Risk Factors of Preinvasive and Invasive Cervical Cancer

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Aims: The objective of this study was to assess the risk factors of preinvasive and invasive cervical cancer.

Methods: This was a prospective hospital based case control study conducted from April 2012 to April 2013, which included 91 patients in each group. Among cases, 34 were Cervical Cancer and 57 were Cervical Intraepithelial Neoplasia. Simple random method was adopted for selecting patients. Prefixed questionnaire was used. Statistical analysis was done using SPSS 19.0.

Results: In multivariate analysis, history of abnormal vaginal discharge and cigarette smoking were significantly associated with cervical cancer (p value of 0.001 and 0.003 respectively) and Cervical Intraepithelial Neoplasia (p <0.001). Whereas, early age at first sexual intercourse ≤ 16 years and more than one sexual partner of husband had only borderline significance for Cervical cancer (p value 0.049 and 0.038 respectively).

Conclusions: Cigarette smoking and abnormal vaginal discharge were significantly associated with Cervical cancer.

Keywords: carcinoma cervix; CIN; risk factor.

INTRODUCTION

Cervical cancer (CA cervix) is the fourth most common cancer in women with 528,000 new cases in 2012 and more than 85% occurs in developing countries.[1] With age standardized incidence rate of 19%, it is the most common cancer among Nepalese women.[2] Regarding prevalence of precancerous cervical lesion, about 26,000–45,000 was estimated by Johns Hopkins Program for International Education in Gynecology and Obstetrics (JHPIEGO).[3]

Human Papilloma Virus (HPV) is the most common sexually transmitted infection, however everyone infected with it does not progress to cervical cancer. Number of cofactors are likely to be involved like sexual and reproductive factors, smoking, contraceptive pills and abnormal vaginal discharge. Some acts as a surrogate of HPV infection whereas some modulates HPV infectivity and host cellular response. In contrast to developed countries, incidence of cervical cancer in Nepal has not markedly decreased. This could be due to ineffective screening program. Thus, identifying risk factors is important in formulating such programs and various public health policies.

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METHODS

A prospective, hospital based, case control study was conducted at Tribhuvan University Teaching Hospital over a period of one year (April 2012 – April 2013). During this period any women with histopathology proven Cervical Intraepithelial Neoplasia (CIN) and CA cervix were enrolled which included all women who were referred, admitted, follow up and those undergoing surgery or cervical biopsy. Equal number of cases and controls were taken. Matching controls were patients within 5 years of age difference as compared to cases, who were found to be negative for CIN or cervical malignancy following biopsy or surgery.

Women who underwent cervical biopsy were enrolled as case after confirmation of the diagnosis on histopathology report. Histopathology diagnosed cases on follow up or those visiting emergency room were immediately enrolled. The matching control fulfilling the inclusion criteria were then taken from the similar setting. Similarly, patient undergoing total or radical hysterectomy for CIN or CA cervix, respectively, were also enrolled and the matching control for these cases included age matched first case of hysterectomy done on the same day, for any benign cause. The control for referred or follow up patient or patient seen in emergency room was age matched women undergoing hysterectomy for benign cause on the same day. The histopathology reports of all the study population were followed up in the

Department of Pathology. Any women falling into exclusion criteria were excluded from the study.

The risk factors studied were:

- Sexual factors: age of first sexual intercourse and number of sexual partner of female and her male partner
- Reproductive factors: age of marriage, age of first childbirth and parity
- Cigarette smoking
- Abnormal vaginal discharge that required some form of treatment
- Human Immunodeficiency virus and other immunocompromised status
- Oral contraceptive use
- Socioeconomic status

Written consent was taken from all the respondents. Prefixed questionnaire was used. Statistical analysis was done using odds ratio with SPSS 19.0 software. P-value less than 0.05 was taken as significant. Approval from ethical committee was taken for the study.

RESULTS

Among 129 cases, only 91 patients had histopathology proven diagnosis of CIN (n = 57, 62.63%) and CA cervix (n = 34, 37.36%) and 38 patients were excluded from the study as they had negative histopathology reports. Similar number of 91 controls was included in a ratio of 1:1 (Table 1).

Table 1. Distribution of CIN and CA cervix (n=91).

Cervical Intraepithelial Neoplasia	
CIN I	57 (62.63%)
CIN II	25
CIN III	13
Carcinoma in situ	15
	04
Invasive Cervical cancer	
Squamous cell carcinoma	34 (37.36%)
Adenocarcinoma	33
	01

The mean age of case was 47.27 years with minimum age of 24 years and maximum of 82 years (SD 13.94). Among control group, mean age was 46.44 years with minimum age of 23 years and maximum age of 77 years (SD 10.59). Mean age among cases progressively increased with the severity of disease with mean age difference between CIN I and CA cervix was 14.34 years (Figure 1).
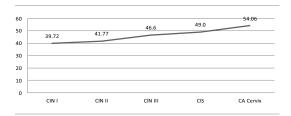

Figure 1. Mean age of cases.

