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Anthro-demographic, clinico-pathological and biochemical risk factors in cervical cancer

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***Abstract*---**Background: In India, cervical cancer (CaCx) ranks second with >1.2 lakh new cases and >77,000 deaths. The main causing agent of cervical cancer is human papillomavirus (HPV). Recently, anthro-demographic and clinico-pathological factors have been implicative of cancer development and progression. Objective: To evaluate the association of anthro-demographic, clinico-pathological and biochemical risk factors in cervical cancer. Methods: CaCx patients were tested for HPV infection using conventional PCR. Anthro-demographic and clinico-pathological characteristics were recorded and samples from patients (n=103) and healthy women (n=108) were analyzed for lipid profile, serum urea, creatinine and uric acid using commercial kits. Statistical analysis was done using SPSS (ver.21.0) and GraphPad. Results: Out of 103 CaCx patients, 86 were HPV+ve and 17 HPV-ve. Anthro-demographic factors like literacy, socio-economic status and obstetrics were found significantly

associated with cervical cancer. BMI was associated with cervical cancer (1.18 folds higher risk). Total cholesterol (TC); triglycerides (TG); high-density lipoprotein (HDL) and low-density lipoprotein (LDL) were found significantly associated with an increased adjusted OR in CaCx patients. Urea levels were found significantly higher in patients (1.11 folds crude OR vs 1.31 adjusted OR). Similarly, creatinine levels were significantly higher in patients (2.64 folds crude OR vs 3.37 adjusted OR). Uric acid showed significantly higher risk with crude and adjusted OR as 1.29 in CaCx patients. Conclusion: Dyslipidemia, renal dysfunction, and uricemia were found clinically significant in CaCx patients. Therefore, TG, HDL, LDL, cholesterol, urea, creatinine, and uric acid levels can be used as prognostic biomarkers in cervical cancer.

***Keywords*---**cervical cancer, anthro-demographic, clinico-pathological, dyslipidemia, renal dysfunction, uricemia.

Introduction

Cervical cancer (CaCx) is the 9th most severe cancer in the world with 3.4 lakh deaths and >6.0 lakh new cases worldwide and ranks 4th among women in 2020 [1]. In India, it ranks 2nd with >1.2 lakh new cases and >77,000 deaths [1]. The main causing agent of cervical cancer is human papillomavirus (HPV). Approximately, 184 HPV strains have been identified including 15 high-risk HPV (HR-HPV) which are responsible for cervical carcinogenesis [2]. Infection by HR-HPV strains activates certain oncogenes which in turn interfere with protective proteins controlling cell growth. Once these proteins are blocked, cell growth accelerates, leading to tumor development and cancer [3]. Although HR-HPV infection is one of the major risk factors, it is not enough for cervical carcinogenesis. In addition to HR-HPV infection, anthro-demographic and clinico-pathological factors such as age, literacy, residence, marriage at an early age, number of abortions, young age at first delivery, parity, oral contraception, multiple sexual partners, low socio-economic status, unhealthy living conditions and smoking are also responsible for the development of cervical cancer [4-5]**.** The development of cervical cancer is a multifactorial interaction of genetic, epigenetic and metabolic risk factors, host nutrition, as well as immune response [6].

Recent studies have suggested that obesity, dyslipidemia [7], and uricemia have significant association with cancer progression [8]. Previous studies have reported that high or low levels of lipids can induce carcinogenesis [9-10]. Hypolipidemia/hyperlipidemia has been associated with different types of cancers including gastric cancer, prostate, and leukemia [11]. Moreover, serum triglycerides have been associated with an increased risk of endometrial cancer while elevated levels of total cholesterol and low-density lipoprotein (LDL) have been reported in colorectal cancer [12]. It has been reported that adipocytes act as energy reservoirs, promoting the rapid growth and metastasis of cancer cells [11]. However, the exact mechanism of lipid (dyslipidemia) mediated cervical carcinogenesis and CaCx is not well studied. The anti-cancerous therapies have been influenced by lipid profile and lipid peroxidative products like

malondialdehyde which cross-links with adenine and cytosine of DNA [13]. This lipid by-product and DNA cross-linking lead to carcinogenicity and mutagenicity in cells [11].

