

Different Risk Factors Associated with Persistence or Regression of Squamous Intraepithelial Lesions of Cervix under Rural Conditions in India

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ABSTRACT

Introduction: In many Human Papilloma Virus (HPV) negative women, the Squamous Intraepithelial Lesions (SIL) of cervix often show persistence or progression of the lesion on follow-up which shows involvement of other risk factors of carcinoma cervix.

Aim: The aim of the study was to evaluate the different risk factors of cervical cancer in persistent, progressed and regressed cases of SIL to identify the prominent ones among them.

Materials and Methods: The study had been of a screening type for early detection of cervical cancer and it was done in the women population of west Lucknow, Uttar Pradesh, India (May, 2013-February, 2020). Cervical smears were collected in 2949 women attending the camps whose cytological examination revealed 498 cases of SIL and follow-up was available in 254 of them done through home visits after 1-4 years. Persistence of SIL was seen in 60 women on follow-up while in the remaining

194, the SIL had regressed to normal. The percentage of different risk factors seen with the persistence or regression of SIL was studied.

Results: Among the different risk factors identified, prominent were of young age between 16-30 years with vaginal discharge and their percentage were insignificantly higher with persistence of SIL than in the regression group. Multiparity was also highly associated with both persistence and regression of SIL. The erosion of cervix was significantly associated with SIL persistence while associated inflammation was insignificantly higher in persistent than in the regression group. The percentage of all these factors except erosion of cervix was found higher in HPV- positive than in the HPV negative women.

Conclusion: It appears that all the identified risk factors are present both in persistent and regression group but their percentage is higher with persistence of SIL. Hence, presence of any of these factors in these two groups should be viewed with caution to rule out any progression/recurrence of SIL.

Keywords: Causative factors of cervical cancer, Human papilloma virus positivity, Non-regression, Reversal

INTRODUCTION

Cervical cancer is most common in Indian women and according to the International Agency for Research on Cancer; the incidence of carcinoma of uterine cervix in India is currently 8.4%. It is well-established fact that 80% of SIL cases have been found to regress to normal on follow-up. The persistence or progression of the lesion is seen in the remaining 20% of the SIL cases and most of these are HPV positive. The cervical cancer is caused by oncogenic HPV infections that commonly infect women worldwide [1]. However, it has been observed that the phenomenon of persistence and progression of SIL was also seen in many women who were HPV negative. It appears that some other risk factors of carcinoma cervix are involved in the non-regression of SIL in such HPV negative cases: Bosch FX et al., Schiffman MH et al., [2,3]. All the possible risk factors of the disease besides HPV infections such as menopausal status, age, parity, gynaecological symptoms, clinical lesions of cervix, associated inflammation and nonviral Sexually Transmitted Diseases (STD) infections were studied in detail in the persistent and progression cases and have been compared with findings obtained in those SIL cases who regressed to normal on next follow-up. On the basis of these comparative findings in the two groups, prominent risk factors were identified and evaluated for their presence with persistence and progression or regression of the SIL.

Others suggested risk factors like number of sexual partners and age at the first sexual intercourse could not be asked from the rural women considering their privacy and sensitivity of the situation in the rural areas. Some investigators have also suggested role of oral

contraceptives and smoking as co-factors responsible for persistence of SIL in HPV negative cases [4,5]. Use of oral contraceptives for birth control is rare in rural women and the habit of smoking is also seldom. Other environmental risk factors like socioeconomic status and nutritional factors have also been mooted [6,7]. Majority of the rural women have poor economic status and they consume mostly low fat diet because of poverty.

The study identifying the prominent risk factors related to the persistence or regression of SIL was not attempted earlier and hence, the study is in itself is a novelty.

MATERIALS AND METHODS

As said before, the present study was screening type through organising camps in the villages for early detection of cervical cancer through Pap smear examination. Rural cervical cancer screening was carried out in the women population of the villages of West Lucknow, Uttar Pradesh, India under the auspices of Era's Lucknow Medical College and Hospital, Lucknow since May, 2013 through camp approach. Till February, 2020, a total of 2949 women were cytologically examined attending 186 camps organised during screening. All the married women upto the age of 60 years were included in the study, while the unmarried young girls, pregnant women and those who have undergone hysterectomy were excluded. The emphasis was given to high-risk women such as women of high age and parity and those with gynaecological symptoms.

