



P53 and Ki67 Expression by Cervical Cancers in Ile-Ife, Nigeria

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Authors' contributions

This work was carried out in collaboration between all authors. Author OOO designed the study, wrote the protocol, carried out the research and wrote the first draft of the manuscript. Author GOO supervised the research and viewed the slides. Author AOK viewed the slides and helped in proof reading the manuscript. Author AA performed the laboratory preparation of all the slides and author BJO also supervised the research and proofread the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Background: Cervical cancer is the second most common cause of cancer deaths in females in Nigeria. The aim of this study is to determine the percentage of cervical cancers in Ile-Ife that express the p53 and Ki-67 protein and to compare the expression of the proteins with the different histological types of the tumour.

Methods: We retrospectively reviewed our data of histological results over the last twenty years and retrieved all the diagnosed cases of cervical cancers over this period. The haematoxylin and

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eosin slides were reviewed to confirm the diagnosis and also to confirm the histological variants. Immunohistochemistry for p53 and Ki-67 was done on selected blocks.

Results: A total of 149 cervical cancer cases were evaluated by immunohistochemistry. The age range at presentation of cervical cancer was 20-95 years (mean 56.6 years). The large cell non-keratinizing variant was the most common histological variant with a percentage of 57.7% followed by the keratinizing variant with a percentage of 29.5%. The basaloid variant was the least common with a percentage of 0.7%. Of all the 149 cases, 59.7% were positive for Ki67 while 40.3% were negative. Sixty-one percent of the cases were positive for p53 while 38.3% were negative. There was no significant association between the histological variants of cervical cancer and age distribution. The association between p53 and Ki-67 and the different histological variants was not found to be statistically significant, although most cases that were positive for both proteins were found to be the large cell non-keratinizing variant.

Conclusion: The expression patterns of p53 and Ki-67 by cervical cancer cases evaluated in Ile-Ife is similar to those obtained in other African countries. The relationship between histological variants and age groups as well as that between p53 and Ki-67 with the different histological variants of cervical cancer were found to be statistically insignificant. More studies on expression of these proteins are needed to confirm their importance in cervical carcinogenesis and prognosis.

Keywords: Cervical cancer; immunohistochemistry; p53; Ki-67.

1. INTRODUCTION

Cervical cancer is the fourth most common cancer among women worldwide with an estimated 528, 000 new cases and 266, 000 deaths in 2012. About 87% of cancer deaths occur in the less developed countries. Worldwide, mortality rates of cervical cancer varies 18-fold between different regions of the world with rates ranging from less than 2 per 100,000 in Western Asia, Western Europe and Australia to more than 20 per 100,000 in melanasia(20.6), Middle(22.2) and Eastern (27.6) Africa [1].

Cervical cancer also ranks as the second most frequent cancer among women with an estimated 10,000 new cases of cervical cancer and 8,000 deaths due to the disease recorded among women yearly in Nigeria [2].

Developing countries bear much of the global burden and a high rate of mortality. As much as 90% of the total number of deaths from cervical cancer also occur in this part of the world [3]. Regional variation in the incidence of cervical cancer has been observed by some researchers [4].

TP53 gene is a tumour suppressor gene that codes for the p53 protein. The protein normally has a short half-life. A mutated *TP53* gene produces an abnormal protein that resists degradation with a consequent longer half-life which makes it detectable by

immunohistochemistry where it shows a nuclear staining pattern [5]. Muted *TP53* gene confers a worse prognosis on tumours that harbor it [6]. Varying levels of p53 expression by cervical carcinomas have been observed in different parts of the world. Researchers have found a positive correlation between p53 expression and higher tumour stage as well as a higher incidence of metastasis in cervical cancer [7].

