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Original Research Article

Role of Interleukin-18 and Associated Risk Factors in Cervical Cancer in North Indian Population

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ABSTRACT

Objectives: Inflammation is now regarded as important hallmark of carcinogenesis. We aimed to evaluate the level of circulating Interleukin-18 in pre-invasive and invasive stage patients of cervical carcinoma with healthy controls along with some additional events and risk factors.

Methods: It was a case-control study, 84 cases with equal number of controls were enrolled and diagnosis of cases was made through biopsy – proven cervical intra-epithelial neoplasia or cervical cancer. Peripheral blood samples were collected from cases and controls. Expression was evaluated in serum samples by ELISA method.

Results: Significant differences were found in the serum level of total Interleukin-18 in cases as compared to healthy controls (CIN I 325.80± 14.46 pg / ml= 340.52± 11.91, p value= 0.000 ; CINII 327.80 ± 12.97 pg / ml= 340.52± 11.91, p value= 0.002; CINIII 323.70 ± 12.22 pg / ml= 340.52± 11.91, p value= 0.000; CC 292.80 ± 6.25 pg/ ml= 340.52± 11.91, p value= 0.000). Moreover, increased risk was observed in passive smoking among cases as compared to controls (OR= 4.38, CI=95%, P=0.000).

Conclusion: In the present study we found that Interleukin-18 and assessed risk factors may play role in cervical carcinogenesis in North Indian population. Age of 1st pregnancy, parity, number of abortion, habit like passive smoking, sexual behaviour, menstrual and hygienic practices are important risk factors.

Keywords: Human papillomavirus infection (HPV), Cervical Cancer (CC), Cervical intraepithelial neoplasia (CIN).

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INTRODUCTION

Cervical cancer (CC) is second most common cancer in women worldwide and HPV infection is an established etiological agent but not sufficient alone. Immortilization of the cervical cell is necessary event for progress of cervical intraepithelial neoplasia (CIN) to invasive cancer and integration of HPV DNA to the host genome is master event for this.[1-4] Since, very less fraction of HPV-infected CINs progress to invasive cancer after a long latent period and additional events or risk factors also play crucial role in making HPV infection persistent and leading to cervical carcinogenesis. These risk factors may be genetic, immunological, sociodemographic.[5] Although previous reports suggested that host's inflammatory system and cell mediated immunity also serve important roles in determining whether HPV infections persist, regress or progress.[6]

A proinflammatory cytokine, Interleukin-18 (IL-18) might be associated with CC. It was discovered as an interferon-γ-inducing factor and plays important role in inflammation and immune response through stimulating natural killer cells and T cells.[7] IL-18 also has ability to enhance Th1 immune response and these activities eliminate cancer cells and virus-infected cells effectively. However, IL-18 has also found with higher expression in many cancer types. Some studies show its role in angiogenesis, migration/metastasis, proliferation and immune escape.[8] So the role of IL-18 needs to be investigated in cervical cancer.

On other hand, studies on risk factors of cc were available since early seventies.[9,10] Most of the studies recruited invasive cancers reporting to cancer clinics. No information was available for early cancerous or pre-cancerous lesions (CIN I, CIN-II, CIN-III). The Institute of Cytology and Preventive Oncology, ICMR New Delhi launched the first study, involving pre-cancerous and early cancerous lesions in 1976. The study was first of its kind in India since it had recruited the subjects based on the cytology screening program and showed the biological behaviour of precancerous lesions. A study of ICMR in 1976 was not only very necessary at that time but very important at present time because India was a developing nation and also the same till now.

Therefore we performed our research study in state's one of the largest medical university of Uttar Pradesh "The KGMU", this institution is completely dedicated for serving medical treatments for such dangerous diseases at minimum cost. So here we could assess many poor rural patients as well as urban patients because KGMU is situated in Lucknow (capital of Uttar Pradesh). This also given us opportunity to mark many undiscovered things and may make it one step forward for upcoming researchers.

