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CLINICO-PATHOLOGICAL FEATURES, OCCUPATIONAL RISK FACTORS AND LIFE STYLE IN THE PATIENTS OF CERVICAL CANCER.

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ABSTRACT

The incidences of cervical cancer nowadays, have shown higher occurrence rate in women belonging to very low socio-economic status as well as residing in unhygienic conditions especially in rural and slum areas. Recently, due to application of various effective screening methods, health care and survey programme conducted in Western countries, due to which the incidence of invasive cervical cancer have been decreased. In spite of effective screening techniques, still cervical cancer remain one of the most common cancer in women, next to breast and lung cancer, which is most leading cause of female patients death in India. Most prevevalent states in India…

The various associated risk factors are multiple sexual partners, high-risk male whose previous partner had cervical cancer and persistent HPV infection, lower socio-economic status, multiple pregnancies, promiscuity, exposure to carcinogens, smoking and long term oral contraceptive pills (OCP) usage. In this present study, we observed a strong association is found between clinico-pathological features, occupational, life style and risk of developing cervical cancer in individuals carrying specific alleles among the population [18,19].

Figures: References: Table: 03

Key Words: Cervical cancer, Occupational, Clinico-Pathological, OCP.

Introduction

Cervix cancer is the most prevalent in women which affecting over 25, 00000 lives annually with 5, 00000 newly diagnosed cases in the world. It is nearly about 80% of cases occurred in low-developing countries. Besides that about 99 % of diagnosed cases had infection of Human papilloma virus (HPV) which is most prevalent viral infection of the reproductive system, it accounts to nearly all cases of cervical cancer**.** Cervical cancer is associated with nearly 5% of the death among female patients suffering from cervical cancer[5.] Cervical cancer is the most prevalent cancer among Indian women between the age group of 15 to 44 years. In recent years approximately 132,000 women in India are being diagnosed with cervical cancer per year, resulting nearly 74,000 deaths due to cervical cancer. However, due to implementation of recent advance screening and diagnostic techniques like histological examination of biopsy and Pap (papanicolaou) smear screening method conducted at larger scale, have greatly decreased the mortality rate in patients of cervical cancer.

Although Pap smear test is moderately sensitive due to its certain limitation. This restricts the present screening attempts that require further diagnostic confirmation using biomarkers. Cervical cancer and invasive cervical neoplasia are known to be largely induced by simultaneous infection of HPV **[1].** Based on their correlation with invasive cervical cancer, about two third of HPV strain are associated with cervical neoplasia, which have been categorized into high and low-risk groups **[12].** Symptoms of

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cervical cancer have been reported are like blood stained discharge per vaginum, post-coital bleeding and low backache etc [10]. The various associated risk factors are multiple sexual partners, high-risk male whose previous partner had cervical cancer and persistent HPV infection [3], lower socio-economic status, multiple pregnancies, promiscuity, exposure to carcinogens, smoking, long term oral contraceptive pills (OCP) usage and immunodeficiency make lesions more likely to progress. While a negligible rate among nuns and virgins are reported [3]. In present scenario cervical cancer is being known as one of the most preventable and treatable forms of cancer in vide arena at global level.

In humans, NAT-1 gene is responsible for N-acetyltransferase activity. Several allelic variants of NAT-1 gene which cause variations in acetylation capacity have been detected [9]. O-acetylation of the N-hydroxyarylamine yields an acetoxy arylamine derivative which breaks down spontaneously to a highly reactive arylnitrenium ion, this metabolite responsible for mutagenic and carcinogenic lesions [7]. Variations in the N-acetyltransferase (NAT-1) gene among different populations could affect the metabolism and disposition of drugs [8]. Therefore, it is required to investigate the role of NAT-1 genotypes and/or phenotypes together with other genetic susceptibility factors, biomarkers, various associated risk factors and carcinogen exposure to understand the role of NAT-1 acetylation polymorphisms in cancer risk [6]. Such analysis of the allelic profile of populations in different geographic locations may help to understand the incidence of cervical cancer in India [18,19].

Hence, the aim of present study is to compare and correlate the various associated clinico-pathological features, occupational risk factors and life style in the patients of cervical cancer and normal healthy control. The various parameters such as clinico-pathological features, life style and occupational risk factors etc., that account for the development of cervical cancer were studied.

