



Original Research Article

A Study of Risk Factors of Cancer Cervix - A Case Control Study

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ABSTRACT

In India, cancer cervix is number one killer cancer among women with incidence rate of 27 per lac population and with a mortality of 15.2 per lac population. It accounts to 23.3 per cent of all cancer deaths in women and 11.4 per cent of total cancer deaths in the country.

Objectives: to study the known risk factors of cancer cervix.

Methodology: a hospital based case control study was conducted where in 60 newly diagnosed cases of cancer cervix and 60 age matched controls were selected from seemingly health female relatives, friends and neighbours. Relevant information about socio-demographic variables, reproductive variables, sexual behavioural variables, sexually transmitted diseases, habits and dietary patterns was collected.

Results: Women with sexual behavioural variables like early age at first coitus, the time interval since first exposure, history of extra marital sex in husband & wife, reproductive variables like parity, lack of genital and menstrual hygiene, previous history of sexually transmitted diseases and lastly dietary factors like lower frequency of fruit consumption have higher odds of cervical cancer these associations were found to be statistically significant.

Keywords: cancer cervix, risk factors, case-control study, India

INTRODUCTION

World-wide cervical cancer is one of the most common cancers among women and the mortality rates associated with cancer cervix are higher in low & middle income countries (LMICs), and in low socio-economic groups within countries. [1,2]

Globally around 80% of cervical cancer cases are in low & middle income countries.

[3] In India, cancer cervix is number one killer cancer among women. It is estimated that during 2008, 134,420 new cases of cancer cervix occurred in the country with

incidence rate of 27 per lac population and with a mortality of 15.2 per lac population. It accounts to 23.3 per cent of all cancer deaths in women and 11.4 per cent of total cancer deaths in the country. [4]

Infection with Human papillomavirus (HPV) has been established as the necessary, but not solely sufficient, cause of cervical cancer. [5] Apart from HPV infection there are additional cofactors such as parity, use of oral contraceptives, tobacco smoking, immunosuppression - particularly related to human immunodeficiency virus

(HIV), infection with other sexually transmitted diseases, and poor nutrition, which in conjunction with HPV influence the risk of disease development. Their specific role in the development of cervical cancer remains unclear, however. Age of sexual debut, lifetime number of sexual partners, history of sexually transmitted infections, and other characteristics of sexual activity are linked to the likelihood of becoming infected with HPV and are not considered to be cofactors for the progression from HPV infection to cervical cancer. [6]

As there is limited information on risk factors of cancer cervix in this part of Hyderabad Karnataka, the present study was undertaken to examine the role of known risk factors of cancer cervix among women attending tertiary care hospital at Bellary, Karnataka, India.

Objectives: To study the known risk factors of cancer cervix.

MATERIALS AND METHODS

Study design and study setting: a case control study was conducted in the setting of Oncology and Obstetrics and Gynaecology (OBG) department of Vijayanagara Institute of Medical Sciences, a tertiary care hospital, Bellary district, Karnataka state, India.

Study subjects and sample size: Clinically and histologically confirmed newly diagnosed cases of cancer cervix were taken as cases. During the study period (1st January to 30th June-2013), a total of 60 cases were included in the study. Patients in moribund state, with other primary cancer and who were not willing to undergo HIV testing were not considered for the study. A total of 60 age matched controls were selected from seemingly health female relatives, friends and neighbours who accompanied the patient at the time of

registration and thereafter and who were willing to participate and undergo HIV testing were considered for the study.

Questionnaire and study variables:

The questionnaire had four parts, where in the first part was structured to elicit the socio-demographic profile, habits and dietary patterns of the study subjects. The second part of the questionnaire consisted of questions structured to elicit information related to reproductive variables menstrual history, and menstrual/genital hygiene. [7] The third part consisted questions to elicit history suggestive of sexually transmitted diseases like Human papilloma virus (history of warts) and other STDs like Gonorrhoea, Chancroid, Trichomonas Vaginalis and Herpes Simplex virus (history of ulcers, vaginal discharge etc.). HIV status of the study subjects was determined by testing for HIV using standard Tridot HIV test at ICTC. The fourth part consisted of questions directed to elicit the sexual behavioural variables of both the study subjects and their respective husbands.

