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A 10-Year Histopathologic Audit of Uterine Cervical Biopsies in Warri, Nigeria

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Abstract. **The objective** of the research was to determine the types, patterns of uterine cervical lesions and specific age distributions in which they occur.

Methods. The data for this study were obtained from the records of patients seen in consultations in the Department of Histopathology, Central Hospital Warri during the 10-year period from 2007 to 2016. Relevant clinical information was extracted from the available histopathology records and permission for this study was conformed with the provision of the Declaration of Helsinki in 1995.

Results. The study revealed that the peak age range for malignant neoplasm was between 40-49 years (27.52%) with the general age range between (20-80 years) mean age 52.39±13.69. Non-keratinizing squamous cell carcinoma constituted majority of squamous cell tumours (55.05%), while the keratinising variety was the second most common (26.61%) one. The study further revealed that ectocervical fibroepithelial polyps were more common than endocervical tumours especially in the reproductive years (30-50 years) with only one case of atrophic polyp recorded in a woman in the sixth decade. The study documented that 58 (22.48%) of the cervical biopsies were inflammatory with most cases occurring in the ectocervix (94.80%). Most cases of inflammation of the cervix (cervicitis) were disposed between 30 and 59 years with the peak age group occurring in the 4th age group (30-39 years).

Conclusions. This audit of uterine cervical biopsies established that malignant tumours were the most common neoplasms. Squamous cell carcinomas accounted for most carcinomas. Similarly, leiomyoma was demonstrated as predominant stromal tumour.

Keywords: uterine-cervix; cancer; cervicitis; adequacy; age; Warri

Problem statement and analysis of the recent research

The uterine cervix, the most distal component of the uterus, is a very important part of the female genital tract [1]. It is composed of an external component, the ectocervix and internal part, the endocervix [2]. This structure undergoes changes in the reproductive life of females from its initial inactive prepubertal phase, through the reproductive period, to the postmenopausal stage [3]. In living humans, the ectocervix is lined by a stratified squamous epithelium which undergoes a transition to simple columnar epithelium of the endocervix [4-6]. The site of transition, the transformation zone, varies with the reproductive stage of life. Occasionally, an outward displacement of this zone exposes endocervical lining into the vaginal cavity giving rise to an ectropion [4-6].

Coitarche, multiple sexual partners, exposure to infectious processes and age, amongst other factors, have been associated with development of pathologies of this vital structure [7-8]. The most common of these include inflammatory lesions (cervicitis), intraepithelial neoplasm and ultimately malignant neoplasms [9-10]. Carcinomas of the cervix (squamous cell or glandular in origin) have been shown to account for the third most common cancers in females worldwide [11-13]. The development of this lesion has a profound effect in the health of females and constitutes a major health burden to the population [14].

Though some causative agents and ill advised sexual practices have been demonstrated to be attributable to this morbidity, adequate management involves adequate knowledge of the patterns of lesion in different locations [7, 15-19]. Indeed, despite the elaborated studies carried out in several regions of Nigeria and beyond it, few studies on the histopathological patterns of injury to the uterine cervix have been conducted. This study is an audit of the patterns of lesions of the uterine cervix observed from biopsies obtained from Central Hospital, Warri, Nigeria. This city is an important oil production hub in South Southern Nigeria.

The objective of the research was to determine the precise types and patterns of lesion, specific age distributions in which they occur. The results of this study will contribute extensively to the World Health Organisations' goal of attaining sustainable health for women [20].

Methods

Ethical approval was obtained from the Ethics and Research Committee of the Department of Human Anatomy and Cell Biology, Delta State University, Abraka (DELSU/CHS/ANA/68/67). The data for this study were obtained from the records of patients seen in consultations in the Department of Histopathology, Central Hospital Warri during the 10-year period from January 1, 2007 to December 31, 2016. Relevant clinical information including age and lesion types was extracted from the available histopathology records and permission for this study was conformed with the provision of the Declaration of Helsinki in 1995 [21-23].

Only cervical biopsies from either the ecto or endocervix were included in the study. Upon obtaining the diagnosis from the register, each slide was first verified and subsequently described with the aid of a light microscope (model number DN-107T). Reprocessing of blocks was performed for slides which were difficult to interpret [24-25].

Classification of the results was based on the current WHO classification of uterine ectocervical lesions [26]. The results were presented in frequency tables with chi-square and Mann-Whitney-U test used for determining the significance of the associations between age and frequencies of the observed patterns [27].

Results

In Table 1, the distributions of malignant neoplasms of the uterine cervix are listed. Generally, the study revealed that the peak age range affected was between 40-49 years (27.52%) with the general age range between (20-80 years) mean age 52.39±13.69. Most tumours were squamous in origin (81.65%) with majority occurring in patients in 4- and 5-year intervals respectively.

