PROFILE OF INTERLEUKIN-1β IN CERVICAL CANCER PATIENTS ATTENDING ONCOLOGY UNIT, USMANU DANFODIYO UNIVERSITY TEACHING HOSPITAL, SOKOTO-NIGERIA.

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ABSTRACT
Introduction: Cervical cancer occurs when the cells of the cervix grow abnormally and invade other tissues and organs of the body. This cancer may affects the deeper tissues of the cervix or may spread to the lung, liver, bladder, vagina and rectum. Cervical cancer is the most common gynaecological malignancy is the second leading cause of cancer associated mortality in females worldwide. Cervical cancer treatment and management has been a major challenge in medical field.
Aim/Objectives: This research was designed to assess the profile of interleukin-β1 (IL-1β) in patients with Cervical cancers and compare with that in the healthy subjects to determine if IL-1β has any role to play in the pathogenesis of Cervical cancers
Materials and Methods: Five ml(5ml) of blood was collected using blood collection bottles from 80 cervical cancer cases and 40 healthy controls. The samples were labelled and allowed to clot, and then centrifuged in a cold centrifuge at 3000 RPM for 10 minutes. The serum was transferred into sterile serum separation tubes and was stored immediately at -20°C until used. The concentration of IL-1β was quantitatively determined, using ELISA kit (MELSIN EKHU-0081). Data obtained were analysed using SPSS 22.0 statistical package. A p-value $\leq$ 0.05 was considered statistically significant.
Result: There was significant increase in the profile of IL-1β in cervical cancer patients, when compared to the healthy control (p-value<0.05).
Conclusion: The result indicates that IL-1β may play an important role in the cervical cancer pathogenesis, but there is a need for a more conserted and a well tailored further research and periodic profiling of IL-1β in patient with cervical cancer.

Keywords: Cervical cancer, Interleukin IL-1β, Profiling, Pathogenesis.

1. INTRODUCTION

Cancer is a systemic disease that initially presents local manifestations, and latest advances in a multistep process with various hallmarks, including rapid proliferation, resisting cell death, neoangiogenesis, local invasion and remote metastasis (Zhu et al., 2015). Cancer is a genetic disease that is caused by changes in genes that control the way our cells function, especially how they grow and divide. The genetic changes tend to affect three main types of genes, namely; proto-oncogenes, tumor suppressor genes, and DNA repair genes. These changes are sometimes called "drivers" of cancer development (NIH, 2015).

All tumor cells show six main characteristics, which are required to produce a malignant cells (Hanahan and Weinberg, 2000). These includes; Absence of normal cell growth and division due to improper signals, uncontrolled growth and division of cells, evasion of programmed cell death, increase rate of cell divisions, promotion of blood vessel construction, invasion of tissue and formation of metastases (Hanahan and Weinberg, 2000).

The progression from normal cells to cells that can form a detectable mass to outright cancer development involves multiple steps known as malignant progression (Hanahan and Weinberg, 2000).

The uterine cervix is the lowest portion of a woman's uterus (womb), connecting the uterus with the vagina. Cervical cancer occurs when the cells of the cervix grow abnormally and invade other tissues and organs of the body. When it is invasive, this cancer affects the deeper tissues of the cervix and may have spread to other parts of the body (metastasis), most notably the lung, liver, bladder, vagina and rectum (Laura, 2018).

Interleukin-1 was originally discovered as a factor that induced fever, caused damage to joints and regulate bone marrow cells and lymphocytes, it was given several different names by various investigators. Later, the presence of two distinct proteins, IL-1α and IL-1β, was confirmed, which belong to a family of cytokines, the IL-1 super family. Ten ligands of IL-1 have been identified, termed IL-1F1 to IL-1F10. With the exception of IL-1F4, all of their genes map to the region of chromosome 2. IL-1s exert their effects via specific cell surface receptors that include a family of about nine members characterized as IL-1R1 to IL-1R9. All family members with the exception of IL-1R2 have an intracellular TLR domain. Each type of receptor in the family has some common and some unique features (Khan, 2008).

Cervical cancer (CC) is one of the most frequent cancers affecting women worldwide and is an important public health problem for adult women in developing countries (Diaz-Chavez *et al.,* 2008). About 200,000 to 300,000 deaths are recorded and 500,000 new cases are diagnosed annually (Daniel *et al.,* 2013). Most of the deaths occur in the developing countries where patients present with an advanced stage of the disease and routine screening is either nonexistence or limited. In Sokoto, cervical cancer accounts for 61.5% of genital tract malignances. Interestingly, cervical cancer is largely a preventable disease (Daniel *et al.,* 2013). But adequate preventive measures and treatment are not in place.

There is paucity of data on cervical cancer treatment at Usmanu Danfodiyo University Teaching Hospital (UDUTH), Sokoto; as such this current research work is design to provide a further means of blocking early or late stages of cervical cancer by accessing the level of pro-inflammatory cytokine such as IL-β, which will provide an insight on effective treatment options, either through inhibiting the productions of the cytokine and the blockage of it receptor binding site, thus preventing aberrant immunological responses that led to cancer and tumor cells proliferation.