About 71% (n = 24) of CA cervix and 56% (n= 32) of CIN had history of abnormal vaginal discharge whereas only 14% (n = 13) of control had similar problem. The p value being < 0.001 showed a significant association of abnormal vaginal discharge with CA cervix and CIN with OR 14.4 and 7.68 respectively (Table 2).

Table 2. History of abnormal vaginal discharge (n=91).

	CA cervix	CIN	Control
History of abnormal vaginal discharge YES	24	32	13
History of abnormal vaginal discharge NO	10	25	78
	OR 14.4 (95% CI 5.6 – 36.9) p value <0.001	OR 7.68 (95% CI 3.4 – 16.8) p value <0.001	

With respect to cigarette smoking, 61.76% (n = 21) of CA cervix, 59.64% (n = 34) of CIN and 25.27% (n = 23) of controls were smoker. More than 68.25% among CA cervix cases had been smoking since last 20 years whereas majority of CIN cases 66.6% had been smoking for less than 10 years. The odds of having a CA cervix and CIN, when compared with control, among smoker was 4.22 (95% CI 1.84 – 9.69) and 4.37 (95% CI 2.15 – 8.8) respectively with p value <0.001, which was statistically significant (Table 3).

Table 3. Smoking as a risk factor (n=91).

	CA cervix	CIN	Control
Smoker	20	34	23
Non Smoker	14	23	68
	OR 4.22 (1.84 – 9.69) P value < 0.001	OR 4.37 (2.15 – 8.8) P value < 0.001	

The median age of first sexual intercourse among case and control were 17.0 and 18.0 years respectively. Approximately, 93.4% of women reported age of first sexual intercourse to be the same as age of first marriage. About one-quarter of women reported age of first pregnancy to be same as age of first sexual intercourse. Cumulatively, 69.70% of women reported giving birth within a year of first sexual intercourse. In univariate analysis, age of first sexual intercourse ≤ 16 years, age at first marriage ≤ 16 years and age at first childbirth ≤ 17 years had significant association with CA cervix with odds ratio 5.11 (p value 0.002), 1.37 (p value 0.004) and 3.9 (p value 0.007) respectively. However these associations were not seen with CIN.

Regarding parity, two cases (one CA cervix and one CIN) and five controls were nulliparous. Similarly, 50% (n = 17) of CA cervix, 26.33% (n = 15) of CIN and 36.26% (n = 33) had parity more than three. However, no significant association could be found between the parity and CA cervix and CIN. The odds of having a CA cervix and CIN, when compared with control, among parity more than three was 1.9 (95% CI 0.5 – 6.7) and 0.7 (95% CI 0.2 – 2.1) respectively. The corresponding p value was 0.29 and 0.59 respectively. Majority of patient population, 97.25% (n = 177) had single lifetime sexual partner and those with more than one sexual partner had married twice. Only one CA cervix, three CIN and one control had more than one sexual partner. No association was noted between number of sexual partner with CA cervix and CIN. Similarly, around 44% (n = 15) of CA cervix, 16% (n = 9) of CIN and 9% (n = 8) of controls had more than one sexual partner of husband. The risk of having CA cervix among women with more than one sexual partner of her husband had seven times higher risk than those who had only one. However this association was not found to be significant with CIN, OR 1.9 and p value 0.19 (Table 4).

Table 4. Number of sexual partner of husband (n=91).

No of	CA Cervix	CIN	Control
sexual partner of husband > 1	1	3	1
sexual partner of husband = 1	33	54	90
sexual partner of husband > 1	15	9	8
sexual partner of husband = 1	19	48	83

The socioeconomic status was based on modified Kuppuswamy classification. The odds of having a CA cervix among low socioeconomic status women was 4.1 (95% CI 1.79 – 9.48) with significant p value of 0.001. But this association was not significant with CIN, OR 1.31 (95% CI 0.65 – 2.63) and p value 0.44.

Among all the risk factors of CA cervix that were found to be significant in univariate analysis were again analyzed in multiple regression analysis controlling the confounding factors. The two risk factors of CA cervix, history of abnormal vaginal discharge and cigarette smoking, were highly significant with p value of 0.001 and 0.003 respectively whereas two other risk factors early age of first sexual intercourse ≤ 16 years and more than one sexual partner of husband had borderline significance of 0.049 and 0.03 respectively. Similarly, in CIN cases, history of abnormal vaginal discharge and cigarette smoking that were found to be significant in univariate analysis were also found to be significant in multiple regression analysis with p value < 0.001.

DISCUSSION

Human Papilloma Virus (HPV) is one of the most common sexually transmitted infection.[4] However, infection by oncogenic HPVs is necessary but not sufficient cause of cervical cancer.[5] Thus, it has been assumed that other factors, in conjunction with HPV, modulate the risk of transition from cervical HPV infection to cervical malignancy. The key risk factors noted in this study were abnormal vaginal discharge and cigarette smoking.