The rates of proliferation of different tumours differ and this parameter could be a prognostic factor in cervical cancers. The rate of proliferation of cervical carcinoma can be measured with the use of a proliferative marker such as Ki-67. Ki-67 is a proliferation marker that is recognized to be a predictive factor for tumour development and is defined as a nuclear antigen (associated with hetero – and euchromatin) expressed during all active phases of cell cycle (G1, S, G2, M) except G0 and early G1 phase [8]. Ki-67 usually has a nuclear staining pattern and is usually positive in most tumours [9]. Ki-67 as a marker for proliferative index gives an idea of how rapid a tumour is dividing. Ki-67 also helps to predict tumour response to therapy as more rapidly dividing tumours generally respond better to therapy [10].

The prognostic value in cervical carcinoma is still controversial. While several studies have not demonstrated any relationship between ki-67 and prognosis in cervical cancer, others have suggested the importance of ki-67 for the evaluation cell kinetics in response to radiation

therapy [11]. Also early changes in ki-67 expression during radiotherapy may characterize subsequent metastasis and relapse [11].

This study aims at determining the level of expression of p53 and Ki-67 in cervical carcinomas. The study also aims at comparing the expression of these proteins to different histological variants of cervical cancer.

2. MATERIALS AND METHODS

This is a retrospective study of all cases of cervical cancer that were diagnosed in the department of Morbid Anatomy and Forensic Medicine at the Obafemi Awolowo University Teaching Hospital (OAUTH), Ile-Ife within a twenty year period (January 1991-December 2010). Purposeful sampling method was used. OAUTH is the only tertiary health centre in Ile-Ife, a sub-urban area with an estimated population of 186,856. It is located in the South-Western part of Nigeria.

The minimum sample size calculated is 113. This was obtained by using a prevalence rate of 7.7% for cervical cancer from a previous study in Nigeria [12]. The sample size was calculated using the formula $N = z^2 pq/d^2$ where N= Desired sample size, z=standard normal deviate at 50% confidence level (which is 1.96), p=prevalence of the disease, Q=1-p and d= absolute standard or precision usually set at 0.05.

The paraffin blocks of the available cases of cervical cancers diagnosed in the study period were retrieved. New sections from retrieved paraffin blocks were cut and stained with haematoxylin and eosin stains to confirm diagnosis. A total of 149 FFPE blocks were adequate for the study. An Immunohistochemical study was done by the indirect immunoperoxidase method on formalin fixed paraffin-embedded sections (FFPE).

Briefly 2-3 μ m thick sections of FFPE tissue blocks were made and mounted on a slide. The tissue section were deparaffinised by passing it through xylene and then rehydrated. The antigens were appropriately retrieved by heat retrieval method with the use of a pressure cooker. Endogenous peroxidase activity was blocked with 3% hydrogen peroxide. The tissues were incubated with the primary antibody, rinsed and then followed by the use of secondary detection system using diaminobenzene (DAB) as chromogen. Heamotoxylin was used as

counterstain and helped to locate nuclei of cells. The primary antibodies are antibodies specific to p53 and Ki-67.

The antibody used to detect p53 was DO7 (DAKO). DO7 detects both wild type and mutant p53. Colorectal cancer tissue known to be positive for p53 was used as positive control while negative control was omission of the primary antibody.

The quantitation of immunostaining for p53 was assessed as follows:

less than 5% of cells positive = negative;
5-24% cells positive = +1;
25-49% cells positive = +2;
50-75% cells positive = +3,
75-100% = +4

For Ki-67, immunohistochemical investigation was performed using Ki-67 antibodies (DAKO) and streptavidin-biotin method. The sections stained for Ki-67 proliferation index were assessed as nuclear staining and evaluated using scores from 0 to 3.

Less than 10% cells positive = Negative.
10-30% cells positive = +1
30-50% cells positive = +2
More than 50% cells positive = +3.

Inclusion criteria included blocks that were found and with representative histological sections. Also tissue blocks with ample tissue needed for immunohistochemistry were included in the study. Exclusion criteria included tissue blocks with inadequate tissue left for sectioning and cases with missing tissue blocks.