A previous study reported the association of metabolic-related factors including lipid, urea, creatinine, and uric acid with tumor prognosis and tumorigenesis [14]. Uricemia is the result of abnormal uric acid metabolism which has been associated with pathogenesis of various diseases like gout [15], cardiovascular diseases (CVD) [16], pulmonary diseases [17], and cancer [16]. Although serum uric acid possesses antioxidant properties, increased levels can lead to inflammation and promote tumorigenesis. It has been clinically established that chronic inflammation is associated with cervical carcinogenesis [18]. Therefore, uricemia (hyper/hypo-uricemia) might be involved in the initiation and progression of cervical carcinoma. However, the pathological role of uricemia in cervical cancer is not well known. The urological complications and renal function (urea and creatinine) also play an important role in prognosis and cancer development [18-19]. Therefore, the present study was undertaken to evaluate the association of lipid profile, renal function, and uric acid along with anthro-demography and clinico-pathology in cervical cancer.

Materials and Methods

Subject Selection

The study was approved by Institutional Ethics Committee (IEC) (256/Ethics/R.Cell-18 Dated 24/09/2018). The study subjects comprised of 108 healthy women as controls and 103 cervical cancer (CaCx) patients of same ethnicity. The patients were enrolled in the outpatient unit of Departments of Radiotherapy as well as Obstetrics and Gynecology, King George's Medical University (KGMU), Lucknow as per inclusion/exclusion criteria.
Inclusion criteria: Histo-pathologically positive for all stages of squamous cell carcinoma (SCC) and adenocarcinoma (AC), age 30-70 years with cervical cancer symptoms such as vaginal discharge, pain in the lower abdomen and contact bleeding and cervical biopsy positive.
Exclusion criteria: Age >70 years, having double malignancy and co-morbidities (diabetes, tuberculosis, HIV), cervical biopsy negative, and those who were not willing to participate in the study.
Inclusion criteria of control subjects: Healthy age-matched with no previous history of any cancer and histo-pathologically negative for all stages of SCC and AC.

Anthro-demographic and Clinico-pathological Characteristics

CaCx patients and healthy women were interviewed extensively for anthropometric (age and body-mass index), demographic data (residence, literacy, socioeconomic status), obstetric profile (parity, age at full-term pregnancy, menstrual cycle, management of menstrual hygiene, menopause and use of contraceptives) and smoking status in a structured proforma and cross verified by medical records of the study subjects to reduce biases. Clinical diagnosis of patients was performed by expert medical personnel following the guidelines of

the International Federation of Gynecology and Obstetrics (FIGO) classification system.

HPV testing and genotyping

Cervix tissue samples from all 103 patients diagnosed for cervical cancer were collected by biopsy punch in RNA*later* for HPV testing/genotyping. The tissues were washed in lysis buffer/PBS and DNA was extracted using a commercially available Purelink DNA isolation kit (Invitrogen, USA). DNA quality and quantity were estimated in a Bio-photometer (Eppendorf, Germany) and stored at -20^{0}C until further use. HPV testing was done by conventional PCR using PGMY09/11primers (Integrated DNA Technologies, IDT, USA) [20]. PCR was performed in a 25 µl reaction mixture containing template (50-100ng), 10pmol of each primer, 200µM dNTPs, and 0.5 U of Taq DNA polymerase (MBI-Fermentas, USA) in a gradient Master Cycler (Eppendorf, Germany) and the amplified products were resolved on 2% agarose gels along with 100bp DNA ladder. The sample was considered as HPV positive if the amplified product showed a 450bp size band on the gel (Figure 1).

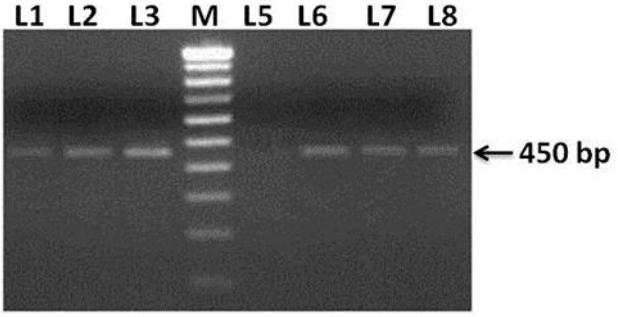

Figure 1: Agarose gel (2.0%) representing amplified product of HPV genome (450bp). Lane 1-3, 6-7 showing HPV positive, lane 5 HPV negative and lane is 100bp ladder

Biochemical Analysis

Two ml of blood samples were collected from CaCx patients and healthy women in non-EDTA vials for serum separation to be used for biochemical analysis. Serum was separated by centrifugation at 3000 rpm at 4^{0}C for 6 minutes and stored at -20^{0}C for further use. Serum samples (200µl) were used for biochemical estimation of lipids (total cholesterol, TC; triglycerides, TG; high-density lipoprotein, HDL; low-density lipoprotein, LDL), renal function tests (serum urea and creatinine) and uric acid levels using commercially available CliniQuant FSR Kits (Meril Diagnostics, India) in a Blood Analyzer, (SelectraProS, ELITech Clinical systems, France).