The informed consent was obtained from each woman at the time of initial smear examination and at follow-up on the pap smear forms

as thumb impression if she was illiterate or signature if literate. The ethical clearance was also obtained from the Ethical Committee of the college when the Rural cervical cancer Screening Program was initiated. (Ethical number- ELMC/Research cell/Fac-1-52/2013).

A scrape smear was collected for each woman from the cervix by the gynaecologist attending the camp and immediately fixed in the absolute alcohol. All the collected smears were stained in the cytology laboratory of the Pathology Department of the College according to the Papanicolaou's technique and the cytopathological changes observed in the cervical smears were graded according to the Bethesda System of Classification revised in 2014 [8].

The women in whom Pap smear had been taken at the camp, were called at a specific date after 10 days at the camp venue for the distribution of the cytology reports. If there was any cytological abnormality, they were given treatment and follow-up schedule was explained to each patient. These information were also provided in Hindi on the back of the cytology report. The women in whom the SIL was diagnosed, were called for follow-up to see whether the SIL lesion is still persisting or has progressed to higher grade or regressed to normal. The duration after which follow-up smears had to be collected was six months in the cases of Low-grade SIL (LSIL) and three months in the cases of High-grade SIL (HSIL). These women were told regarding the importance of follow-up and were advised to visit the hospital of the college for repeat smear examination but unfortunately no one turned up. Similarly the women showing HSIL were called for cervical biopsy after three months but none of them visited the hospital. When contacted, they expressed their inability to visit the hospital due to financial and transport problems. Since follow-up is the essential part of any cancer screening program, it was planned to also include follow-up by paying home visits to these women stressing to them necessity of the follow-up and calling them for repeat smear examination on the next day at the camp venue. Though the response was not so encouraging even after providing them some monetary incentive for purchasing the medicines, more than 50% of follow-up was achieved.

STATISTICAL ANALYSIS

Different risk factors of the cervical cancer including HPV infection have been analysed in the followed cases to study their relation with persistence or regression of the SIL. All the collected data were statistically analysed using Chi-square test with Statistical Package for the Social Sciences (SPSS) as software used and the version 22.

RESULTS

Cytological evaluation of cervical smears was carried out in 2949 women revealed SIL in 498 cases (16.8%). The SIL was of LSIL in 472 (16.0%) and of HSIL in only 26 (0.8%). Follow-up after 1-4 years was available in 254 of the 498 women (51%) including 11 cases of HSIL. On follow-up, persistence or progression of SIL was seen in 60 (23.6%) including six cases of HSIL while in the remaining 194, the SIL has regressed to normal (76.4%) including five HSIL cases. In 60 cases in whom persistence or progression was seen, persistence of SIL was found in 57 (22.4%) and progression from LSIL to HSIL was observed in the remaining 3 (1.1%). Different risk factors of cervical cancer have been studied in detail in women showing persistence and progression or regression of SIL. These are HPV infection, menopausal status, age, parity, gynaecological symptoms, clinical lesions of cervix, associated inflammation and nonviral STD infections. These are summarised below:

a) HPV infection

HPV-DNA testing was done in 130 of the 254 cases followed, 29 in the persistence and progression cases and 101 in the regressed cases. The distribution of HPV positive and HPV negative cases in these two cohorts are given in [Table/Fig-1]. As expected, HPV positivity was higher in the persistent and progressed cases (31.1%)

than 7.9% seen in the regressed cases and the difference in the HPV positivity rate in the two groups was found to be statistically significant (Chi-square=12.6; p-value=0.001) (a16). Vice-versa, HPV-negativity was higher in the regression cases (92.1%) as compared to 68.9% observed in the persistence or progression cases and the difference here, too, was statistically significant (Chi-square=12.6; p-value=0.001). The persistence of SIL was seen in the 11 of the 20 HPV negative cases and this most probably indicates involvement of other risk factors in the persistence and progression of SIL. Further HPV positivity observed in eight women in the group of the 101 regressed cases shows that HPV infection is transient in nature and is resolved in 1-2 years' time resulting in the regression of SIL.

