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A Cross sectional Study on Association of Human Papilloma Virus Infection in Cervical Malignancy: Record based Regression Analysis

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Abstract

Papilloma viruses are small, non-enveloped, epitheliotropic, double stranded deoxyribonucleic acid (DNA) viruses that infect mucosal and cutaneous epithelia in a wide variety of higher vertebrates in a species-specific manner and induce cellular proliferation. The study was conducted to observe the association & prevalence of Human Papilloma Virus (HPV) infection in suspected (pre-malignant lesion) and known cases of cervical malignancy and to study the risk factor of HPV infection. Study design is based on observational record-based hospital study via cross-sectional survey and review, and conclusion was drawn on primary data collection and analysis. Patients (Women) coming to out-patient department (OPD) and emergency department of Obstetrics and Gynecology at Rajendra Institute of Medical Sciences (RIMS), Ranchi, Jharkhand, India from March 2018 to February 2019 with cervical growth and unhealthy Cervix with abnormal uterine bleeding (AUB) or history of contact bleeding were considered as population. Sample size of 177 patients were considered for this study. Written and informed consent was obtained from all the participants after brief explanation of the procedure. Menstrual and obstetric history was taken in relation to the presenting complaints and then these patients were examined. Observational parameters recorded from each patient were age, socio-demography, age at first intercourse, age at first childbirth, reproductive history, marital history, tobacco consumption, type of cancer, type of HPV and clinical staging. It was found that association of HPV with unhealthy cervix which were either diagnosed as cancer or premalignant lesion (low grade squamous intraepithelial lesion or high grade squamous intraepithelial lesion) was found to be 94%. In the study, prevalence of HPV was found high in women in mid age group, women belonging to low socio-economic strata, women who were married at young age and women with high parity.

Keywords: Human papilloma virus,Cervical Malignancy ,Record based, Regression analysis

Introduction

According to World Health Organization (WHO), cervical cancer is the fourth most common cancer among women and 2nd most common cancer in India after breast cancer [1,2]. WHO's global strategy for cervical cancer elimination, endorsed by world health assembly in 2020, calls for 70% of women globally to be screened regularly for cervical disease with a high performance test, and for 90% of those need it to receive appropriate treatment [3]. Alongside vaccination of girls against HPV, implementing this global strategy could prevent more than 62 million deaths from cervical cancer in next 100 years [3]. According to American Cancer Society (ACS) the mortality rate has declined by 50% within the last 40 years due to advent

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of pap-smear (papanicolau stained) screening. ACS estimates for cervical cancer in United States of America for year 2021 are (a) about 14,480 new cases of invasive cervical cancer will be diagnosed, (b) about 4,290 women will die of cervical cancer [4].

Etio-pathogenesis of cervical cancer is multifactorial. Risk factors associated with cervical cancer are persistent HPV infection, multi-parity, low socio-economic status, tobacco consumption, lack of vaccination in past, sexually transmitted disease (STD) and young age at first delivery. However, majority of cervical cancer cases are associated with persistent HPV infections [5]. High risk HPVs, and particularly HPV-16 and HPV-18, are proven to be the main motive of cervical cancer. Other high risk HPVs include type 31, 33, 34, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68 and 70.

In developed countries, the extensive usage of cervical screening plans led to tremendous reduction in cervical cancer rates [6,7]. In early detection key role of pap-smear cannot be denied. This technique is considered as screening tool that investigate changes in cells of the cervix transformation zone. Generally, these changes tend to be caused by HPV. Sample is collected from the squamo-columnar junction and distal endo-cervix by scraping the cervical surface for at least one complete rotation. Cytology smears are received in the cytopathology division for staining and reading. The classification of pap-smear reports have developed and improved over time. The current reporting system is the Bethesda system which was updated in 2014 [8]. Type-specific polymerase chain reaction (PCR) assays are also used for HPV detection. It is based on the sequence variations present in E6 and E7 genes of HPV subtypes. It is the most common cancer found during pregnancy, with an incidence of 1.5 to 12 cases per 100,000 pregnancies [9].

In present study we will discuss the prevalence, determinants, and risk factors of cervical human papilloma virus infection among women of age group 30 - 69 years coming to RIMS, Jharkhand, India and the association of Human Papilloma Virus infection in suspected and known cases of cervical malignancy.