Statistical analysis

Demographic, obstetrics and smoking data are given in percentage while Body Mass Index (BMI), Lipid Profile, Renal Function Test parameters, and Uric acid

levels are given as mean±SEM. Chi-square (π^2) test was used to compare healthy women with CaCx patients. Multivariate analysis was performed by fitting logistic regression models to yield odds ratios (ORs) and 95% confidence intervals (CIs), adjusting for variables that were found to have a significant association with biochemical risk factors, anthro-demographic and clinico-pathologic variables, wherever appropriate. All P values were two-sided and differences were considered statistically significant for $P<0.05$. The statistical analyses were performed by SPSS (Version 21.0). The missing data was rectified by using zero (0) as per the statistical tool.

Results

All analyses were carried out on 108 healthy women and 103 CaCx patients. Out of 103 CaCx patients tested for HPV, 86 (83.5%) were found positive while 17 (16.5%) were negative.

Anthro-demographic Characteristics

The age distribution of CaCx patients with respect to healthy women did not show a significant association (p=0.174) (Table 1). The percentage of CaCx patients in the 40-49 years age group was 29.1% and 50-59 years was 36%. Therefore, the mean age for development of cervical cancer was 49.8years (Table 1). The residential distribution of CaCx patients also did not show any significant association (P=0.268) (Table 1). However, 72.8% of cervical cancer patients were from rural areas. Illiteracy among CaCx patients was observed to be higher (62.1%) and showed significant association (P=0.003) in comparison to healthy women (42%) (Table 1). The lower socio-economic status (44.7%) of cervical cancer (CaCx) patients showed a significant association (p=0.001) in comparison to healthy women (28.7%) (Table 1). The smoking status of CaCx patients did not show any significant association (P=0.145) in comparison to healthy women (Table 1).

Table 1: Anthro-demographic characteristics and smoking status of healthy women and cervical cancer (CaCx) patients

Demographic Profile		Healthy Women N=108 (%)	CaCx Patients N=103 (%)	P-value
Age (in years)	30-39	30 (27.8)	16 (15.5)	0.174
	40-49	25 (23.1)	30 (29.2)	
	50-59	33 (30.6)	37 (35.9)	
	60-69	20 (18.5)	20 (19.4)	
Residence	Rural	71 (65.7)	75 (72.8)	0.268
	Urban	37 (34.3)	28 (27.2)	
Literacy	Illiterate	45 (41.7)	64 (62.1)	0.003
	Literate	63 (60)	39 (37.9)	
Socio-economic status (SES)	Upper	18 (16.7)	04 (3.9)	0.001
	Middle	59 (54.6)	53 (51.5)	
	Lower	31 (28.7)	46 (44.7)	
Smoking	Non-	51 (47.3)	59 (57.3)	0.145

	Smokers			
	Smokers	57 (52.7)	44 (42.7)	

Clinico-pathological Characteristics

Abnormal obstetrics profiles such as high parity, higher age at first full-term pregnancy, irregular menstrual cycle, menopausal age (>45 years), and adverse menstrual hygiene and use of contraception showed significant association (P<0.001) with CaCx (Table 2). More than two children were recorded in 85% of CaCx patients. Full-term pregnancy age <20 years was seen in 54% of CaCx patients. An irregular menstrual cycle was reported in 70% of CaCx patients and menopause was attained at the age of >45 years in 50% of patients.