MATERIALS & METHODS

Subjects

It was case- control study, conducted in King George's Medical University Lucknow, a tertiary care hospital. Included were 84 cases with 84 controls. Patients were registered at the OPD (Outpatient Department) and IPD (Inpatient Department) of the Department of Obstetrics and Gynaecology, KGMU, Lucknow, India. Diagnosis of cases was made through biopsy – proven cervical intra-epithelial neoplasia or cervical cancer. Papanicolaou test (Pap smear test) or Liduid Based Cytology (LBC) followed by colposcopy and biopsy are the steps for diagnosis. Peripheral blood samples were collected from all subjects. Cases were classified according to the International Federation of Gynecology and Obstetrics (FIGO) staging system and the control group were consisting of those with normal Pap smear (or LBC) and normal colposcopic finding. All the study procedures were approved by the institutional ethics committee. Informed consent was obtained from all the study subjects.

Interview Through Standardized Questionnaire

Both the cases and controls were interviewed in the department using a standardized questionnaire which covered their basic information such as religion, age, education, husband's education, socioeconomic status, habits- smoking or passive smoking, diet, hygine and marital information (age of first pregnancy, history of contraception, abortion, parity, menstrual duration, menopause). All 84 cases and 84 controls were interviewed, despite the sensitive nature of the interview and the rural background from which the women came, the participation rates were almost 100% for both cases and controls. None of the cases refused the interview and all give her consent. Although a few women were initially reluctant to answer the personal questions, particularly those related to their sexual history, all of them later co-operated, after it was explained that it was a research issue and they were assured that strict confidentiality would be maintained about their personal identity.

Here two types of variable continuous and categorical. In continuous variables are age, parity, age of first pregnancy, menstrual duration, age of menopause and how many times a woman get abortion. The categorical variables are religion, education, husband's education, history of contraception, family history of genital and breast cancer, hygiene, diet, smoking, socioeconomic status. The socioeconomic status is estimated through a questionnaire, which is based on kappuswami scale but we made some changes according to our requirements and we classified upper, middle and lower status according to their score obtained. Modification was done according to need for assessing both rural and urban women. This modification was based on literature review. The maximum aggregate score was 60. Based on the final score, the socio-economic states of the family is divided into three socio-economic categories, namely high (combined score of 50-60), middle (combined score of 30-50) and lower (combined score is less than 30).

Serum Collection & ELISA

Five ml of blood sample was taken carefully and allowed to clot at room temperature. Each sample was centrifuged at 2400 g rpm for 10 minutes to separate the serum. All the serum samples were stored at -80^{o}C until assayed. The levels of total Interleukin-18 was measured using enzyme-linked immunosorbent assay (ELISA) by commercially available kit (RayBio® Catalog #: ELH-IL-18). Procedure was followed as per manufacturer's protocol. The optical density of the samples was determined at 450 nm with i Mark microplate absorbance reader.

Statistical Analysis

Before entering the data into the computer, individual forms were scrutinized thoroughly for accuracy and consistency. Statistical analyses were performed using SPSS 16 .0 version (Chicago, Inc. USA), as statistical tool. The results are presented in mean ± SD. The continuous variables were compared with t-test. Categorical variables were determined by Chi-square test. Associations between various study parameters and the risk of CC were determined by comparing each case variable separately with the controls in the univariate analysis. The risk was calculated at 95 % of confidence interval. The p-value was set at <0.05 as significant.

RESULTS

This study had total 168 subjects (84 cases and 84 controls). Table 1 shows that socioeconomic status and dietary details of cases and controls. In the present study, 76.2% of the cases and 17.9% of the controls were belong to low socioeconomic status (LSS) ($p<0.05$). Protective association was found in univariate analysis of hygiene practices which explained that those cases (77.4%) and controls (32.1%), reuse the sanitary napkins or cloth during their menstrual cycle were at more risk. Moreover, passive smoking also play a significant role in cervical carcinogenesis in north Indian women and increased risk was observed among cases as compared to controls (OR =4.38, CI= 95%, p=0.000).This is because smoking is related in causing defects in DNA repair system in biological cell and leads to carcinogenesis, and DNA damage has been also found in cervical tissue of smokers. Besides this, women suffering from cc found 83.3% were educated up to middle school certificate and mostly are illiterate (47.6% in control), 15.5% were graduate (47.6% in control), 1.2% were professional (4.8% in control) and p-value found significant (p value= <0.05). Husband's education also shows the same.

Table 2 shows the clinical characteristics of the studied population. We have found significant association in Pariety, Age at 1st pregnancy and Number of abortion among cases as compared to controls ($p <0.05$).