Data was analyzed using simple descriptive statistics. Chi-square test was used to measure associations with level of significance $p < 0.05$. The above analysis was done using SPSS version 17.0.

Ethical approval was obtained from the Research and Ethics committee of Obafemi Awolowo University Teaching Hospitals Complex, Ile-Ife, Nigeria.

3. RESULTS

One Hundred and forty-nine (149) cases of cervical cancer were used for the study. The age range at presentation was 20-95 years (Mean 56.6 years). The peak age incidence is 50-59

years with a frequency of 54 (36.2%) followed by 60-69 age range with a frequency of 34 (22.7%). Majority of cases of cervical cancer were between 40 to 69 years (75.7%). Most histological variants are also found in this age group (Table 1).

The commonest histological variant of cervical cancer was the large cell non-keratinizing variant with a frequency of 86 (57.7%). This was followed by the keratinizing variant with a frequency of 44 (29.5%). The adenocarcinomas and adenosquamous carcinomas had a frequencies of 5 (3.4%) each. The small cell non-keratinizing variant had a frequency of 3 (2%). The basaloid variant had the least frequency of 1 (0.7%).

Of the 149 cases, p53 immunohistochemistry was positive in 61.7% of cases. Of these, 26.2% showed +1 expression, 16.8% of the cases had +2 positivity while 12.6% had +3 positivity. Six percent of the cases had +4 positivity. 38.3% were negative for p53 expression. (Fig. 1 shows photomicrograph of a case stained with p53 antibody).

About 59.7% were positive for Ki67 while 40.3% were negative. 33.6% had ki-67 values of +1. 18% showed +2 positivity and 7.4% had +3 positivity. (Fig. 2 shows photomicrograph of a positive case for Ki67 staining).

For p53, the large cell non-keratinizing variant had the highest expression of +4 positivity as 5 cases of this variant expressed +4 positivity. The keratinizing variant had 3 cases with +4 positivity of p53. All the others variants of cervical cancer did not express this level of p53 positivity (Table 2).

Six cases of large cell non-keratinizing variant had +3 positivity of ki-67, while 4 cases of keratinizing variant had +3 positivity of ki-67. Just 1 case of adenocarcinoma had +3 positivity of ki-67. All the other variants did not show +3 positivity of ki-67.

Fifteen cases of large cell non-keratinizing variant had +2 positively while 10 cases of adenocarcinomas had +2 expression of ki-67. One case each of adenocarcinoma, adenosquamous carcinoma and verrucous carcinoma variants had +2 positivity. Close to half (43.2%) of the keratinizing variants were negative for ki-67 and 40.7% of the large cell non-keratinizing variant were negative for ki-67. (Table 3).

4. DISCUSSION

The relationship between aging and cancer development is unclear; however it is worthy to note that frequencies of specific cancers are age specific [13].

Analysis of data from this study revealed that the peak age of occurrence of cervical cancer was from 50-69 years having a frequency of 57%. This has a close relationship with the figures quoted by Gustafsson et al. [14] in his own study where he got a peak value of 50-70 years and also to the study by Koulibaly et al. [15]. The study by Koulibaly et al. [15] in Guinea revealed the peak age incidence of cervical carcinoma to be 50 years. The peaking of occurrence rates of cervical cancer at a certain age and downward trend at another age group may signal the existence of a susceptible subpopulation at risk. The susceptibility at this age group may be due to the long and variable duration required from

Table 1. Frequency of histological variants in different age groups

Age	ADEN	ADENSQ	BASALOID	CLEAR	KER	LCNK	SCNK	VERR	Total
20-29	0	1	0	0	0	3	0	0	4(2.7%)
30-39	1	0	0	0	2	12	0	0	15(10.1%)
40-49	0	2	0	0	7	16	0	0	25(16.8%)
50-59	3	2	0	1	23	23	1	1	54(36.2%)
60-69	0	0	0	0	9	22	2	1	34(22.8%)
70-79	1	0	1	1	2	9	0	1	15(10.1%)
80-89	0	0	0	0	0	1	0	0	1(0.7%)
90-99	0	0	0	0	1	0	0	0	1(0.7%)
Total	5(3.4%)	5(3.4%)	1(0.7%)	2(1.3%)	44(29.5%)	86(57.7%)	3(2%)	3(2%)	149(100%)