Non-keratinizing squamous cell carcinoma constituted majority of the squamous cell tumours (55.05%), while the keratinising variety was the second most common (26.61%) one. The characteristic feature of the keratinised variety was the presence of both intra and extracellular keratin in the lesion. Keratin pears are also a prominent feature in contrast to the non-keratinised group lacking keratin but retaining the signs of

Table 1. Malignant neoplasms of the uterine cervix

S/N	Patterns		Age							Total
			20-29	30-39	40-49	50-59	60-69	70-79	80-89	
1.	Squamous cell carcinoma									
	a.	keratinizing		4	5	8	8	3	1	24
	b.	non-keratinizing	2	9	17	14	10	7	1	60
	c.	papillary				1		1		2
	d.	clear cell			1					1
2.	Adenosquamous carcinoma				3	1	2			6
3.	Adenocarcinoma			2	3		2			7
4.	Sarcomas									
	i.	MPNST		1						1
	ii.	alveolar rhabdomyosarcoma		1						1
5.	Poorly differentiated carcinoma		1		1					2
	Total		3	17	30	24	22	11	2	109

squamous cells (relatively high nuclear cytoplasmic ratio albeit with the vesicular nuclei and evidence of abnormal mitotic activity as shown in Fig. 2a). In this group, two cases of papillary squamous cell carcinoma and a case of clear cell differentiation were also seen.

Only 6 cases of adenosquamous carcinoma (5.51%) and 7 cases of adenocarcinoma (6.42%) were recorded. These tumours were characterised by pleomorphic glandular epithelial cells with pleomorphic and vesicular nuclei, and evidence of attempts of gland formation. Stromal invasion with foci of squamous differentiation was usually overt and prominent. Most of the glandular tumours were observed to peak in the fourth decade in both lesions.

Similarly, two cases of sarcoma, constituting 1.83% of malignant lesions, were observed. Both lesions, malignant peripheral nerve sheath tumours and alveolar rhabdomyosarcoma, were recorded in patients in the 3rd decade of life. Two cases of poorly differentiated carcinoma were also identified. These tumours were seen in patients in the second and fourth decades respectively.

As shown in Table 2, cervical intraepithelial neoplasm grade 1 (CIN 1) was the most common premalignant lesion constituting 9 (75%) premalignant cases. Unspecified CIN 1 and CIN 1 with chronic cervicitis were the most common lesions in this class. In addition, a single case of CIN 1 with papilloma was recorded in this study.

Generally, CIN 1 displayed a moderately raised nuclear-cytoplasmic ratio and mild distortion of the nuclear membrane of the epithelium in the distal third of the ectocervix. There were

koliocytic changes in the squamous epithelia of the proximal two thirds in most cases.

Three cases, characterised by one or more foci of dysplastic epithelial cells extending along the whole length of the ectocervix, CIN 3, were noted. The age involved was mostly within the 30-49-year age range. Generally, the mean age of CIN was 44.50±12.25.

Table 3 shows the pattern of benign neoplasms of the cervix. The mean age involved was 45.69±14.51 years. Fibroepithelial polyps were the most common benign lesions. These polypoid lesions were composed of benign proliferating fibroblast overlain by an epithelial layer. Most tumours were located in the ectocervix and therefore lined by squamous epithelium, while mucous epithelial tissue was associated with endocervical disposed polyps.

The study further revealed that ectocervical fibroepithelial polyps were more common than endocervical tumours, polyps were lined by columnar epithelia cells, especially in the reproductive years (30-50 years) with only one case of atrophic polyp recorded in a woman in the sixth decade.

The next most common benign neoplasm was leiomyoma. As displayed in Fig. 1, tumours were composed of pale white well circumscribed firm masses with whorl like appearance on cut sections. These masses completely obliterated the structure of the uterus in this case. In Fig. 2b, tumour showed matured spindle-shaped smooth muscle cells with cigar-shaped nuclei and eosinophilic fibrillary cytoplasm. Individual cells were separated by a thin connective tissue stroma with perimysium binding muscle fibres haphazardly in irregular fascicles. A pseudocapsule of dense myometrial tissue was observed in some biopsy specimens.

Other benign tumours included haemangioma and fibromatosis constituting 2.38% each. In addition to fibrous polyps, leiomyomas were the next most common group accounting for 40.48% of benign tumours with age involvement from 20 to 60 years.