As shown in table 3, significant differences were found in the serum levels of total Interleukin-18 in cases as compared to healthy controls (CIN I 325.80± 14.46 pg / ml= 340.52± 11.91, p value= 0.000; CINII 327.80 ± 12.97 pg / ml= 340.52± 11.91, p value= 0.002; CINIII 323.70 ± 12.22 pg / ml= 340.52± 11.91, p value= 0.000; CC 292.80 ± 6.25 pg / ml= 340.52± 11.91, p value= 0.000).

Table 1: Demographic, socioeconomic and dietary details of the studied population

Variable	Case [n (%)]	Control [n (%)]	P-value
Religion			
Hindu	77(91.7)	79(94.0)	0.186
Muslim	5(6.0)	1(1.2)	
Sikh	2 (2.4)	4(4.8)	
Education			
Up to middle school certificate	70 (83.3)	40(47.6)	
Up to graduate	13(15.5)	40(47.6)	**0.000**
Up to professional	1(1.2)	4(4.8)	
Husband's education			
Up to middle school certificate	46 (54.8)	6 (7.1)	
Up to graduate	37 (44.0)	13 (15.5)	**0.000**
Up to professional	1(1.2)	65 (77.4)	
Socioeconomic status			
Lower	64 (76.2)	15 (17.9)	**0.000**
Middle	19 (22.6)	62 (73.8)	
Upper	1 (1.2)	7 (8.3)	
Hygiene			
Fresh use napkin	19 (22.6)	57 (67.9)	**0.000**
Reuse napkin	65 (77.4)	27 (32.1)	
Smoking			
Passive smoker	41 (48.8)	15 (17.9)	**0.000**
Non- smoker	43 (51.2)	69 (82.1)	
History of contraception			
OCP	14(18.2)	36 (52.9)	
No Contraception	52(67.5)	20(29.4)	**0.000**
Condom	9 (11.7)	11(16.2)	
Safe cycle	2 (2.6)	1(1.5)	
Diet			
Vegetarian	71 (84.5)	68 (81.0)	0.540
Non-vegetarian	13 (15.5)	16 (19.0)	

Note- The p-value in bold was set at <0.05 as significant.

Table 2: Clinical Characteristics of the studied population

Variable	Case (n=84) [Mean ± S.D]	Control (n=84) [Mean ± S.D]	P-value
Age	53 ± 10.39	54 ±12.02	0.551
Parity	4 ± 1.67	2 ± 1.30	**0.000**
Age at 1st pregnancy	17 ± 3.49	19 ± 4.82	**0.001**
Menstrual duration	2 ± 0.49	2 ± 0.54	0.301
Age of menopause	32 ± 24.95	32 ± 24.83	0.848
Number of abortion	0.71 ± 0.96	0.30 ± 0.77	**0.003**

Note- The p-value in bold was set at <0.05 as significant.

Table 3: Mean Serum levels of IL 18 in cervical cancer patients

	Control (n=84) (pg/ ml)	Mean serum level of Interleukin -18 (pg/ ml)	P value
CIN I (n=10)		325.80± 14.46	**0.000**
CINII (n=10)	340.52± 11.91	327.80 ± 12.97	**0.000**
CIN III (n=10)		323.70 ± 12.22	**0.000**
CC (n=54)		292.80 ± 6.25	**0.000**

Note: CIN I= cervical intra-epithelial neoplasia I; CIN II- cervical intra-epithelial neoplasia II; CIN III= cervical intra-epithelial neoplasia III, CC= cervical cancer subjects; n=Number. Values are expressed as mean ± SD. The p-value in bold was set at <0.05 as significant.

DISCUSSION

Cervical cancer, a largely preventable disease but accounts second number of deaths by cancer in women worldwide.[1,2] Although epidemiological and experimental studies have provided evidence that human papillomavirus (HPV) infection is a main player in cancer cervix. High risk oncogenic HPV (HPV 16 most prevalent) are major cause of almost all cases of carcinoma cervix.[11] However, focussing on persistence of HPV infection, other risk factors and body's immune system is crucial.