P value= 0.707

Keys to Tables 1, 2 and 3: ADEN- Adenocarcinoma, ADENSQ- Adenosquamous carcinoma, BASALOID- Basaloid carcinoma CLEAR- Clear cell carcinoma, KER- Keratinizing squamous cell carcinoma, LCNK- Large cell non-keratinizing squamous cell carcinoma, SCNK- Small cell non-keratinizing squamous cell carcinoma, VERR- Verrucous carcinoma

Table 2. Frequency of expression of p53 by different histological variants of cervical cancer

Histological variant	p53 expression					Total
	0	+1	+2	+3	+4	
ADEN	2	1	0	1	1	5(3.4%)
ADENSQ	3	1	1	0	0	5(3.4%)
BASALOID	0	1	0	0	0	1(0.7%)
CLEAR	0	1	1	0	0	2(1.3%)
KER	15	13	8	5	3	44(29.5%)
LCNK	33	21	14	13	5	86(57.7%)
SCNK	2	1	0	0	0	3(2%)
VERR	2	0	1	0	0	3(2%)
TOTAL	57(38.3%)	39(26.2%)	25(16.8%)	19(12.8%)	9(6%)	149(100%)

P value=0.974

Table 3. Frequency of expression of Ki-67 by different histological variants of cervical cancer

Histological variants	Ki-67 expression				Total
	0	+1	+2	+3	
ADEN	2	1	1	1	5(3.4%)
ADENSQ	0	4	1	0	5(3.4%)
BASALOID	0	1	0	0	1(0.7%)
CLEAR	0	2	0	0	2(1.3%)
KER	19	11	10	4	44(29.5%)
LCNK	35	30	15	6	86(57.7%)
SCNK	3	0	0	0	3(2%)
VERR	1	1	1	0	3(2%)
TOTAL	60(40.3%)	50(33.6%)	28(18.8%)	11(7.4%)	149(100%)

P value= 0.541

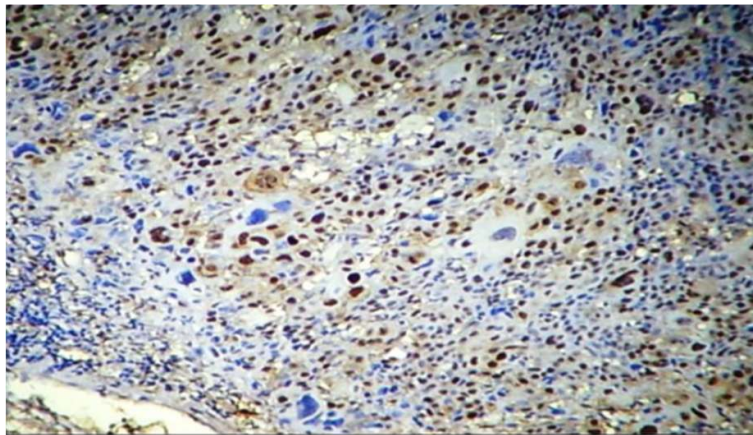


Fig. 1. A large cell non-keratinizing squamous cell carcinoma showing +4 positivity to P53 antibody. The reaction is seen as nuclear staining in tumour cells (IHC for P53 x200)

intraepithelial neoplasia to invasive carcinoma considering that intraepithelial neoplasia is likely to have started after commencement of sexual intercourse due to acquisition of the human papillomavirus (HPV).

The most common histological variant of cervical carcinoma observed in the study is the large cell non-keratinizing variant which accounted for 50.3% of all the cervical carcinomas studied.