Method of data collection:

Information was collected by standardly trained interviewers using face to face interviews based on a structured, pre-tested questionnaire. Pre testing was done on outpatients in the same age group (30-50 years) attending oncology and OBG department, in a similar setting, to screen for potential problems in the questionnaire.

Statistical analysis: Data were entered into an electronic database and analysis was done to ascertain the risk factors of cancer cervix among the study subjects. The study variables were subjected to univariate analysis where associations between various study parameters and the risks of cervical cancer were determined by comparing each group separately with the control subjects. For each of the study factors, risk was estimated by calculating the odds ratio (OR) as approximation of the

relative risk (RR), together with 95% confidence intervals (CI), by using Epi Info version-7 software package. For those factors which could be classified into more than two categories, the tests for linear trend in risk were done by use of the method given by Mantel. [8]

Ethical considerations: The study was given ethical approval and clearance by Ethical Review Committee of Vijayanagara Institute of Medical Sciences. All ethical requirements like written informed consent including confidentiality of responses and were stringently ensured throughout the project.

RESULTS AND OBSERVATIONS

Table no. 01: Socio-demographic profile of the study cases and controls.

Socio-demographic profile		Cases (n=60)	Controls (n=60)	P-value
Age group	30-40yrs	7(11.7%)	5(8.3%)	0.567
	40-50yrs	16(26.7%)	21(35%)	
	>50yrs	37(61.7%)	34(56.7%)	
	Mean \pm SD	50.92 \pm 9.807	50.38 \pm 8.070	
Religion	Hindu	52(87.7%)	55(91.7%)	0.378
	Muslim	8(13.3%)	5(8.3%)	
Education	Illiterate	54(90.0%)	49(81.7%)	0.284
	Primary	3(5.0%)	8(13.3%)	
	High school	3(5.0%)	3(5.0%)	
Occupation	House wife	15(25.0%)	24(40.0%)	0.166
	Unskilled	43(71.7%)	33(55.0%)	
	Skilled	2(3.3%)	3(5.0%)	
Type of family	Nuclear	34(56.7%)	35(58.3%)	0.853
	Joint	26(43.3%)	25(41.7%)	
Income (BG Prasad)	III	4(6.7%)	5(8.3%)	0.283
	IV	13(21.7%)	20(33.3%)	
	V	43(71.7%)	35(58.3%)	
Address	Rural	53(88.3%)	55(91.7%)	0.543
	Urban	7(11.7%)	5(8.3%)	

Table no. 02: Estimated relative risks (OR) of cervical cancer in relation to sexual behavioural study variables.

Sexual history		Cases (n=60)	Controls (n=60)	OR (95% CI)	P value
Age at first coitus	12-13yrs	7(11.7%)	5(8.3%)	4.7(0.98-22.9)	0.005
	14-15yrs	33(55.0%)	20(33.3%)	5.4(1.7-18.9)	0.002
	16-17yrs	15(25.0%)	18(30.0%)	2.7(0.84-10.2)	0.09
	>18yrs	5(8.3%)	17(28.3%)	1	
				$X^2 = 10.34, df-3$	0.015
Latency period*	≤ 20 yrs	7(11.7%)	24(40%)	1	
	21-30yrs	24(40%)	16(76.7%)	5(1.78-15.2)	0.001
	>30yrs	29(48.3%)	20(33.3%)	4.8(1.74-14.3)	0.001
				$X^2 = 12.58, df-3$	0.001
Extramarital sex wife	Yes	16(26.7%)	6(10%)	3.2(1.19-9.71)	0.018
	No	44(73.3%)	54(90.0%)	1	
Extramarital sex husband	Yes	25(41.7%)	7(11.7%)	5.3(2.1-14.5)	0.0002
	No	35(58.3%)	53(88.3%)	1	
Circumcision	Yes	2(3.3%)	3(5%)	1	0.207
	No	58(96.7%)	57(95%)	1.52(0.21-13.19)	

*Latency period = Current age – Age at first coitus.