Fate on follow-up	HPV positive	HPV negative
Persistent and Progressed cases (60) HPV-DNA testing done- 29	9 (31.1%)	20 (68.9%)
Regressed cases (194) HPV-DNA testing done- 101	8 (7.9%)	93 (92.1%)

[Table/Fig-1]: The percentage of HPV positive and negative cases associated with persistent or progression and regression of SIL.

b) Menopausal Status and Age

The percentage of perimenopausal (menstruating) women was six times higher than the postmenopausal women in both persistent and progression and regression groups. Both the persistent and progressed cases and regressed cases of SIL on follow-up were found higher in the young girls between 16-30 years (58.3% and 48.9% respectively) but the difference was found to be statistically insignificant (Chi-square=2.68; p-value=0.102). There was a decrease in percentage seen in the adult and postmenopausal women in both the groups [Table/Fig-2].

Fate on follow-up	Age group (years)			
	16-30	31-40	above 40	
Persistent and progressed cases (60)	35 (58.3%)	21 (35%)	4 (6.7%)	
Regressed cases (194)	95 (48.9%)	72 (37.1%)	27 (14%)	
Fate on follow-up	Parity group			
	Nulliparity	Parity 1 and 2	Parity 3 and above	
Persistent and progressed cases (60)	4 (6.6%)	12 (20%)	44 (73.3%)	
Regressed cases (194)	2 (1.1%)	38 (19.5%)	154 (79.3%)	
Fate on follow-up	Gynaecological symptoms			
	Vaginal discharge	Pain in lower abdomen	Menstrual disorder	Asymptomatic
Persistent and progressed cases (60)	30 (50%)	19 (31.6%)	3 (5.0%)	8 (13.3%)
Regressed cases (194)	73 (37.6%)	61 (31.4%)	17 (8.8%)	43 (22.2%)
Fate on follow-up	Clinical status of cervix			
	Erosion of cervix	Hypertrophied cervix	Endocervical lesions	Healthy cervix
Persistent and progressed cases (60)	18 (30%)	2 (3.3%)	3 (5%)	37 (61.6%)
Regressed cases (194)	19 (9.8%)	3 (1.5%)	12 (6.2%)	160 (82.4%)
Fate on follow-up	Nonviral STDs			
	Associated inflammation	<i>C. albicans</i>	<i>T. vaginalis</i>	
Persistent and progressed cases (60)	28 (46.6%)	1 (1.6%)	2 (3.2%)	
Regressed cases (194)	65 (33.5%)	11 (5.6%)	4 (2.1%)	

[Table/Fig-2]: Prevalence of the different risk factors such as age, parity, gynaecological symptoms, clinical status of cervix and associated inflammation in the persistent and progressed cases and regressed cases.

c) Parity

Both persistence and progression or regression of SIL was highly associated with multiparity, the incidence being identical in both

the groups (73.3% and 79.3%, respectively) and hence, statistically there was no significant difference between the two groups (Chi-square=6.38; p-value=0.041). A high percentage of women showing persistence and progression or regression in the multiparous women may be because the majority of the rural women undergoing Pap test at the camps belonged to this category.

d) Gynaecological Symptoms

Both persistent and progression or regression of SIL were highly associated with vaginal discharge and the corresponding figure was higher in persistent and progressed cases (50%) as against 37.6% in the regressed cases but the difference was found to be statistically insignificant (Chi-square=3.31; p-value=0.069). The percentage of the women showing other symptoms like vague pain in lower abdomen and menstrual disorders and even in the asymptomatic women was low in both the groups [Table/Fig-2].

e) Clinical Lesions of Cervix

Erosion of cervix was present in 30% of the cases showing persistence and progression of SIL while this was seen in only 9.8% in the regressed cases and the difference was found to be statistically highly significant (Chi-square=15.5; p-value <0.001). Other lesions like hypertrophied cervix and endocervical abnormalities like cystocoele and nabothian follicles were found low in the both groups [Table/Fig-2]. However, healthy cervixes were seen in the 82.4% of women in the regressed cases than 61.6% in the persistent and progressed cases and the difference was found to be statistically significant (Chi-square=15.5; p-value <0.001).

f) Associated Inflammation and Nonviral STD Infections

The SIL associated with inflammatory changes in the cervix was present in 46.6% of the persistence and progression cases and in 33.5% in the regressed cases and the difference was found to be statistically insignificant (Chi-square=3.42; p-value=0.064). Nonviral STDs like *Candida albicans* and *Trichomonas vaginalis* were not so common in both the groups [Table/Fig-2].