This was followed by the keratinizing variant with a percentage of 32.2%. Gien et al. in Canada also observed that majority of the cervical carcinomas he reported are squamous cell carcinomas, however a recent increase has been observed in the occurrence of adenocarcinoma of the cervix accounting for 25% of all invasive cancers [16]. The percentage of adenocarcinoma in this study is also quite significant and other researchers have found high values of

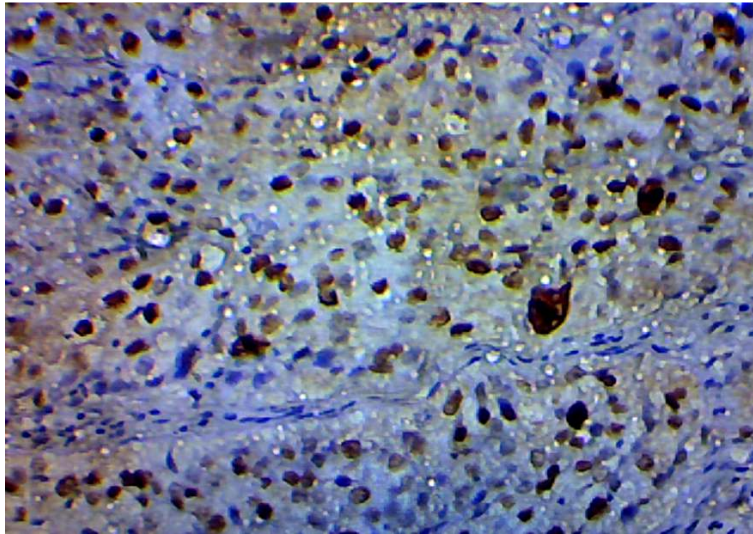


Fig. 2. Large cell non-keratinizing squamous cell carcinoma showing +3 positivity to Ki67 antibody. (IHC for Ki67 X400)

adenocarcinoma of the cervix in their local environment [17]. The reason for the relative increase in adenocarcinoma variant lately is poorly understood. It is thought that this may be a result of the ability of Pap smear screening tests to detect squamous precursor lesions more than precursor lesions of adenocarcinoma as the ectocervix is more accessible compared to the endocervix during pap smears [18].

The peak age of occurrence of squamous cell carcinoma and adenocarcinomas fell in the 50-59 year age group while that of adenosquamous carcinomas was found to be highest and same in the 40-49 and 50-59 year age groups. This is in contrast to studies in American women that found the peak age of occurrence of squamous cell carcinomas to be in the 45-49 year age group and that of adenocarcinomas and adenosquamous carcinomas to be in the 35-39 year age group [18]. This indicates that the commoner variants of cervical cancer tend to appear in a younger age group in American women than in patients in this study. More studies may be required to unravel the mystery behind this differential occurrence.

4.1 p53 Positivity in Cervical Cancers

There are wide variations in the expressions of p53 antigen in cervical carcinoma cells studied in different parts of the world. In this study, the positivity of p53 in the cervical tumour cells is 61.7%. This value is close to that in the study

conducted by Cheah et al. in Malaysia where he got 70.1% p53 positivity in Malaysian women. [19] The result is however different from the study by Hunt et al. in Manchester where a p53 positivity of 17.1% was observed in 80 cases of cervical carcinomas studies [20]. Other studies with lower p53 values are those by Oka et al. in China [21], Kainz et al. [22] in Australia and Busby- Earle et al. [23] in Edinburgh where positivity of 25.5%, 20.2% and 14% p53 positivity were gotten respectively from their studies. Ngan et al. in Hong Kong studied expression of p53 protein in 55 cases of cervical cancer and found out that only 3.6% of them expressed the protein [24].

In a study in South African patients by Chetty et al. [25] out of 50 cases of cervical cancer cases studied, 48 (86%) were positive for p53 protein. In a study conducted by El All et al. [26] in Egyptian women, all (100%) the 38 cases of cervical carcinoma studied expressed the nuclear p53 antigen.