Materials and Methods:

This was a record based cross-sectional Analytical study. The Study was initiated after the approval of Institutional Ethics Committee, of Rajendra Institute of Medical Sciences (RIMS), Ranchi, Jharkhand.Place of study was Department of obstetrics and gynaecology, Rajendra Institute of Medical Sciences (RIMS), Ranchi. RIMS is atertiary care centre established in year 1960 which caters whole of the Jharkhand population for the medicalneeds of patients coming for treatment irrespective of age, sex, ethnicity, religion, and residence. So,being a government setup and premier institute of Jharkhand almost all the medical services including some tests are freeand hospital is thronged mostly by thepeople who belongs to below poverty line. The duration of the study was fromMarch 2018 to February 2019to understand the Proportion of cervical malignancy in the HPVPositive patients attending hospital settings.

Data collection in the study was restricted to women aged 30 - 70 years. Sample size of 177 numbers of women were randomly selected by lottery method. Inclusion criteria were women with (a)cervical growth, (b) unhealthy cervix, (c) history of contact bleeding, (d) diagnosed cases of cancer cervix, (e) cases with unhealthy cervix with Pap-smear or biopsy diagnosed low-grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion (HSIL) and cancer coming to RIMS whereas exclusion criteria were women (a) who have

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had a hysterectomy with the removal of cervix, (b) having infective pathology. Patient data such as present age, age at marriage, age at first childbirth, parity, tobacco consumption and socio-economic status were taken.

Data was collected using pre-tested semi-structured questionnaire. Data was entered in the MS Excel 2017 and template was generated.All the statistical analysis was done using IBMStatistical Package for Social Sciences(SPSS) for Windows, Version 20.0. Armonk, NY: IBM Corp, Released 2011. Frequencies and proportions of the studyvariables were calculated in our primary analysis for socio demographic profile. The quantitative data was represented in the form of mean ± standard deviation.All the factors were cross-tabulatedwith HPV Status to estimate any association. Binary logistic regression was used to evaluate the associated risk factors of cervical carcinoma. A p-value of < 0.05 was said to be statistically significant andtheir 95% confidence interval was reported along with the P- value in our present study.

Results

Out of the total 177Participants, the mean age was found to be 50 ± 9.42 years, with a rangefrom minimum of 30years to maximum of 70 years. Out of 177 participants 69 (39.0%) werebetween age group of 40-50 years and 53(29.9%) participants were between age of 50-60 years. Regarding Socio economic status 128(72.3%) participants belongs to lower Socio-economic status. The majority, 119 (67.2%) of participants were Hindu followed by Muslims 33 (18.6%). 123 (69.5%) Participants were Non-Tribalwhereas 54 (30.5%) were Tribal(Table 1).

Table 1: Socio demographic Profile of the Participants, n=177

Variables	Frequency	Percent
Age (Years)		
30-40	31	17.5
40-50	69	39.0
50-60	53	29.9
60-70	24	13.6
Religion		
Hindu	119	67.2
Muslim	33	18.6
Christian	25	14.1
Social Economic Status (SES)		
Lower Socio-Economic status (LSE)	128	72.3
Middle Socio-Economic status (MSE)	48	27.1
Higher Socio-Economic status (HSE)	1	0.6

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Ethnicity		
Tribal	54	30.5
Non-Tribal	123	69.5

Table 2:According to age of First intercourse, delivery, and age of Menstruation of the participants

Variable	Frequency	Percentage
Age (years) at menarche		
11	16	9.0
12-13	136	76.8
>13	25	14.1
Age (years) at marraige		
<18	71	40.1
18-21	95	53.7
>21	11	6.2
Age (years) at first delivery		
<18	24	13.6
18-21	125	70.6
>21	28	15.8
Parity		
<4	41	23.2
4	50	28.2
>4	86	48.6

71(40.1%) of participants hadfirst intercourse before 18 years of age. 125(70.6%) of participants had first delivery between 18-21 years of age group. Maximum 136(76.8%) of participants had menstruation between 12-13 years.86 (48.6%) of participants were having parity of more than 4. (Table -2).

Table 3: According to HPV status of participants

Variable	Frequency	Percent
HPV Status		
Positive	165	93.2
Negative	12	6.8

Out of 177 Participants 165(93.2%) were found to be HPV Positive.