One of the common causes of abnormal vaginal discharge is infective in origin like Bacterial Vaginosis (BV), Trichomoniasis, Chlamydial infection and Candidiasis. BV and other infections are associated with high levels of anaerobic microorganisms and their by-products (enzymes), which can damage the vaginal epithelium, degrade cervical mucus cells, and cleave immunoglobulin-A (Ig-A).[4] Raised nitrosamines seen in BV also causes host cell DNA damage and change in cytokine profiles will alter immune response to HPV.[6] Therefore risk of developing cervical cancer is higher among women with abnormal vaginal discharge and HPV co-infection than those with HPV mono-infection. These clinical effects are seen in few epidemiological studies and keeping up with those, index study also finds

significant association between abnormal vaginal discharge with CA cervix and CIN (p<0.001). This effect can only be counteracted with early diagnosis and treatment along with proper screening. But as PAP smear rate is just 2.4% in Nepal,[7] proper health policies needs to be implemented.

According to World Health Organization's (WHO) study carried out in Nepal in 2007, 15% of women smoked which is highest in WHO South-East Asia Region.[8] Tobacco products are freely available in Nepal, even for minors. Many of them are from low socio economic group and also illiterate.[9] About 61.76% and 59.64% of respondent among CA cervix and CIN respectively were found to be smokers in this study. Significant association was noted even after adjusting for confounding factors (p<0.001). Similar effect was noted by Kjellberg et al.[10] where a dose dependent relationship of smoking with CIN 2–3 was present (p = 0.002). This association between smoking and CA cervix was also seen by Green et al[11] and Chichareon et al.[12]

Smoking results in early onset of more aggressive form of cervical cancer and smokers tend to be younger than nonsmoker at the time of diagnosis. Polycyclic aromatic hydrocarbons present in smoke could potentially have direct transformation effect on cervix. However, chemical carcinogens in tobacco, such as cotinine and nicotine, exerts their effect in different ways. The mitogenic effect occurs by activating carcinogenic nitrosamines that damages host DNA.[10] It also has immunosuppressive effect to HPV by reducing number of Langerhans' cells that alters local cellular immunity.[13] This modulates HPV life cycle potentially enhancing viral persistence and malignant transformation. All these effects are dose dependent. The greatest risk of HPV infection coincides with the greatest metaplastic activity that occurs at puberty. High level of estrogen causes cervix to evert forming a new transformation zone. This newly formed area is vulnerable to HPV as metaplastic squamous epithelium here principally consist of immature basal and parabasal cell type. Thus the reproductive risk factors like early age of sexual intercourse, early age of marriage and early age of childbirth along with high parity helps to breach the superficial epithelium, enhancing entry of HPV to the basal layer of epithelium where replication starts. During malignant transformation, viral genome is integrated into host genome.

According to Nepal Adolescent and Youth Survey 2010/11, the mean age at first sexual intercourse is 18 years and among them, three fourth (72%) had sexual intercourse with their spouse.[14] However, in the index study 67.64% of CA cervix and 33.33% of CIN had their first sexual intercourse by the age of 16. Age of first marriage is often used as a proxy measure for age of first sexual intercourse, and those who engage in early sexual intercourse may also consequently become pregnant at an early age. This temporal relation was also noted in this study. Though these risk factors were found to be associated in univariate analysis, only age of first sexual intercourse had independent borderline association with CA cervix (p value 0.049). Similarly, Louie et al reported a 2.3 – 2.5 fold increase in risk of CA cervix among women with age of first sexual intercourse ≤ 16 years.[15] However the effect of early sexual intercourse was not seen with CIN as majority of respondents in this groups were CIN I (44%) who had late sexual intercourse. Li et al. also found no significant association between early age of first sexual intercourse with cervical lesion.[16]

An individual is at greater risk of becoming infected with multiple HPV strains if she had multiple sexual partners at any time or is the partner of someone who has had multiple sexual partners.[17] This increases the risk of infection with multiple high risk HPV strain or transmission of other sexually transmitted agents that can act as a cofactor of HPV.[12] The effect of multiple sexual partner on cervical carcinogenesis has been consistently supported by different epidemiological studies, including a case control study in Thailand, where the odds of having a cervical cancer among women with multiple partner ≥ 3 was 5.5.[12] However, this effect was not seen in our study as 97.25% of total respondents had a single sexual partner. In Nepal, sexual promiscuity among women is very low and multiple marriages among them are less acceptable. Thus women are in monogamous relationship reducing the risk of cervical cancer as noted by Biswas et al. in rural India.[18] However, Li et al.[16] have demonstrated the significant association between more than two sexual partner of husband and cervical lesions with odds ratio of 3.19 as in current study. More than one sexual partner of husband in this study was 44.11% and 15.78% among CA cervix and CIN, respectively. Thus significant association was noted with CA cervix only (p value 0.03).

CONCLUSIONS

Though sexual and reproductive issues of women are important risk factors in the carcinogenesis of cervical malignancy, this study highlights the significant association of abnormal vaginal discharge and cigarette smoking with it. Considering these conditions are very common, larger studies are required to accurately determine the causal relationship between it.

DISCLOSURE

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