Materials and Methods

Patient's Sample: In present study, a total of 75 patients of cervical cancer were included, after full filling the selection criteria and a total 75 subjects with non-malignant lesions of cervical tissue were taken as control after obtaining the human ethical clearance from Institutional Ethical Committee (wide letter no. 116 / Ethical Committee/ S.C.-1/2018 Dated 10/01/2018 issued from Principal office, Maharani Laxmi Bai Medical College, Jhansi, U.P. India).

Inclusion criteria were that those patients who were diagnosed as Squamous cell carcinoma (SCC), their blood sample was taken. Exclusion criteria were those patients with the history of prior radiation exposure to the site (prior radiotherapy) and history of chemotherapy. The written informed consent was taken from all participating subjects / Patients.

Life style and occupational risk factors: The relevant clinical history of all cases was collected in a pretext performa and clinical history was used for the selection of appropriate cases as per exclusion/inclusion criteria of the study.

Clinico-pathological features: All clinico-pathological features and other risk factors for cervical cancer cases of the study conducted were recorded in a pretext performa.

Result:

In present study a total number of 75 cases of cervical carcinoma were examined. All the cases fell in the age range between 18 to 70 years. The maximum number of cervical cancer cases i.e. 49.33% (37/75) was in the age group of 45-60 years whereas 20% (15/75) of cases were < 45 years of age and 30.67% (23/75) cases were > 60 years of age. The median age of cases in the study group was 48 years, while the mean age was 48.69 years[18,19]. (Figure 1).

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Analysis of clinico-pathological and other risk factors

All clinico-pathological and other risk factors for cervical cancer cases of the study conducted are recorded in Table No.1 & 2. Clinically highest cases (52%) with respect to histological grades observed in grades III and lowest 16% in grade I respectively. More than 70% cases were in postmenopausal age. Histological grades show highest 97.43% in grade type III positivity for NAT-1while lowest 33.33% in grade type I. Histological grades show highest 89.74% in grade type III positivity for NAT-1while lowest positivity 8.33% in grade type I (Table No.1 & 2).

Positive correlation was found with other clinicopathological features like age of menarche and menopause, smoking, menopausal stage, occupation, personal hygiene, consumption of red meat, workout physical activity, onset of symptoms and disease, vaginal bleeding, weight loss, fatigue, blood loss, abdominal pain and pain during coitus, loss of appetite, Urogenital discomfort (Table No.1 & 2).

However age wise highest positivity 89.18% for NAT-1 in age more than 60 years while lowest positivity 40% in age ranging less than 45 years. Age wise highest positivity 75.67% in age more than 60 years while lowest positivity 26.66% in age ranging less than 45 years. Expression for NAT-1 protein in 77.33% cervical cancer cases with highest positivity for NAT-1 protein while highest negativity for NAT-2protein. Lowest Negative cases 22.67% for NAT-1 protein expression and 38.67% for NAT-2 protein expression. Lowest positivity (61.33%) observed for NAT-2 protein expression (Table No.3).

Discussion: The number of cases of cervical cancer has increased in recent years, particularly in urban areas of developing and less developed nations, which continues to be highly common malignancy in women globally and the primary cause of deaths due to cancer. INDIAn context

In our study, the median age 48 years, while the mean age was observed 48.69 years.

While the National Cancer Institute in the USA reports that the mean age 49 years at diagnosis for cervical cancer the National Cancer Registry Programme (NCRP) reports that the Indian population has a lower mean age. Our findings are consistent with the majority of other studies. Variations in expression of different regulatory and oncoproteins are linked to genetic changes. Thus many oncologists are now taking on an opinion that exploring the genetic basis of tumors is important. It is now understood that oncogenes mutations, which are involved in many of the fundamental cellular processes, cause the majority of carcinomas **(World Health Organization, 2002).** The oncogenes play a highly significant role for controlling cellular proliferation, differentiation, and survival. It also affects how the cervix grows and develops normally in females.

Like oncogenes, apoptosis-related genes are also distorted as an amplification or mutation and play very essential role in development and progression of cervical cancer. Positive correlation was found with other clinicopathological features like age of menarche and menopause, smoking, menopausal stage, occupation, personal hygiene, consumption of red meat, workout physical activity, onset of symptoms and disease, vaginal bleeding, weight loss, fatigue, blood loss, abdominal pain and pain during coitus, loss of appetite, Urogenital discomfort which was found in accordance with previous studies.