Table 2: Clinicopathological characteristics and smoking status of healthy women and cervical cancer (CaCx) patients

Obstetrics profile		Healthy Women N=108 (%)	CaCx HPV+ve N=103 (%)	P-value
Parity	None	13(12.0)	03 (02.9)	<0.001
	<2	55(50.9)	13 (12.6)	
	>2	40(37.1)	87 (84.5)	
Age at first full-term pregnancy	>20	80(74.1)	47 (45.6)	<0.001
	<20	28(25.9)	56 (54.4)	
Menstrual Cycle	Regular	105(97.2)	31 (30.1)	<0.001
	Irregular	03(2.8)	72 (69.9)	
Menopausal Age	None	28(25.9)	08 (07.8)	0.003
	<45	40(37.1)	51 (49.5)	
	>45	40(37.0)	44 (42.7)	
Menstrual Hygiene	Napkins	52(48.1)	25 (24.3)	<0.001
	Cloths	56(51.9)	78 (75.7)	
Use of Contraception	None	107(99.07)	97 (94.2)	0.047
	OCPs	01(0.93)	06 (05.8)	

Biochemical Characteristics

Body Mass Index (BMI) was found to be significantly associated (<0.001) in CaCx patients compared to healthy women (Table 3). Multinomial regression analysis suggested that although BMI increased the risk in CaCx patients by 1.14 folds, it was non-significant. However, when BMI was adjusted with literacy, socioeconomic status and obstetric biomarkers the risk was found to increase significantly by 1.18 folds (p=0.011) when compared to healthy women (Table 3). The levels of Triglycerides (TG), High-density lipoprotein (HDL), Low-density Lipoprotein (LDL), and Cholesterol were found to be higher in CaCx patients as compared to healthy women (Table 3).

Multinomial regression analysis predicted the risk of TG, HDL, LDL and cholesterol in CaCx patients and showed a significant association (p=<0.05) with a crude odds ratio of more than 1.0-fold. When dyslipidemia was adjusted with

literacy, socioeconomic status, and obstetric biomarkers, the adjusted odds ratio (OR) of LDL significantly increased up to 1.04 and others were equal to crude OR (Table 3).

Urea and creatinine levels were found to be highest in CaCx patients (Table 3). Likewise, creatinine levels also increased the risk significantly by 2.64 folds in CaCx patients (Table 3). However, after adjustment renal dysfunction parameters were found to increase the relative risk up to 1.12 folds, while creatinine level showed an odds ratio of 3.37 folds (Table 3). The uric acid level was found higher among CaCx patients compared to healthy women which indicated hyperuricemia. Hyperuricemia was associated significantly (<0.001) in CaCx patients with crude odds ratio adjusted odds ratio of 1.29 folds (Table 3).

Table 3: Multinomial logistic regression analysis of biochemical parameters in healthy women (n=108) and cervical cancer patients (n=103).

Parameters	Healthy Women	CaCx patients	P-value Crude Odds Ratio (95% CI)	P-value Adjusted Odds Ratio (95% CI)
BMI	22.5±0.3	24.3±0.5	0.092 1.14(0.98-1.33)	0.011 1.18(1.04-1.35)
TG	61.7±2.5	189.0±13.6	<0.001 1.03(1.02-1.04)	0.001 1.03(1.02-1.04)
HDL	70.7±3.2	115.4±4.4	<0.001 1.03(1.02-1.04)	0.001 1.04(1.02-1.05)
LDL	80.5±3.6	141.0±6.6	<0.001 1.03(1.02-1.04)	0.004 1.04(1.02-1.05)
TC	150.5±2.8	182.2±9.3	0.048 1.01(1.00-1.01)	0.066 1.01(1.00-1.01)
Urea	18.2±1.0	42.9±2.1	<0.001 1.11(1.07-1.14)	<0.001 1.12(1.08-1.17)
Creatinine	0.8±0.04	2.4±0.2	0.001 2.64(1.48-4.50)	<0.001 3.37(1.78-6.42)
Uric Acid	5.1±0.2	8.1±0.5	<0.001 1.29(1.13-1.48)	<0.001 1.29(1.15-1.45)

Significance =<0.05; BMI=Body-Mass Index; TG=Triglyceride; HDL=High Density Lipoprotein; LDL=Low Density Lipoprotein. *National Cholesterol Education Programme (NCEP) guidelines, 2001 [21]. Dyslipidemia (≥170mg/dl for hypertriglyceridemia; <30mg/dl for Low HDL; and ≥160 High LDL; ≥250mmol/l for hypercholesterolemia), Renal dysfunction (≥18md/dl for Urea; 1.1mg/dl for Creatinine), Uricemia (≥6.8mmol/l for uric acid) [8].