The studies above show that most cervical cancer cases from African patients have higher values of p53 protein expression compared to values from non-African patients, the only exception being that of Cheah et al. in Malaysia [19]. Though most studies have not been able to establish a direct relationship between the level of p53 expression and cervical carcinoma, this study points out the possibility of a link between differential expression of p53 in cervical cancer

cases from different regions or races in the world.

The values of p53 from Europe as pointed out by Hunt et al. [13] and Kainz et al. [22], Asia as pointed out by Oka et al. [14] and Ngan et al. [24] are low compared to those from African studies where the p53 expression rates are from 50% and above. Parkin et al. found out that 83% of mortality from cervical carcinoma occurs in lower resource areas of which Africa especially Sub-Saharan Africa is a prime example [27]. This study tends to support the notion that *TP53* gene mutation may be an important event in cervical carcinogenesis and may affect prognosis because higher mortality from this tumour tends to occur in the areas with higher expression of the protein. Besides the usual cases of late presentation and lower treatment compliance in Africa, the higher level of p53 expression in cervical cancers from this part of the world may partly explain the higher mortality of cervical cancer observed in this region as tumours that express higher level of p53 tend to have higher mortality rates [7].

4.2 Ki67 Positivity in Cervical Cancers

The tissue blocks stained with the ki-67 antibody shows that 59.7% of the total numbers of cervical cancer cases were positive for the ki67 antigen. This figure correlates with other studies where Ki-67 positivity rates found were about 57.8 and 80.7% [28,29]. Some other researchers found that the ki-67 positivity in cervical cancers in some Chinese women was 94.4% [30].

These studies show that the ki67 positivity of cervical cancers is fairly uniform and most studies have reported greater than 50% positivity, however the level of positivity in the present study is lower than that in other similar studies. This may be due to a few factors.

This study showed that the tissue blocks that were positive for Ki67 were mostly obtained from the most recent years while the much older tissue blocks had a lower expression for Ki67. This could be as a result of antigen loss in the much older blocks. It seems obvious that tissue blocks that are to be used for Ki67 should preferably be the more recent ones. It is expected that all malignant tumours would express the Ki-67 antigen but figures well below 100% have been observed in many studies cited earlier. The period of storage of the tissue blocks may have contributed to these results.

Though, the relationship between p53 and Ki-67 expression and the different histological variants of cervical cancer was not found to be statistically significant, p53 and Ki67 expression were expressed more in the large cell non-keratinizing and the keratinizing squamous cell carcinoma than in adenocarcinomas. Other studies have also discovered this differential expression of p53 in different histological variants [20]. This differential pattern of p53 and Ki-67 expression was probably due to the fact that a lot of the cases in this study fell into one of these two variants of squamous cell cervical carcinoma.

4.3 Limitations to Study

A major limitation to the study was the inability to retrieve many tissue blocks of cervical cancer as they were not found. Also, some of the tissue blocks had inadequate tissue left for immunohistochemistry. A few blocks also did not have representative histological sections appropriate for immunohistochemistry. The study was hospital based and this means that not all cases of cervical cancer in Ile-Ife were included in the study because some patients with cervical cancer never presented to the hospital for treatment.

5. CONCLUSION

The peak age for the occurrence of cervical cancer in this study is from 40-69 years of age with the most common histological variant being the large cell non-keratinizing squamous cell carcinoma. p53 was expressed in 61.7% of all the cases of cervical cancer studied and Ki-67 was expressed in 59.7% of cervical cancer cases. Although the relationship of p53 and Ki-67 staining was not found to be statistically significant to the histological variants of cervical cancer, most cases that were positive were found to be of the large cell non-keratinizing variant.

The cases that were positive for the two antibodies were found to be more in recent tissue blocks. It is recommended that more studies are needed to establish the relationship between p53 and Ki-67 with cervical cancer and that immunohistochemistry especially for Ki-67 should be done on recent tissue blocks.

CONSENT

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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