2. MATERIALS AND METHODS
Study Area

This study was carried out in Usmanu Danfodiyo University Teaching Hospital Sokoto, Sokoto State (UDUTH). UDUTH is a tertiary institution located within the Sokoto metropolis. Sokoto is the capital city of Sokoto State located in the extreme North-Western Nigeria, near the confluence of the Sokoto River and the Rima River. The State is in the dry Sa-

hel, surrounded by sandy savannah and isolated hills, with an annual average temperature of 28.3^{o}C (82.9^{o}F). Sokoto is a very hot area, maximum day-time temperatures are for most of the year generally under 40°C (104.0^{o}F) and the dryness makes the heat bearable. The rainy season is from June to October during which shower is a daily occurrence.

Study Design

This is a descriptive, cross sectional study design to determine the profile of interleukin-1β (IL-1β) in patients with cervical cancer admitted to Oncology Unit, Usmanu Danfodiyo University Teaching Hospital (UDUTH) Sokoto.

Study Subjects

A total of 80 patients with Cervical cancer, admitted at Usmanu Danfodiyo University Teaching Hospital (UDUTH), Sokoto and 40 healthy controls, who passed the inclusion creteria were randomly recruited for this study.

Data Collection

A semi structured questionnaire was administered to all consenting parents or patients to obtain information on their social-demographic and medical history.

Informed Consent and Ethical Approval

Informed consent for inclusion in the study was obtained from the patients or the child's parent/guardian using a standard informed consent form. Approval for the study was obtained from the Ethics and Research Committee of Usmanu Danfodiyo University Teaching Hospital, Sokoto.

Sample Collection

Five ml (5ml) of whole blood was aseptically collected using Monovette® blood collection bottles from 80 cervical cancer cases and 40 healthy control subjects. The collected blood samples were labelled and then allowed to clot. Using a cold centrifuge, the clotted blood was centrifuged at 3000 RPM for 10 minutes. The serum was transferred into sterile serum separation tubes and was stored immediately at -20°Cuntil

Estimation of Interleukin-1β (IL-1β)

Serum level of interleukin-1β (IL-1β) was measured using quantitative ELISA method using assay kit from MELSIN EKHU-0081.

3. Data Analysis

Data obtained was entered into SPSS version 22 for analysis. Independent variables were expressed as mean ± SD. The P value of ≤ 0.05 was used to determine the level of statistical significance. The results obtained were presented using Tables.

4. RESULTS

Socioeconomic and Demographic characteristics of the study population

Table 1 shows the demographic characteristics of the study population. The result in this table indicate that age ranges 38-45, 46-51 and 52-57 have 27.5% (11/40) of the cervical cancer subjects respectively. 47.5% (19/40) of the subjects were of Hausa tribe, 80% (32/40) of the cervical cancer subjects were from rural areas, 87.5% (35/40) were unemployed/house wife, 70% (30/40) has no formal education, and 97.5% (39/40) were married.

Table 1: Socio-Demographic Characteristic of the study population

Characteristics		Subject (n=80)	Control (n=40)	Total
Ages	38- 45	22(27.5%)	14(35%)	36
	46 - 51	22(27.5%)	6(15%)	28
	52 – 57	22(27.5%)	16(40%)	38
	58-61	14(17.5%)	4(10%)	18
Tribes	Hausa	38(47.5%)	(60%)	31
	Fulani	14(17.5%)	6(15%)	20
	Yoruba	8(10%)	2(5%)	10
	Igbo	8(10%)	2(5%)	10
	Others	12(15%)	6(15%)	18
Residence	Rural	64(80%)	8(20%)	72
	Urban	16(20%)	32(80%)	48
Occupa-tion	UE/H.wife	70(87.5%)	24(60%)	94
	Civil servant	8(10%)	16(40%)	24
	Famer	2(2.5%)	0(0%)	2
Education	Informal	60(75%)	12(30%)	72
	Primary	8(10%)	0(0%)	8
	Secondary	6(7.5%)	12(30%)	18
	Tertiary	6(7.5%)	16(40%)	22
Marital status	Married	78(97.5%)	36(80%)	114
	Single	2(2.5%)	4(20%)	6

Table 2: Age distribution among subjects and controls

Ages	Subject (n=80)	Control (n=40)	Total	X^2	P- value
38 - 45	22(27.5%)	14(35%)	36	2.301	0.512
46 – 51	22(27.5%)	6(15%)	28		
52 – 57	22(27.5%)	16(40%)	38		

This table shows the age distribution of the subjects and controls, with p-value of 0.512 which not significant, because age- matched subjects and controls were used in this study.

n = Minimum sample size, x^2 = chi square, p- value = level of significance

Table 3. Urban and Rural Dwellers among subjects and controls

Residence	Subject (n=80)	Control (n=40)	Total	X^2	P-value
Rural	64(80%)	8(20%)	72	20.000	0.000
Urban	16(20%)	32(80%)	48		