The patient's age influences how NAT-1 and NAT-2 proteins are expressed, whereas highest expression of NAT-1 and NAT-2 was observed in those above the age of 60 years. This association was statistically significant. In the current study, we observed a strong correlation between NAT-1 and NAT-2 Immunohistochemically expression in cervical cancer. However age wise highest positivity

89.18% for NAT-1 in age more than 60 years while lowest positivity 40% in age ranging less than 45 years. Age wise highest positivity 75.67% in age more than 60 years while lowest positivity 26.66% in age ranging less than 45 years. Expression for NAT-1 protein in 77.33% cervical cancer cases with highest positivity for NAT-1 protein while highest negativity for NAT-2protein. Lowest Negative cases 22.67% for NAT-1 protein expression and 38.67% for NAT-2 protein expression. Lowest positivity (61.33%) observed for NAT-2 protein expression.

Even though NAT-1 and NAT-2 genotype and cancer of cervix have a significant relationship in the Indian population, according to our data, the etiology of cancer of cervix can be explained by allelic variation at a single locus. Instead, the basic cause of cancer of cervix in the population is most likely an outcome of long-term interactions between several hereditary and environmental factors **(Coughlin et al., 1999).** Further study may aid in our understanding of polymorphism and how lifestyle choices, hormonal states and the environment may affect these polymorphisms. The population that is being studied, together with a number of environmental and dietary parameters that have an effect on that population, may have an influence on how much genetic variation contribute to cancer of cervix risk.

In cancer, expression of protein and functions are found to be influenced by different mutations. Genotypic alterations in NAT-1 gene may play important role in cervical cancer initiation and progression as this contains series of target genes involving various cancer suppressor genes and oncogenes. Further advance study, along with findings of present study, might be useful in development of better technique for prevention, screening, diagnosis of cancer of cervix. The cause of our findings may be attributed to this fact that a larger population coming to MLB hospital reside in rural areas and in districts like semi urban with fewer facilities of an urban area or in closer proximity to urban area approximately within 100 KM.

That will help to understand the effect of life style risk factors and gene polymorphism in causing cervical cancer [18,19].

Conclusion:

The cause of our findings may be attributed to this fact that a larger population coming to MLB hospital reside in rural areas and in districts like semi urban with fewer facilities of an urban area or in closer proximity to urban area approximately within 100 KM. Based on these observations and findings, we propose that each group should assess its own genetic profile for cancer risk, which would help us understanding the regional and racial variations in cervical cancer incidences and deaths that have been reported.

The findings of our analysis were generally in accord with those of numerous previous research studies. Other approaches to studying the expression of these genes, such as mRNA analysis using RT-PCR, have also been used in the literature.

However, no conclusive and significant association could be identified due to smaller patients sample size. In order to research the exact probability of cancer of cervix in the Indian population, it is necessary to understand prevalence of the different genotype of primary genes that contributed in progression of disease and to increase patients sample size. The genetic risk factors identification can be useful in predicting the occurrence of cervical cancer and defining high risk individual. Therefore we have proposed that each particular population is required to evaluate its own genetic profile for cervical cancer risk that may be helpful for better understanding of racial and geographic differences reported for cervical cancer prevalence and death. The findings will be useful to for future prospects in health

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improvement at each level by prevention and final mitigation in short time.

Table No. 1. Occupational risk factors and Life style in the patients of cervical cancer and normal healthy control.

