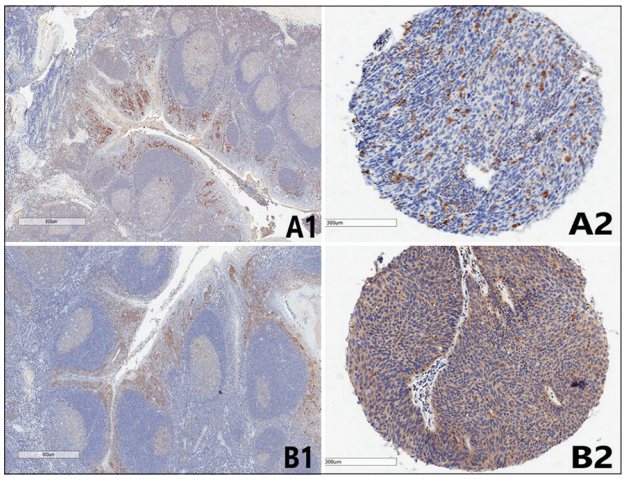

Figure 1: Photomicrographs showing negative controls and positive cases for the assessed biomarkers. A1 and B1 show negative controls for RIPK1 and NF-κB, respectively. A2 and B2 show positive cases for RIPK1 and NF-κB, respectively

Clinicodemographic characteristics

The ages of the cases ranged from 31 years to 115 years, with a mean of 58.9 years and a standard deviation of 17.88 years. Cases in the "50–59" year bracket therefore formed the modal age group. The cases were almost entirely (96.3%) of the Squamous cell carcinoma histological type. The distribution of cases among the various histological grades showed an increase from Grade 1 (17.04%) through Grade 2 (33.33%) to Grade 3 (49.63%). Table 1 below details the clinicodemographic characteristics of the cases.

Expression of RIPK1 and NF-*κB*

Few cases were lost to sectioning of the TMA for immunohistochemistry. In all instances however, the available cases can confidently be assumed as representative of the study population. A total of 122 cases were assessed for the expression of RIPK1. The majority (56.6%) of these overexpressed RIPK1. In a similar fashion, 88 (69.3%) of 127 cases

Table 1: Clinicodemographic characteristics of cases

Clinicodemographic characteristic	Mean	Standard Deviation
Age	58.9	17.88
	Frequency	**Percent**
Age groupings		
30–39 years	27	20.0
40–49 years	17	12.6
50–59 years	36	26.7
60–69 years	19	14.1
70 years and older	36	26.7
Total	135	100
Histological type		
Adenocarcinoma	5	3.7
Squamous cell carcinoma (SCC)	130	96.3
Total	135	100
Histological grade		
Grade 1	23	17.04
Grade 2	45	33.32
Grade 3	67	49.63
Total	135	100

Table 2: Expression profiles of RIPK1 and NF-κB among the cases

Marker	Frequency	Percent
RIPK1		
Positive	69	56.6
Negative	53	43.4
Total	122	100
NF-kB		
Positive	88	69.3
Negative	39	30.7
Total	127	100

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Table 3: Associations between RIPK1 and NF-κB and clinicodemographic characteristics

	RIPK1		
	% Positive within group	Chi-squared	*P*
NF-kB		12.58	0.001
Positive	67.1		
Negative	32.4		
Age groupings		9.04	0.06
30–39 years	55.6		
40–49 years	36.4		
50–59 years	69.7		
60–69 years	75.0		
70 years and older	42.9		
Histological type		0.58	0.652
Adenocarcinoma	40.0		
Squamous cell carcinoma (SCC)	57.3		
Histological grade		1.59	0.451
Grade 1	70.6		
Grade 2	53.7		
Grade 3	54.7		

Table 4: Associations between NF-κB and clinicodemographic characteristics

	NF-kB		
	% Positive within group	Chi-squared	*P*
Age groupings		11.82	0.019
30–39 years	85.2		
40–49 years	33.3		
50–59 years	69.7		
60–69 years	78.9		
70 years and older	63.9		
Histological type		2.10	0.168
Adenocarcinoma	40.0		
Squamous cell carcinoma (SCC)	70.5		
Histological grade		1.14	0.566
Grade 1	77.8		
Grade 2	64.4		
Grade 3	70.3		

overexpressed NF-kB. Table 2 presents details of the immunohistochemistry assessment. Figure 1 also displays sample photomicrographs of positively stained cases for RIPK1 and NF-κB, as well as their negative controls.

Tests for association between markers and clinicodemographic characteristics

The Chi-Squared test for association was computed to determine relationships between RIPK1 and NF- κB, then between RIPK1 and the clinicopathological characteristics, and lastly, between NF- κB and the clinicopathological characteristics. RIPK1 expression was significantly associated with NF- κB expression. Similarly, NF- κB expression was statistically significant when considered with the age-groups. RIK1, however could not arrive at a statistical significance when compared with the age-groups, however that P value was close to the cut-off of a statistical significance. Tables 3 and 4 present details of the tests for associations.