Table 4: Association of different variables with HPV status

Variables	Negative HPV (%)	Positive HPV (%)	χ^2, (df), p
Age			
30-40	3 (9.09)	30 (90.91)	4.5, (3), 0.151

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40-50	3 (4.41)	65 (95.58)	
50-60	2 (3.84)	50 (96.15)	
60-70	4 (16.67)	20 (83.33)	
Religion			
Hindu	6 (5.04)	113 (94.96)	4.5, (2), 0.104
Muslim	5 (15.15)	28 (84.85)	
Christian	1 (4.00)	24 (96.00)	
Socio-Economic Status			
LSE	4 (3.13)	124 (96.88)	10.2, (2), 0.006
MSE	8 (16.67)	40 (83.33)	
HSE	0 (0.00)	1 (100.00)	
Ethnicity			
Tribal	1 (1.85)	53 (98.15)	1.9, (1), 0.161[#]
Non-Tribal	11 (8.94)	112 (91.05)	
Age of menarche			
11	0 (0)	16 (100.00)	4.7, (2), 0.095
12-13	8 (5.88)	128 (94.12)	
>13	4 (16.00)	21 (84.00)	
Age atmarraige			
<18	3 (4.23)	68 (95.77)	8.1, (2), 0.018
18-21	6 (6.32)	89 (93.68)	
>21	3 (27.27)	8 (72.73)	
Age of first delivery			
<=21	8 (5.36)	141 (94.63)	1.7, (1), 0.189[#]
>21	4 (14.29)	24 (85.71)	
Parity			
<4	7 (17.07)	34 (82.93)	9.7, (2), 0.008
4	3 (6.12)	46 (93.88)	
>4	2 (2.30)	85 (97.70)	

[#]Yate's correction

Significant association ($p<0.05$) with HPV is observedin Socio economic Status, age of first sexualintercourse and parity in cross tab analysis. P-value of participants with lower socio-economic status, age of first sexual intercourse and parity is found to be 0.006, 0.018 and 0.008 respectively using linear by linear association.

Table 5: Binary logistic regression for HPV status.

Variables	**Category**	**P value**	**Odds ratio**	**95% Confidence Interval**	
				Lower	**Upper**
Age	30-40	0.026	23.89	1.46	391.35
	40-50	0.012	10.76	1.69	68.52

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	50-60	0.037	11.25	1.16	108.97
	60-70	Reference			
Ethnicity	Tribal	0.44	0.40	0.04	3.97
	Non-Tribal	Reference			
Socio-Economic Status (SES)	LSE	0.013	7.45	1.53	36.34
	MSE	Reference			
Age at First delivery	<21 years	0.26	2.52	0.50	12.62
	>=21 years	Reference			
Parity	<4	Reference			
	4	0.027	7.75	1.26	47.75
	>4	0.002	25.12	3.21	196.7

Table 5 Binary logistic regression was performed to derive odds ratio. Odds ratio is higher for participants who were in age group 30-40, 40-50, 50-60 than participants in age group 60-70 which means women in earlier age-group have higher probability of getting HPV infected. The odds ratio is also higher for women belonging to low socio-economic zone than women belonging to medium socio-economic zone which means women in low socio-economic zone have high probability of getting infected by HPV. Women with parity <4 have less odds ratio than women with parity >4, which means that women with parity >4 higher probability of getting infected by HPV than women with parity <4. It is also found that women who had their first delivery in age <21 years have higher odds ratio than women who had their first delivery in age > 21 years which means that women having their first delivery in age < 21 years have higher probability of getting infected by HPV.

Table 6: Logistic regression for HPV status with types of carcinoma

Types of Cervical cancer	Negative HPV (%)	Positive HPV (%)	χ^2, (df), p
Ascus	0 (0.00)	4 (100.00)	0.417, (3), 0.937
LSIL	1 (5.26)	18 (94.73)	
HSIL	3 (7.70)	36 (92.30)	
Cancer	8 (6.95)	107 (93.05)	

Logistic regression analysis was done to find out the relationship of Cervical Carcinoma with HPV status.

Discussion

Our presentstudy was done in the Indian tertiary care setup which showed that the mean age for cervical carcinoma in the women was found to be 50 ± 9.42 years. Out of which only 13.60% patients in age group 60 - 70 years reached for treatment. This probably indicates poor health and dependence on others for seeking health facility. HPV association is maximum in age group 50-60 years which is 96.15%. But overall association of HPV with disease remains high in all the age group. Saurabh bobdey et al. conducted a study and concluded that maximum number of cases were reported in 50-60 years of age group amounting to 27.37% of all cervical cancer cases [10].