Occupational risk factors and Life style			Cases (Cervical Cancer)				Normal healthy control			
Sr. no.	Parameters/ Characteristics	Present	%	$p<0.05$ *	Absent	%	Present	%	Abs	%
1	Status of Smoking/Chewing Tobacco	47	62.66 %	*	28	37.33 %	---	---	75	100 %
	(Bidi/ Cigrette/ Gutka/ Day)									
2	Alcohol Consumption - (Amount in ml/Frequency)	21	28%		54	72%	4	5.33%	71	
3	Occupational - Pesticides/Industries/Chemicals/ Dyes/Carcinogens	57	76%	*	18	24%	7	9.33%	68	
4	Personal Hygiene-Spouse with any Genital, STD & other infection	62	82.66 %	*	13	17.33 %	---	---	2	
5	Dietary History									
a	Red Meat-Mutton (Weekly Frequency)	37	49.33 %	*	---	---	12	16%	----	
b	White Meat-Chicken	14	18.66 %		---	---	29	38.66 %	---	
c	Fruits/Vegetables	24	32%		---	---	34	45.33 %	---	
d	Coffee/ Tea - Yes/No	68	90.66 %		7	93.33 %	71	94.66 %	4	
6	Workout/Physical Activity:	22	29.33 %	*	53	70.66	68	90.66 %	7	

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Table No. 2. Clinico-pathological features in the patients of cervical cancer and normal healthy control

Clinico-pathological features			Cases (Cervical Cancer)				Normal healthy control			
Sr. no.	Parameters/ Characteristics	Present	%	*p*< 0.05 *	Absent	%	Present	%	Abs	%
	Surgery in Past if any	23	30.66 %	*	52	69.33		4.00%	72	
	Family History of Cancer	8	10.66 %		67	89.33 %	nil	----	75	
	Onset of symptoms and Disease	63	84%	*	12	16%	---	---	75	100%
	Bleeding P/V	69	92%	*	6	8%	---	---	75	100%
	Unexplained Weight Loss	71	94.66 %	*	4	5.33%	---	---	75	100%
	Fatigue	73	97.33 %	*	2	2.66%	---	---	75	100%
	Problems Related to Blood Loss	69	92%	*	6	8%	---	---	75	100%
	Abdominal Pain	73	97.33 %	*	2	2.66%	---	---	75	100%
	Loss of Appetite	64	85.33 %	*	11	14.66 %	---	---	75	100%
	Age of Menarche (< 12 yrs)	66	88%	*	9	12%	70 (apx12 Yrs)	93.33 % *	5 (> 12 yrs)	6.66 %
	Age of Menopause (> 45 years)	70	93.33 %	*	5	6.66%	(apx 45 years)72	96% *	3	4%
	Age of Sexual activity (average)	13 Yrs	---		---	---	19 Yrs *	---	---	---
	H/o STD if any	8	10.66 %		67	89.33 %	---	---	75	100%
	Duration	(> 5 Yrs) 61	81.00	*	(<5 Yrs) 14	18.66 %	---	---	75	100%
	Urogenital Discomfort	74	98.66 %	*	1	1.33%	---	---	75	100%

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Figure No. 1 Correlation between Age wise groups, Histological Grades and NAT-1 and NAT-2 protein expression in cervical cancer patients.

age groups	Cases	(n = 75)	%		positively for NAT-1			positively for NAT-2		
<45 yrs	15	75	20%	Lowest	6	40%	min.	4	26.66%	min.
45 – 60 yrs	23	75	30.67%		19	82.60%		14	60.86%	
> 60yrs	37	75	49.33%	Highest	33	89.18%	max.	28	75.67%	max.
Histological grades					positively for NAT-1			positively for NAT-2		
grade type I	12	75	16%	Lowest	4	33.33%	Lowest	1	8.33%	min.
grade type II	24	75	32%		16	66.67%		10	41.67%	
grade type III	39	75	52%	Highest	38	97.43%	Highest	35	89.74%	max.
	Positive cases	(n = 75)	%	Negative cases	(n = 75)	%				
Expression for NAT-1 in cervical cancer cases .	58	75	77.33%	17	75	22.67%	Highest positivity for NAT-1			
Expression for NAT-2 in cervical cancer cases.	46	75	61.33%	29	75	38.67%	Highest negativity for NAT-2			

Data Availability: The various pretexts Performa used and/or analyzed during the present study are available with the corresponding author.

Human Ethical Approval: Institutional Ethical Committee (wide letter no. 116 / Ethical Committee/ S.C.-1/2018 Dated 10/01/2018 issued from Principal office, MLB Medical College, Jhansi) approved the present study.

Conflicts of Interest: Authors has no conflicts of interest.

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Abbreviations: OCP: Oral Contraceptive Pills (OCP)
HPV: Human papillomavirus
NAT-1: N-acetyltransferase-1 gene

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