The study documented that 58 (22.48%) of cervical biopsies were inflammatory with most cases occurring in the ectocervix (94.80%). While most ectocervical lesions were chronic inflammation characterized by the infiltration of the fibroconnective tissue stroma by lymphoplasmacytic cellular infiltrates, acute inflammation (inflammation characterized mainly by neutrophilic infiltrates) was recorded in a single case. Table 4 shows that 14 (24.14%) chronic inflammations developed metaplastic changes (squamous keratinization).

Most cases of inflammation of the cervix (cervicitis) were disposed between 30 and 59 years with the peak age group occurring in the 4th age group (30-39 years). Both Nabothian cysts and tissues with squamous metaplasia were the most common lesions within the adaptive change

Table 2. Premalignant lesions of the uterine cervix

Patterns	Age					Total
	20-29	30-39	40-49	50-59	60-69	
CIN1						
CIN 1 (unspecified)		1	1	1		3
CIN 1 and endocervicitis			2			2
CIN 1 and papilloma	1					1
CIN 1 and chronic cervicitis		2		1		3
Carcinoma in situ						
Carcinoma in situ		1			1	2
Carcinoma in situ and CIN 3					1	1
Total	1	4	3	2	2	12

Table 3. Benign neoplasms of the uterine cervix

Patterns	Age								Total
	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	
Fibroepithelial polyp									
ectocervical polyp									
squamous papilloma			4	6	4	2		1	17
atrophic polyp					1				1
endocervical polyp		1	3						4
Leiomyoma		4	4	4	1	4			17
Angiofibroma						1			1
Haemangioma			1						1
Fibromatosis						1			1
Total		5	12	10	5	9		1	42

group constituting 27.27% each. The next most abundant lesion was lobular endocervical glandular hyperplasia (18.18%). Arteriovenous malformation, large cell keratinosis, adenomyosis and squamous cell metaplasia were also identified during the period of the study.

The study recorded 11 cases of tissues which were inadequate for histologic assessment. This included 8 cases of tissues which were insufficient, 2 cases of autolysed tissues and one case where tissue was non-representative.

Fifteen cases were recorded as normal with 13 cases of the ectocervix and 2 cases of the normal endocervix. The normal ectocervix was composed of a non-keratinised stratified squamous epithelium overlying a dense irregular fibroconnective tissue stroma in which there were some scant lymphocytic infiltrates as shown in Fig. 2c. Mucous type columnar epithelium lined the endocervix.

Discussion

The index study revealed that malignant neoplasms accounted for over two-fifths of the lesions present in the study. Amongst malignant neoplasms, squamous cell carcinoma accounted for most lesions as has been earlier established in several related

Fig. 1. Uterine fibroids; gross section. Section shows multiple intramural fibroids obliterating the architecture of the uterus. The arrow shows entry into the endocervix

studies carried out in Nigeria and beyond it [28-34]. The percentage of non-keratinizing squamous cell carcinoma (55.05%) amidst malignant tumours was more closely aligned to the reports from Ibadan (63.00%) and Ilorin (60.10%) than the reports from Kano (46.20%) [12, 32, 34]. Despite these differences, both Fattaneh et al. and Rosa et al., however, asserted that the occurrence of keratin in grading was trivial in prognostication [35-36].

According to some authors, both adenocarcinoma and adenosquamous carcinoma portended a poorer prognosis than pure squamous cell carcinoma [35, 37]. Both lesions, glandular and mixed glandulo-squamous, however, displayed a similar age and percentage frequency distribution as had earlier been demonstrated [9-10]. These findings were, however, different from the rising profile of adenocarcinoma of the cervix as explained by Lax in his review of precursor and cancerous lesions of the cervix [38]. His argument was that human papillomavirus (HPV), the established primary aetiologic agent in the development of squamous cell carcinoma, displayed similar actions on columnar cells of the endocervix. He further maintained that these glandular cells had been shown to harbour the HPV DNA serotypes 16, 18 and 45 [39]. The very close similarity between uterine cervical and endometrial lesions could explain the results obtained in most studies especially as clinical information was mostly relied upon small biopsy samples. Wells et al. recommended immune-histochemical stains that would readily differentiate adequately, the origin of samples from both locations [40].

Several factors including immune and socioeconomic status, the level of education and availability of adequate health facilities which are all strongly related to exposure to HPV have been shown to facilitate the development of these lesions [7, 16]. This virus has been implicated as one of the main aetiologic factors in the development of cancer of the uterine cervix [7].