This **is** the residential distribution of the subjects and controls, with p- value of 0.000 which is highly significance between the profile of interleukin-1 and those staying in Rural and Urban centers.

n = Minimum sample size, x^2 = chi square, p- value = level of significance

Table 4. Occupational distribution among subjects and controls

OCCUPATION	SUBJECT (n=80)	CONTROL (n=40)	TOTAL	X^2	p- value
UE/H.WIFE	70 (87.5%)	24(60%)	94	7.787	0.020
CIVIL SERVNT	8(10%)	16(40%)	24		
FARMER	2(2.5%)	0(0%)	2		

This table shows the occupational status of subject and controls, with p-value of 0.020, which is highly significance between the profile of interleukin-1 and those that are unemployed/house wife, civil servant and farmers.

n = Minimum sample size, x^2 = chi square, p- value = level of significance, UE = unemployed

Table 5. Educational level of the subjects and controls

Education	Subject (n=80)	Control (n=40)	Total	X^2	P-value
Informal	60(75%)	12(30%)	72	18.682	0.000
Primary	8(10%)	0(0%)	8		
Secondary	6(7.5%)	12(30%)	18		
Tertiary	6(7.5%)	16(40%)	22		

Table 5 shows the educational level of the subjects and controls, with p-value of 0.000 which is highly significance when compared with the profile of interleukin-1 and informal,primary,secondary and tertiary institutions.

n = Minimum sample size, x^2 = chi square, p- value = level of significance

Table 6. Marital status among subject and controls

Marital status	Subject (n=80)	Control (n=40)	Total	X^2	P- value
Married	78 (97.5%)	36 (80%)	114	1.579	0.209
Single	2 (2.5%)	4 (20%)	6		

This table shows the marital status of the subjects and controls, and the variables are not significance when compared with the profile of interleukin-1**β**

n = Minimum sample size, x^2 = chi square, p- value = level of significance

Table 7. Profile of IL-1β of the study subjects and controls

Participant	N	Mean	Std. Error Mean	T	p value
Subjects	80	28.57 ± 7.92	1.25	2.41	0.014
Controls	40	23.61 ± 6.56	1.47		

The profile of interleukin-1**β** in the study subjects and controls is presented in Table 7. The result indicates that, profile of IL-1**β** in cervical cancer patient (28.57±7.92pg/ml) is significantly higher (p <0.05) compared with the corresponding values in controls (23.61 ± 6.56pg/ml).

n= Minimum sample size, t= independent t-test.

5. DISCUSSION

Increased levels of IL-1 α/β and IL-10 were observed in cervicovaginal secretions of women with CIN, HPV and HIV indicating the adverse effect of Sexually transmitted infections on cytokine profile (Dinarello, 2011). In the current study, majority of the cervical cancer subjects with highest frequency of the disease were found in three categories of age ranges, 38-45, 46-51 and 52-57 years, with 58-61 years having the lowest frequency.

The significant increase in the profile of interleukin-1β in cervical cancer patient (28.57±7.92pg/ml) compared with the corresponding values in controls (23.61 ± 6.56pg/ml), in this study (Table 7), is in agreement with the report of higher values recorded by Dinarello, 2011. IL1β was the first identified soluble factor from macrophageswith para crine proinflammatory activity. Later it was found that it also expressed by several other immune cells that fight against infections, including the lymphocytes.

Several important individual covariates, such as age, education, employment, marital status, and place of residence, were significantly associated with less likelihood of receiving cervical cancer screening, which lead to increase development of the disease due lack of awareness, as a result of low educational level e.t.c (Akinyemiju, 2012).

Result has shown in table 2 that age is not statistically significant in this study, because age- matched subjects and controls were recruited for these studies. Leaving in a rural areas has significant effect on the development of cervical cancer and profile of interleukin-1β as shown in table 3, this is in agreement with Akinyemiju, (2012). The involvement in one or two jobs has significant impact on the development of cervical cancer and increase level of IL-1β, this is in agreement with Compaore *et al.,* (2016). In table 4, it was indicated that women who were employed tend to seek screening more than those who were not employed, this tends to reduces the risk of developing cervical cancer and decreased level of IL-1β.

The educational level of women has been shown to have a statistical significance relationship with cervical cancer development and the level of IL-1β (Table 5). This is in agreement with Akinyemiju, (2012), who stated that the more educated women are, the more likelihood, they are to seek more medical attension.

Marital status has shown to have no statistical significance relationship cervical cancer development and increased level of IL-1β (Table 6).

CONCLUSION AND RECOMMENDATION

From the findings of the present study, it can be concluded that, the profile of interleukin-1β is significantly increased in cervical cancer patients. Most of the married patients, who have no formal education and most of the rural dwellers have a higher incidence of Cervical cancer, as seen in this study.

It is therefore recommended that periodic profiling of IL-1β in patient with cervical cancer, to enable for effective management and treatment. Well tailored and concerted further research should be undertaken to elucidate the roles and mechanisms of IL-1β/α in the pathogenesis of cervical cancer.

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