From the above comparative evaluation of different risk factors in the two groups, it was evident that following factors besides HPV infection have been identified to play prominent role in the development of cervical cancer as the corresponding figures were comparatively very high in women showing SIL persistence and progression:

a) Young women between 16-30 years; b) multiparity; c) vaginal discharge; d) erosion of cervix; and e) associated inflammation.

To ascertain the role of these five prominent risk factors in the persistence and progression or regression of SIL, their percentage was also analysed in relation to HPV positivity and the findings are summarised in [Table/Fig-3]. It is worth mentioning here that percentage of cases showing different risk factors was higher in HPV positive cases (except erosion cervix) than in HPV negative cases. However in the HPV negative group, in the HPV negative group, the percentage of different risk factors except young age was comparatively higher in the regressed cases than in the persistent and progressed cases.

Prominent risk factors	Persistent cases (29)		Regressed cases (101)	
	HPV +ve	HPV -ve	HPV +ve	HPV -ve
Young age (16-30 y)	6 (66.6%)	11 (55%)	6 (75%)	37 (38.6%)
Multiparity (Parity 3 and above)	9 (100%)	16 (80%)	5 (62.5%)	85 (91.3%)
Vaginal discharge	5 (55.5%)	4 (40%)	7 (87.5%)	42 (42.5%)
Erosion cervix	- -		-	18 (18.2%)
Associated inflammation	5 (55.5%)	4 (40%)	5 (62.5%)	43 (44.5%)

[Table/Fig-3]: Prevalence of prominent risk factors in HPV positive and negative cases.

DISCUSSION

In the present study, different risk factors of cervical cancer were evaluated in cases showing persistence and progression or regression of SIL to find out the prominent risk factors among them. The regression of the SIL in the present series was found to be 76.4% which was lower than 90% rate observed by many investigators [9-11] but was higher than 66.2% seen by Apiwattanasevee W et al., and Oster AG [12,13]. Further, we have found persistence of SIL in 23.6% of cases and progression from LSIL to HSIL in 1.1% of cases. These figures were slightly lower than by those reported by Apiwattanasevee W et al., [12]. The persistence or progression observed in the approximately 25% of SIL cases in the rural women in the present screening needs for coloposcopy evaluation of such cases for the presence of CIN and aggressive but non-invasive treatment if the CIN is present.

Since the persistence and progression of SIL has been observed in HPV negative women, some other factors appear to be involved with the persistence of the disease. These risk factors have been compared in the persistent and progressed cases with regressed cases which do not show any major difference in the pattern but the corresponding figures were higher with the persistence of SIL. The first prominent factor noticed was younger age of women between 16-30 years in whom both persistence and progression or regression of SIL was maximum but the corresponding figure was lower in the regression group (58.3% as against 48.9%). Srivastava M et al., Nikhumbh DB et al., and Rajput N et al., have also found a high SIL rate in young rural women between 21-40 years [14-16]. As in the villages of India, the marriage of girls are performed at early age, they are exposed to prolonged early sexual activity. The impact of early sexual activity has also been emphasised as potential risk factor of carcinoma cervix by many investigators. Iyer SS and Shah SK, Caslenda-Iniguez MS and Toledo CR, Misra JS et al., [17-19]. Green J et al., have also correlated early age at the first sexual intercourse and subsequent child birth as a risk of carcinoma cervix [20]. Dietsch E et al., have found Cervical Intraepithelial Neoplasia (CIN) peak in 20-24 years of age and Lulla M et al., have also observed early marriage and years of married life as significant risk factor of the disease [21,22]. Kashyap N et al., have also found significant association of cervical cancer with young age at marriage [23]. The sexual behaviour was also emphasised as influential factor in carcinoma cervix development by Li X et al., [24].