The general age distribution of most lesions in this study (20-80 years, peaking at the fifth decade) was not new. Several investigators of uterine cervical lesions have demonstrated an age range of 20-80 years for cervical cancers specifically, a gradual rise to peak at the fifth decade, plateau soon after (6th decade) and eventually decline thereafter [10, 12, 41].
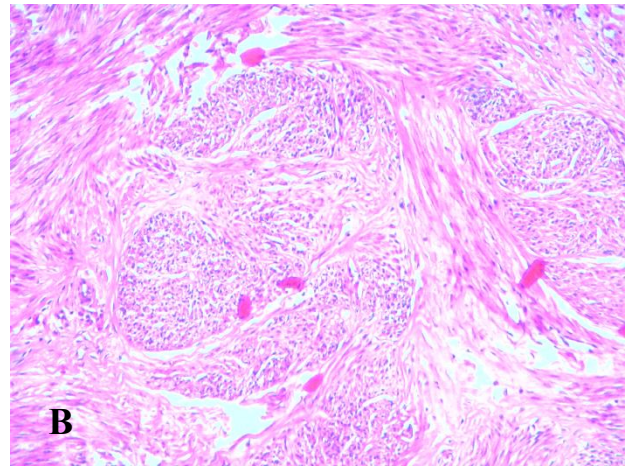
The precursor lesions for squamous cell carcinoma include CIN 1-3 which the most recent Bethesda classification designated high-grade intraepithelial lesion (HSIL) for CIN 2 and 3, and low-grade intraepithelial lesion (LSIL) for CIN1 [38]. There are overwhelming documentations implicating HPV with
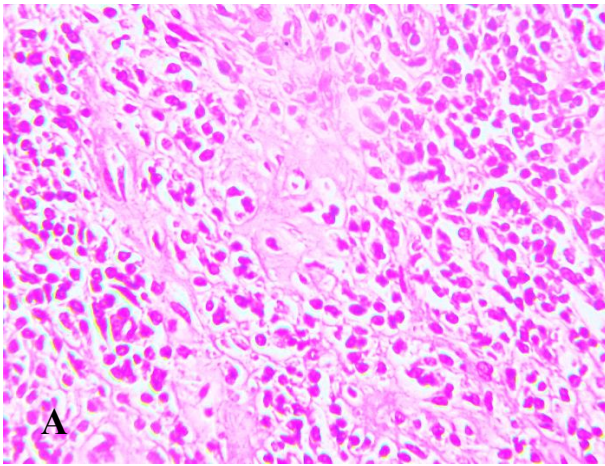
Invasive squamous cell carcinoma
H and E x 100

Uterine cervical leiomyoma
H and E x 100
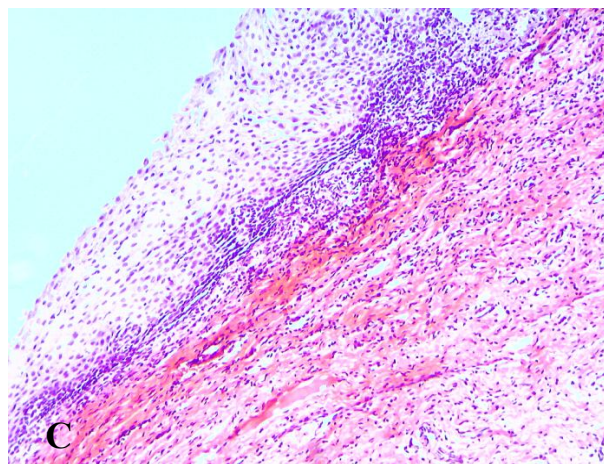
Normal (ectocervix)
H and E x 100

Fig. 2. Micrographs of some uterine cervical biopsies. A) invasive squamous cell carcinoma; b) uterine cervical leiomyoma; c) normal uterine cervix (ectocervix)

development of both precancerous and malignant lesions of the cervix. The virus is known to possess several serotypes. While HPV 6 and HPV 11 (low serotypes) are associated with the development of CIN 1, CIN 2 and CIN 3 have been linked to HPV 16-45 (high serotypes) [38]. Cviko et al. explained that while the lower serotypes of HPV affected terminally differentiated cells (cells in post mitotic phase of the cell cycle), the superficial ectocervical cells, the sites of action of the higher HPV serotypes were the basal and parabasal cells which were in the premitotic phase when the cell is most vulnerable [42]. The outcome of exposure to this viral agent could therefore be inoculation into the squamous cell nuclear material with subsequent production of cells with malformed DNA. The index study provided sufficient evidence of carcinoma in situ co-existing with CIN 3 which strongly suggested a progressive lesion. The demonstration of cervicitis with CIN 1 further corroborated the mechanism of lesion development. Melnikow et al., 1998, however opined that generally, LSIL gradually regressed with age although a subset of CIN 1 has been demonstrated to possess the capacity to transform into HSIL [38, 43].