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In the present study 72.3%, 27.1% and 0.6% of study sample were from low, middle, and high socioeconomic class respectively. This shows that females from higher affordability group prefer private hospitals for their morbidities. Low number of their participation may be due to low incidence of health problems in them due to better nutritional status and better hygiene. As the study was limited to RIMS and only 1 patient from high socioeconomic status turned up so it is difficult to analyze the association of HPV in this class. In the study "Epidemiology of cancer of the cervix: global and national perspective", Shanta V, et al. suggested socioeconomic factors (education and income) one of the important determinants of cervical cancer [11].

Average age at marriage for those patients who later became HPV positive or had cancer cervix was 18.04 years. Thus, marriage in younger age shows early and protracted sexual life which leads to high chances of HPV infection and cervical carcinoma. It was due to the fact that during early age of marriage and during pregnancy more estrogen is secreted which forms glycogen. Lactobacilli acts on glycogen to make potential of hydrogen (pH) of vagina acidic. This leads to squamous metaplasia and increased risk of HPV persistence and cancer cervix. The same was echoed by A K Prabhakar and G R Menon, who concluded that marriage at early age brings a great risk factor for HPV infection and cancer cervix [11]. Over the past 8 decades there has been a rise in age at marriage from 14 years in 1901 to 18 years in 1981. Consequently, a significant reduction of cervical cancer cases & 6.3% reduction in invasive cancer cervix is observed [12].

Pregnancy at younger age leads to increased incidence of cancer cervix and HPV association. Thus, age of first pregnancy like age of marriage and parity also shows the sexual activity and sexual behavior of the patient. K S Louie and S de Sanjose et. al. published their study in the year 2009 - named "Early age at first sexual intercourse and early pregnancy are risk factors for cervical cancer in developing countries" [13]. The study describes the result that invasive cervical cancer (ICC) incidence increases with first sexual intercourse at younger age. In most developing countries it has been observed that age at first pregnancy (AFP) and ICC are strongly interrelated. Age at first sexual intercourse and age at first marriage were highly related and had similar ICC risk estimates [14].

Most of the participating patients had high parity (i.e. greater than or equal to 4) and prevalence of HPV infection was found higher with increased parity. In studies restricted to HPV DNA-positive women, population with high parity is consistently related with high risk of cervical cancer [13], but generally no association is observed in populations with low parity [15].

The data in ASCUS, LSIL and HSIL relates to patient with clinically suspected cancer cervix and unhealthy cervix. This shows that patients with abnormal Pap Smear had high HPV association. As per Cancer Research Centre UK around 7 to 8 out of 10 cervical cancers are squamous cell cancer (SCC) (70 to 80%) [16]. Worldwide, incidence of squamous cell cancer has ranked one among the various types of cervical carcinoma with its obvious association with HPV infections [17]. In a study by Kulkarni and Kulkarni reveals that multiple infection of HPV 16 and 18 is quite high in cervical cancer and especially in squamous cell carcinoma [18]. Further study by R M Pillai and M Babu et al suggested that prophylactic HPV 16 /18 - L1 vaccines would provide greater than 75% protection against SCC in India [19].

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The most common type of HPV association with cancer cervix or pre-malignant lesion is HPV 16. Overall association of HPV with unhealthy cervix who were either diagnosed as cancer or pre-malignant lesion was found to be 94%. The HPV is assessed from a single smear and it is possible that some infection is missed. Repeated sampling would have provided better estimates. There may be chances of samples being damaged during transport thus, effecting sensitivity of HPV testing.

Conclusions

Cervical cancer is associated with considerable morbidity and mortality all over the world. High incidence of mortality in cervical cancer is due to HPV infection persistence with low public awareness and absence of HPV screening. Hence screening programs are important, as this type of malignancy is preventable. Prevention can be achieved by making people aware about personal hygiene, limiting sexual partners, use of barrier contraceptive, limiting number of childbirths, preventing first childbirth in younger age and vaccination. The knowledge of HPV prevalence and type distribution could contribute to successful vaccination program implementation as most of the cases of cervical cancer come to seek medical care in advanced stages. Also, HPV infection is more common in younger age group, hence screening programs detecting infection in earlier age can prevent cervical cancer. WHO suggests HPV DNA detection in a screen-and-treat approach at age of 30 years with regular screening every 5 to 10 years.