Discussion

Epidemiological and clinical data suggested that cervical cancer development is a multifactorial and complex process in which human papillomavirus (HPV) infection takes a central role [2] along with other risk factors such as advanced age, illiteracy, low socioeconomic status (SES), smoking, parity, age at first full-term pregnancy, irregular menstrual cycle, menopause age, menstrual hygiene, sexual behavior and family history [4-5, 22]. The association of HPV infection

illustrated that in females this might be due to sexual transmission of the virus as well as the possibility of autoinfection by urogenital contact among women as a result of poor sanitation and hygiene [5, 23]. In the present study, the prevalence of HPV infection is approximately 83% in cervical cancer cases. HPV testing is expensive; thus, screening is not common in the general population specially in developing countries. Although HPV infection is the major risk factor in CaCx, the present study was undertaken to evaluate the association of anthro-demographic and clinico-pathological factors with CaCx.

The present work investigated age, demographic profile, anthropometric profile, and clinico-pathological characteristics of CaCx patients and healthy women. Most studies have shown that malignancy is presented more in the elderly population as compared to young ones [23], therefore, age is a crucial factor in malignancy. The cervical cancer cases belonged to the higher age group (>40 years) with a mean age of 49.8 years (Table 1) and showed a significant association in the study population as reported by Afroj et al. (2017) [24]. Since cervical cancer progression takes 10-15 years to manifest, cases with HPV infection are subjected to several other risk factors and the disease manifests beyond 40 years of age [3, 5]. However, there is a report that girls of 15-19 years are more susceptible to HPV infection [23].

Socio-economic status (SES) is a major demographic risk factor that affects the health and hygiene of individuals in a community. Socio-economic status refers to social and economic factors including residency, literacy, income or wealth which influence the attitude of an individual or group within the community [5]. Low-income, less educated and working-class population are less likely to have cancer screening options. The results showed that 45% of patients were from lower SES and 52% were from middle SES (Table 1). A similar study was conducted in 22 European countries which showed that SES inequalities influence the Otani based screening programs, and careful consideration of early disease detection [11].

In the present study, it was found that the CaCx patients comprised of a higher percentage of illiterate women (Table 1). Therefore, illiteracy also seems to be a co-factor associated with cervical cancer [25]. This observation is along the line that women from less educated, socially backward, and low economic backgrounds are less aware of cervical cancer and need to be educated about sexual habits, personal hygiene and their implications.

Cigarette smoking is an environmental risk factor for many cancers including cervical cancer and is independent of sexual behaviour and SES [4, 24-26]. Smoking has been linked to the secretion of tumor-specific metabolites in cervical mucus. This mucus maintains cervical oncogenic infection [25] and also increases the production of reactive oxygen species (ROS) in cells, resulting in oxidative lesions in DNA [26]. Exposure to cigarette smoke and carcinogens induce gene mutation and other genetic effects in targeted tissues, which are hallmarks of cancer [27]. The present study observed 43% of smokers among CaCx patients (Table 1). However, a previous study reported that termination of smoking facilitated the decline of cervical cancer [26]. The effects of smoking have been well studied and showed a strong association with cervical cancer [22, 26].

Early age of marriage (<20 years) indicates exposure to sexual activities leading to HPV infection and early pregnancy, a well-known etiological factor for cervical cancer [5, 22]. Obstetric biomarkers showed a significant association in CaCx patients (Table 2). A significant decline in cervical cancer is likely due to changes in marriage and family planning, supported by underlying improvements in education and SES [4-5]. National programs on screening for cervical cancer reduced the incidence and mortality rate in developed countries such as Denmark and Finland. The present study also suggested that multiparity is significantly associated with a higher risk of cervical cancer (Table 2). Age at full-term pregnancy and high parity can put women at a higher risk of HPV infection and thereby cervical cancer [22, 26].

Women using oral contraceptive pills (OCPs) for more than 5 years showed significant correlation to CaCx (Table 2). Long-term use of oral contraceptives could be a cofactor that increases the risk of cervical carcinoma up to four-folds [2, 28]. Menstrual management and prevention of pregnancy were major risks found in the study. These factors can prevent or delay the symptoms of cervical cancer. However, not much information is available worldwide, thus further work is required to enrol long-term users of oral contraceptives in CaCx screening programs [22, 28].