The other prominent risk factor related to carcinoma cervix was found to be multiparity though its percentage was found to be identical in both the persistent and progressed cases and regressed cases [25]. Reason behind this may be that majority of the rural women undergoing Pap smear examination at the camps were multiparous (more than 70%). Multiparity as a risk factor of cervical cancer has also been emphasised in their rural findings by Rajput N et al., Das Gupta A et al., and Ray Chaudhary S et al., [16,26,27]. Castellsague X et al., have found parity inconsistently associated with the low-grade lesions of the disease [28].

The other risk factor commonly encountered in the rural women has been vaginal discharge. This may be due to the fact that majority of the rural women are illiterate and therefore, have poor knowledge of personal genital hygiene. This results into persistent vaginal infections which remain undetected and untreated due to the lack of medical amenities in the villages. Many authors like Raychaudhari S and Mandal S, Thulaseedharan JV et al., and Zhang ZF et al., have also stressed illiteracy as contributory factor in the development of carcinoma cervix in rural women [27,29,30]. The majority of women complaining of vaginal discharge were from the younger age group in the present study and the similar findings have also been reported by Srivastava M et al., Rajput N et al., and Nikhumbh DB et al., [14,16,31].

Another risk factor evaluated in the present series was erosion cervix which was higher in the persistent and progressed cases (30%)

than 9.8% observed in the regressed cases. A high SIL rate with erosion cervix had also been found in the rural women by Rajput N et al., and Nikumbh DB et al., [16,31]. Further a large number of women showing normal healthy cervix in the persistent group is quiet amazing but it may be due to the fact that in the initial stages of ongoing rural cancer screening program, the Pap smears were taken by the trained nurses who might have missed the cervical lesions in difficult cases.

Inflammatory changes associated with SIL were commonly seen in the persistence and progressed cases (46.6%) as against 33.5% in the regressed cases. The studies conducted by Bhutia K et al., and Dasari P et al., have also pointed out association of development of SIL with inflammatory smears [32,33]. Tao L et al., have found cervical inflammation as a high risk for HSIL [34]. Ryan M et al., have also emphasise a role of Chlamydia in the development of cervical cancer along with HPV infection [25].

The present study revealed young age between 16-30 years multiparity and illiteracy as prominent factors related to the persistence and progression or regression of SIL. If these women were cytologically examined and showed cervical erosion or inflammatory changes associated with SIL, these were also treated as prominent risk factors of the cervical cancer.

Limitation(s)

The rural women showing SIL were found reluctant for follow-up inspite of persuasion and motivation during home visits. It appears that there is fear in their minds that some undesired outcome like development of cervical cancer may be seen on follow-up which will cause them mental harassment and financial burden on the family. They have been clearly told that in the event of any progression of SIL seen on the follow-up, they will be called at the hospital for further investigations which include cervical biopsy and colposcopic evaluation to rule out the presence of CIN and planning for non-invasive therapy if CIN is present.

Future Prospective

All the SIL cases whether they have shown persistence and progression or regression of the lesion should be followed for a prolonged period till they regress to normal. In the persistent and progressed cases, yearly follow-up should be carried out after adequate treatment till the lesion has regressed to normal. In the regressed cases, long term follow-up after every one year should be done to rule out any recurrence of SIL. If any recurrence of SIL is seen, such cases should be followed every year after adequate treatment till recurred SIL has regressed to normal. Such a strategy will check the occurrence of carcinoma cervix in the rural women through the management of the cases showing any tendency of progression.

CONCLUSION(S)

The present study revealed presence of all the prominent risk factors (except erosion cervix) in a large percentage in HPV positive cases than observed in HPV negative cases. It appears that all the prominent risk factors discussed above was present both in women showing persistence and progression or regression of SIL but their percentage were higher in the persistence group. Hence, the presence of any of the three prominent factors such as young age, multiparity and vaginal discharge should be viewed with caution especially in the persistent and progressed cases and their long term follow-up has to be done as a precautionary measure to rule out whether these cases have regressed to lower grade of SIL or normal or have progressed to a higher grade and eventually to malignancy.

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