This was a case–control study on North Indian population. We aimed to evaluate the serum protein level of Interleukin-18 in pre-invasive and invasive lesions of cancer cervix cases as compared to healthy controls. We found a positive association between the marker and study disease. As shown in table no-3, protein level of IL-18 significantly decreases from control to pre-invasive lesions followed by invasive state of cancer cervix (<0.05). Similar to present study, Qi. T. et al conducted a study in year 2008.[12] Contrary to the anti-cancer effect of IL-18, its pro-cancerous evidence also found in squamous cell carcinoma (SCC), melanoma and skin cancer cell lines, gastric cancer patients, breast cancer.[8] Our risk factors study findings confirmed the many previous studies, which demonstrated that risk factors other than HPV infection play a significant role. When we talk about categorical variables education is a basic indirect cause of CC in north India, it always hinder the progression of monthly income, life style, thinking and awareness. As result shows that awareness about health is significantly varied with the level of educational attainment, this is also supported by many studies.[13-16] This study provides useful information that could be utilized by both researchers and those involved in public health programs.[17-19] Education also promotes several habits which further established as risk factors such as age at first sexual intercourse (AFSI), early age at first pregnancy and high parity. In addition to these, next factor abortion is also occurs more frequently in this population due to lack of knowledge about right age of conceiving, nutrition and diet during pregnancy. So our study found that all these things make women weaken physically and immunologically for latent HPV infection which may lead to cervical carcinogenesis as women get old. Because up to older age body get many exposures to carcinogenic substances and microbes which accumulated and may involve in alterations of gene expressions.[20] AFSI has been associated with an increased risk of high-risk human papillomavirus (HPV) infection. AFSI is also associated with riskier sexual behaviour such as having unprotected sex and having multiple sexual partners. Immature cervix during adolescence is more susceptible to persistent HPV infections therefore have a greater risk of cancer development, the study supported by Jessica A. Kahn et.al, in 2002.[21] Secondly, AFSI is also related to early age at first pregnancy and high parity. These two factors contribute in hormonal changes in body and may play a significance role in cervical carcinogenesis.[20] The role of multi parity have also been explored in the development of cervical cancer. It was hypothesized that multi parity could be one of the confounding variables. This variable is highly correlated with other marital factors. However some of the recent studies have revealed multiparty to be an independent risk factor.[22-24] IARC multicentric case-control study in 2002 proved a direct association between the number of full-term pregnancies and squamous-cell cancer risk.[21]

Other risk factors like- socioeconomic status and habits of hygiene are very important and interrelated, because due to poverty women with LSS cannot afford new napkins or cloth during every menstrual cycle. Some studies of west on same issue did not reveal any association between type of material and cervical neoplasia.[25,26] The Indian study revealed that risk associated with the use of unclean cloth was 2.5 fold higher for the development of CIN III and malignancy as compared to the use of clean cloth or use of sanitary napkins.[27] Many times poor hygiene may result of persistent infection of pathogenic microbes as well as HPV, due to lack of soap or running water to rinse vaginal organ finely. Reusing napkins in menstrual duration and the deliveries which were conducted at home were account significantly higher risk. Same studies conducted on, also find same result.[28,29]

Like hygiene, nutritional value also directly proportional to monthly income. A large body of epidemiologic literature indicates that as many as 30% of all cancer cases are linked to poor dietary habits. Some studies have suggested that diet full with vitamin C, E carotenoids and folate may reduce the risk of cervical cancer.[30,31] Some laboratory studies also supported its chemopreventive effect is related to the high levels of numerous phytochemicals in this food. These phytochemicals interfere with several cellular processes involved in the progression of cancer and also with inflammatory processes that foster development of cancer. These studies suggested that daily intake of plant-based food containing anticancer and anti-inflammatory phytochemicals thus represents a promising approach to preventing the development of cancer.[32-34] In LSS, women's diet is so poor because of limited healthy food material that scarified for her family and vitamins, antioxidants deficient diet cannot maintain body's defence mechanism.[35-39] As we all know that smoking have causative role in many types of cancer as well as in cc, previously it was consider as confounder but now it is establish as a main player. The first biological evidence was the finding that levels of nicotine, and its major metabolite cotinine, were increased in the cervical mucus of smoker women. Same kind of result also found in a meta-analysis study where meta-analysis showed that risk of squamous cell cervical cancer is increased by 50% in current smokers.[40-42]

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