Body mass index (BMI) is an extensive risk factor for the assessment of morbidity and mortality of complex diseases. It has been associated with diabetes, dyslipidemia, renal dysfunction, cardiovascular diseases, hypertension, gallbladder stone, breathlessness, and certain cancers including breast and cervical [28-29]. Raised BMI contributes to various pathophysiological roles in chronic inflammation, hormone dysregulation, and metabolic disturbances which lead to the weakening of immune system and increased susceptibility to viral and bacterial infections [29]. In case of cervical cancer, women with raised BMI are more prone to HPV infection or incapable of clearing an acquired infection. However, the role of BMI and HPV infection are poorly defined and are open to debate. Previous cross-sectional studies reported that the prevalence of HPV infection increased with obesity [28-29]. Unlike, Liu et al (2015), the incidence, clearance, and persistence of HPV were similar in normal to overweight and obese women [28]. In the present study, BMI showed a significant maximum likelihood estimation in CaCx patients with a 1.18-folds risk when adjusted with literacy, SES and obstetric risk factors. This indicated that raised BMI may be a contributing factor for HPV infection and its persistence.

Lipids are important constituents of cell membranes that have been utilized by tumour cells for the fulfilment of bioenergy and biomass production [13]. Although various epidemiological reports were controversial regarding the association of dyslipidemia with cervical cancer, the present study showed significant differences (p=<0.001) in triglyceride (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and cholesterol levels. Hence, dyslipidemia may be a causative factor for CaCx with HPV infection. Our findings resembled that of Mary et al, (2021) [18] and Jiang et al, (2022) [30]. However, there are controversial studies regarding the association of lipid profiles in CaCx patients [31]. Dyslipidemia has also been reported in breast cancer patients in support of the present study [7,9-10]. Dyslipidemia was found to be significant (p=0.001) in

CaCx patients as compared to healthy women (Table 3). Therefore, CaCx is coupled to a disordered lipid profile characterized by high TG, HDL, LDL and cholesterol levels.

Renal dysfunction is a frequent complication in various cancers of prostate, bladder, uterus, and cervix. It can be acute/chronic and preventable/reversible with prompt diagnosis and treatment [32]. In the advanced stage of cancer, the connective tissues at the distal ureter develop tumor parametrium in cervical cancer [18]. In the present study, elevated levels of urea and creatinine were found to be significantly different (p=<0.001) in CaCx patients (Table 3). This is the first report to our knowledge indicating elevated levels of creatinine during HPV infection and that urea is associated with CaCx independently. Similarly, creatinine levels were reported to be higher in the liver, colon, uterine, and CaCx [8, 28, 32]. The findings indicate a significant association between renal dysfunction and CaCx (<0.001). Urea levels impacted the cancer progression with or without HPV infection independently (<0.001) with increasing risk upto 1.11 folds in comparison to healthy women.

Previous studies suggested that metabolic by-products and related factors play an important role in cancer development, incidence, diagnosis, and prognoses like dyslipidemia and hyperuricemia [14]. Impairment of uric acid leads to hyperuricemia and it is involved in the physiopathogenesis of gout, cardiovascular diseases, respiratory diseases, and cancer [15]. In the present study, increased levels of uric acid showed significant difference (p=<0.001) in CaCx patients compared to healthy women (Table 3). In multinomial regression analysis, uric acid showed a 1.29 risk in comparison to healthy women. Two groups have independently reported that hyperuricemia is a major metabolic indicator for the poor prognosis of CaCx [16, 18]. Although uric acid possesses antioxidant properties but its increased level leads to chronic and systematic inflammatory responses in the human body and thus promotes tumorigenesis. The limitations of this study warrant consideration. The size of study population was small and only included patients from northern India. It is also possible that there might be unmeasured confounding variables.

Conclusion

The present study dealt with the clinical association of dyslipidemia, renal dysfunction, and uricemia in cervical cancer patients and healthy women. BMI, TG, HDL, LDL, cholesterol, urea, creatinine, and uric acid were elevated in CaCx patients along with literacy, SES and obstetrics profile as cofactors. Age (40-49 years) and multiparity are major co-factors responsible for HPV-mediated cervical cancer. Furthermore, dyslipidemia may be a major complication of hypertension and heart-related disease in the advanced stage of cervical cancer. Similarly, renal dysfunction and uricemia may cause kidney failure in the future or patients may have a poor treatment outcome. However, women with advanced age can prevent or delay the disease by managing their clinico-pathological characteristics. TG, HDL, LDL, cholesterol, urea, creatinine, and uric acid can be used as prognostic biomarkers for HPV-mediated cervical cancer.

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Statement of Ethics

All subjects and their guardians were informed by duly written consent in compliance with the Helsinki Declaration before the study and sample collection procedures. The study was approved by the Institutional Ethics Committee (256/Ethics/R.Cell-18 Dated 24/09/2018).

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