The current study further demonstrated that precursor lesions (CIN 1) occurred most commonly in the reproductive age range probably indicating the transmission through sexual intercourse in contrast to CIN 3 which was a disease of women in the postmenopausal period [38]. The terminal lesion, squamous cell carcinoma, on the other hand, occurred chiefly in women in their sixties. Some authors have suggested that age-related changes, especially mistakes in the apoptotic processes, inheritance of peculiar genes or acquisition of genetic defects could also contribute to the development of morbidities of the cervix [44, 45].

Fibroepithelial polyps accounted for less than a tenth of lesions in this study. Saravanan et al., 2015, documented only about six percent of cases in their study of cervical lesions [46]. These fibroepithelial proliferations were observed to occur most commonly in the 4th and 5th decades of life as had been described earlier [47-50]. The current study has shown that inflammatory squamous (ectocervical) polyps were the most abundant variety in contrast to that described by Sidhalingreddy et al., 2013, where most polyps were endocervical in origin [51]. Well et al. explained that these lesions might actually be precursors to condylomas, benign tumours induced by exposure to HPV [52]. The exposure to this highly infectious agent is common in the reproductive years and is often present in the ectocervix.

Leiomyomas were demonstrated to be the most abundant

Table 4. Non-neoplastic lesions, normal and inadequate for diagnosing biopsies of the uterine cervix

Patterns			Age								Total
			10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	
Inflammatory lesions											
	Ectocervical										
		chronic cervicitis		4	14	11	8	1	1		39
		chronic cervicitis with metaplasia			5	6	3				14
		acute cervicitis			1						1
		cervical erosion				1					1
	Endocervical										
		endocervicitis				1	1	1			3
Adaptive changes											
		Nabothian cyst			1	1	1				3
		large cell keratinosis							1		1
		lobular endocervical glandular hyperplasia			2						2
		adenomyosis					1				1
		squamous metaplasia	1			1	1				3
	arteriovenous malformation			1							1
	Inadequate for assessment										
		insufficient				2	4	1	1		8
	autolysed			1		1					2
		not representative				1					1
	Normal tissue										
		ectocervix		2	2	5	2	1	1		13
		endocervix						1	1		2
Total			1	8	25	30	22	5	4		95

stromal neoplasm in this study. This finding was not surprising as an earlier study had indicated a similar result [53]. Post mortem studies have reliably indicated that over two-thirds of women possessed leiomyomatous lesions in the uterus while only in about a third of females, fibroid became apparent before menopause [53-56]. The current investigation, however, demonstrated an age of involvement between twenty and sixty years. The possible explanation for this is that surgical excision of fibroids is indicated in cases of infertility, especially when the lesion has been implicated as the major cause [57-59]. Similarly, myomectomy is strongly advised in cases associated with miscarriage and severe dysmenorrhoea [60-63].

Cervicitis, in the index study, was the most common non-neoplastic lesion with most cases occurring in the fourth decade of life. Kumari et al. also observed that cervicitis was the most common non-neoplastic lesion with majority of cases identified within 30-41 years of age [64]. Craig and Lowe, 2003, revealed a similar result with rarity of the lesion in females below twenty years in contrast to the report presented by Omoniyi-Esan et al., whose findings showed that 10% of cervicitis was observed in adolescence [65-66]. Several factors including chemical irritation, exposure to foreign materials (e.g. sanitary pads), bacterial/viral infection and parasitic organisms have been attributed to the development of this lesion [67]. It is also noteworthy that the peak age involvement ascertained in this study coincides with the period of maximal sexual interactions in women which may explain why they succumb to some of these factors.

It is important to note that while about 6% of the diagnoses were normal, less than 5% were inadequate for histologic assessment. Inadequacy for diagnosis has been demonstrated to arise from sample collection to histologic interpretation [68]. In addition to the subjectivity of this diagnosis, no specific features have been outlined to clearly define a tissue as inadequate (insufficient) [69-73]. The storage in a 10% formal saline is cheap and effective for preservation of most tissues. It has also been advised that biopsied tissues should be wrapped in lens paper to avoid loss during tissue processing. The tissues should be embedded perpendicular to the mucosal surface to facilitate epithelial and stroma outlines during microscopy. This will also enhance three level sectioning best suited for histologic interpretation [67].

Conclusions

This audit of uterine cervical biopsies has established that malignant tumours were the most common neoplasms observed

during the 10-year period. Squamous cell carcinomas accounted for most carcinomas with the non-keratinizing forms being the most abundant. Similarly, leiomyoma was demonstrated as the predominant stromal tumour. The index study corroborated pre-existing reports that the cervical lesions were associated with age.

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