References

1. Cervical Cancer. (2018). Accessed: January 14,2021: https://www.who.int/health-topics/cervical-cancer#tab=tab_1.
2. Gupta S: Breast cancer: Indian experience, data, and evidence. South Asian J Cancer. 2016, 5:85-6. 10.4103/2278-330X.187552
3. New recommendations for screening and treatment to prevent cervical cancer. (2021). Accessed: 23-August-2021: https://www.who.int/news/item/06-07-2021-new-recommendations-for-screening-and-treatment-to-prevent-cervical-cancer.
4. Key Statistics for Cervical Cancer. (2021). Accessed: 15-08-2021: https://www.cancer.org/cancer/cervical-cancer/about/key-statistics.html#:~:text=The%20American%20Cancer%20Society's%2....
5. Mark Schiffman, Philip E Castle, Jose Jeronimo, Ana C Rodriguez, Sholom Wacholder, : Human papillomavirus and cervical cancer. Lancet. 2007, 370(9590):890-907. 10.1016/S0140-6736(07)61416-0
6. Mishra GA, Pimple SA, Shastri SS: An overview of prevention and early detection of cervical cancers. Indian J Med Paediatr Oncol. 2011, 32:125-32. 10.4103/0971-5851.92808
7. Mosiur Rahman, Abdur R. Mia, Syed Emdadul Haque, Mostofa Golam, NowsheenSharminPurabi, S. A. R. Choudhury: Beating Cervical Cancer in the Developed Countries: A Dream or a Reality?. IntechOpen. Alfonso J. Rodriguez-Morales (ed): IntechOpen, 2013. 10.5772/52881
8. Ritu Nayar, David Wilbur: The Bethesda System for Reporting Cervical Cytology. Ritu Nayar, David Wilbur (ed): Springer International Publishing, 2015. 10.1007/978-3-319-11074-5

ISSN: 0975-3583, 0976-2833 VOL10, ISSUE 02, 2019

9. Origoni M, Salvatore S, Perino A, Cucinella G, Candiani M: Cervical Intraepithelial Neoplasia (CIN) in pregnancy: the state of the art. Eur Rev Med Pharmacol Sci. 2014, 18:851-60.
10. Bobdey S, Sathwara J, Jain A, Balasubramaniam G: Burden of cervical cancer and role of screening in India. Indian J Med Paediatr Oncol. 2016, 37:278-85. 10.4103/0971-5851.195751
11. Shanta V, Krishnamurthi S, Gajalakshmi CK, Swaminathan R, Ravichandran K: Epidemiology of cancer of the cervix: global and national perspective. J Indian Med Assoc. 2000, 98:49-52.
12. Prabhakar AK, Menon GR: Age at marriage and cervical cancer incidence. Indian J Cancer. 1995, 32:63-8.
13. Louie KS, de Sanjose S, Diaz M, et al.: Early age at first sexual intercourse and early pregnancy are risk factors for cervical cancer in developing countries. Br J Cancer. 2009, 100:1191-7. 10.1038/sj.bjc.6604974
14. Nubia Muñoz, Silvia Franceschi, Cristina Bosetti, et al.: Role of parity and human papillomavirus in cervical cancer: the IARC multicentric case-control study. Lancet. 2002, 359(9312):1093-1101. 10.1016/S0140-6736(02)08151-5
15. Castle PE, Wacholder S, Lorincz AT, et al.: A prospective study of high-grade cervical neoplasia risk among human papillomavirus-infected women. J Natl Cancer Inst. 2002, 94:1406-14. 10.1093/jnci/94.18.1406
16. Cervical Cancer - Stages, types and grades. (2020). Accessed: 14-March-2021: https://www.cancerresearchuk.org/about-cancer/cervical-cancer/stages-types-grades/types-and-grades.
17. Bijeta Singh, Neelam Nalini: Study of incidence and different aspects of cervical malignancy in tertiary centre of Jharkhand, India. International Journal of Reproduction, Contraception, Obstetrics and Gynecology. 2017, 6(7):3118-3123. 10.18203/2320-1770.ijrcog20172945
18. Kulkarni SS, Kulkarni SS, Vastrad PP, et al.: Prevalence and distribution of high risk human papillomavirus (HPV) Types 16 and 18 in Carcinoma of cervix, saliva of patients with oral squamous cell carcinoma and in the general population in Karnataka, India. Asian Pac J Cancer Prev. 2011, 12:645-8.
19. Pillai RM, Babu JM, Jissa VT, et al.: Region-wise distribution of high-risk human papillomavirus types in squamous cell carcinomas of the cervix in India. Int J Gynecol Cancer. 2010, 20:1046-51. 10.1111/IGC.0b013e3181e02fe0