Discussion

We present a comprehensive analysis of the clinicopathological characteristics of our cohort of cervical cancer cases. Consistent with previous studies[17,18] conducted on cervical cancer in the same institution, the mean age at diagnosis has not seen any appreciable change, hence, remaining at 58 years. This figure is like that observed among cervical cancer patients previously in Ghana and other low- and middle-income countries.[19-21] Nonetheless, our mean age at diagnosis is higher than is recorded in most developed countries, where national screening programs have been instituted, or at least, where screening is much more accessible to the population to facilitate early diagnosis. In such countries, the reported mean ages of cervical cancer patients fall below 55 years.[22,23] Considering that old age is significantly associated with reduced disease-free survival and therefore lower 5-year survival rates,[24] the late age at diagnosis undeniably contributes significantly to the high mortality rates observed in low – and middle – income countries.

The histopathological characteristics of cervical cancer have long been important in the diagnosis and management of this cancer. Although there are some contradictory reports on the prognostic significance of the histological types of cervical cancer presented by women, a large body of recently published literature has shown that the histological type is of prognostic relevance, with significant influences on disease recurrence and survival outcomes. In almost all instances where a prognostic significance was observed, Squamous cell carcinoma (SCC) was noted to confer better prognosis, as compared to Adenocarcinoma.[12,25-27] Although our study recorded a higher proportion (96.3%) of cases with the SCC histological type and may indicate a comparatively better prognosis, it is not reflective in conferring desirable survival outcomes in the population due to the fact that patients mostly present at later stages, with high-grade carcinomas. It is therefore not surprising, that majority (49.63%) of our cases presented with grade 3 tumours, followed by grade 2 tumours (33.32%). Similarly, other studies conducted in Ghana and elsewhere in Africa reaffirm this trend, where most cases are of stages II to IV, and mostly of grades 2 and 3.[18-21]

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Moving beyond the histopathological characteristics, this study delved into the molecular characteristics, by examining the expression of RIPK1 and NF-κB. RIPK1 is a multi-domain serine/threonine kinase protein that possesses a kinase domain, an intermediate domain, a RIP homotypic interaction motif (RHIM) domain and a death domain (15). With these different domains, RIPK1 can interact with numerous adaptors and effectors, and hence, is found at the crosstalk of several regulatory signalling pathways that principally concern inflammatory response, cell death and survival. RIPK1 can switch through these signalling pathways depending on its ubiquitylation, phosphorylation and cleavage status, since those dictate the downstream proteins, it is able to interact with.[28,29]

Currently, we are not aware of any study in Africa, which previously assessed the expression of RIPK1 in cervical cancer samples. Even in other cancers, literature on RIPK1 expression and prognostic significance is scant. A high proportion (56.6%) of our cases overexpressed RIPK1. RIPK1 expression was significantly (P = 0.001) associated with NF-κB expression, which was also highly expressed among our cohort. This significant association is not surprising, considering the fact that NF-κB is activated downstream of tumour necrosis factor (TNF) signalling by ubiquitinated RIPK1.[15,29] Along this pathway, NF-κB may lead to the transcription of genes that mediate inflammatory responses, repress apoptosis and/or enhance proliferation.[30] Although no statistical significances were reached between the histological grades and either of RIPK1 and NF-κB, it is reasonable to speculate that the actions of the two proteins are pro-survival and/or proliferative rather than pro-death. This is especially true, because the vast majority (49.3%) of the cases are grade 3 tumours, signifying active proliferation and likely, inhibited apoptosis.

Limitations

The study is limited in several respects. First, we were unable to access information on the HPV and pathological stages of the case. Additionally, we were unable to obtain follow-up data, hence could not make inferences based on patient survival. Other proteins associated with signalling pathways that involve RIPK1 and NF- κB ought to have been assessed, to make conclusive remarks on the roles played by both proteins in the pathophysiology of cervical cancer.

Conclusion

Although there has been a marked decline in incidence of cervical cancer in high-income countries, it continues to gain prominence in Ghana and other low- and middle-income countries, due to the lack of adequate screening and Human papilloma virus (HPV) vaccination programs in these countries. Considering this, most patients present for diagnoses late, when the disease has far advanced. The limitations recognized in the clinical management of these advanced cases necessitates improvements through a comprehensive understanding of the molecular characteristics of the disease. We therefore explored the expression profiles and plausible effects of RIPK1 and its downstream effector NF-κB in the pathophysiology of cervical cancer cases among Ghanaian women. In our cohort, RIPK1 and NF-κB appear to be more active in signalling pathways leading to repression of apoptosis, while promoting survival and proliferation.

Author contribution

BMD, conceptualized and designed the study. BMD, EKA, KBA, EAM and FRN were involved in data collection/acquisition and statistical analysis; All authors (BMD, EKA, KBA, EAM and FRN) were involved in the writing and revising the manuscript for intellectual content. All authors read, and approved the final manuscript and agreed to be accountable for all aspects of the work.

Ethical approval

The study was subsequently carried out at the Department of Pathology, Kwame Nkrumah University of Science and Technology (KNUST) under the ethical clearance (CHRPE/AP/314/20) obtained from the Committee on Human Research Publication and Ethics.

Informed consent

Written informed consent was not required for a retrospective design

Declaration of Helsinki

The study was conducted according to the ethical principles of Helsinki Declaration.

Availability of research data

Authors are available and ready to supply the data upon any requests through the corresponding author.

Acknowledgement

We acknowledge the support of Ashley Penton of Brigham and Women Hospital, Boston, MA, USA in the construction and sectioning of TMA blocks for IHC.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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