Table no.01 shows the socio-demographic profile of the cases and controls where in 61.7% of cases and 56.7%

of controls were aged above 50 years. The mean age of the cases and controls was quite close however, being 50.9 and 50.3 years

respectively. Majority of the study subjects were Hindus, illiterate and coming from a rural area in both cases and controls. Nearly 72% of cases and 58.3% of controls were from lower socio-economic status (Class V of modified BG SES scale). There was no significant difference between the cases and controls with respect to socio-demographic variables.

Younger the age at first intercourse was associated increased risk of cervical cancer wherein the women who had their first intercourse at the age of 12-13 years [OR 4.7, 95% CI 0.98 – 22.9] and 14-15 years [OR 5.4, 95% CI 1.7 – 18.9] had higher odds of having cervical cancer and this association was found to be statistically significant. The risks showed a significantly

increasing trend (P , 0.015) with decreasing age at first coitus.

As the time interval between the current age and age at first coitus increased (latency period) the risk of cervical cancer also increased and maximum risks were observed in those women who had a latency period of 21–30 years [OR 5, 95% CI 1.78 – 15.2].

Women who had extramarital relationships [OR 3.2, 95% CI 1.19 – 9.71] and whose husbands had extramarital relationships [OR 5.3, 95% CI 2.1 – 14.5] had higher risk of cervical cancer and was found to be statistically significant. There was no significant association between male circumcision and the cervical cancer.

Table no. 03: Estimated relative risks (OR) of cervical cancer in relation to Reproductive variables.

Reproductive variables		Cases (n=60)	Controls (n=60)	OR (95% CI)	P value
Age at menarche	10-13yrs	51(85%)	49(81.4%)	1.27(0.47-3.44)	0.625
	>13yrs	9(15.4%)	11(18.3%)	1	
Age at menopause	30-50yrs	55(91.67%)	52(86.6%)	1	0.378
	>50yrs	5(8.3%)	8(13.3%)	1.69(0.52-5.50)	
Parity	≤ 3	21(35%)	35(58.3%)	1	0.01
	> 3	39(65%)	25(41.7%)	2.57(1.23-5.47)	
Use of napkins	Homemade	44(73.35%)	20(33.3%)	5.41(2.49-12.15)	<0.000
	Sanitary pads	16(26.7%)	40(76.7%)	1	
Bathing	Irregular	55(91.6%)	44(73.3%)	3.9(1.38-12.92)	0.009
	regular	5(8.3%)	16(26.7%)	1	
Washing of genitals	No	54(90%)	42(70%)	3.9(1.3-12.9)	0.008
	Yes	6(10%)	18(30%)	1	
Menstrual Hygiene	Absent	45(75%)	32(53.35)	2.6(1.20-5.76)	0.013
	Present	15(25%)	28(46.7%)	1	

Women with early age of menarche (10-13 years) [OR 1.27, 95% CI 0.47 – 3.44] and late onset of menopause (> 50 years) [OR 1.69, 95% CI 0.52 – 5.5] had more risk of cervical cancer; however we did not find a statistically significant association with cervical cancer.

Women who used homemade napkins [OR 5.4, 95% CI 2.49– 12.15], bathed irregularly [OR 3.9, 95% CI 1.38 – 12.92], without washing the genitals after coitus, toilet [OR 3.8, 95% CI 1.3 – 12.9] and lack of menstrual hygiene [OR 2.6, 95%

CI 1.2 – 5.76] had higher risk of cervical cancer and it found to be statistically significant.

Women with higher parity (>3) had increased risk [OR 2.57, 95% CI 1.2 3– 5.47] of cervical cancer and this association was found to be statistically significant.

Women with lower frequency of fruit consumption (≤ 2 times a week) [OR 4.7, 95% CI 1.81– 14.05] and green vegetable consumption (≤ 3 times a week) [OR 1.59, 95% CI 0.77 – 3.3] had more risk of cervical cancer. However only the

frequency of fruit consumption had a statistically significant association with cervical cancer.

Table no. 04: Estimated relative risks (OR) of cervical cancer in relation to sexually transmitted disease variables.

Infectious risk factors		Cases (n=60)	Controls (n=60)	OR (95% CI)	P value
History of Warts(HPV)	Yes	4(6.7%)	1(1.7%)	4.1(0.50-105.9)	0.17
	No	56(93.35)	59(98.2)	1	
HIV Status	Yes	3(5.0%)	1(1.7%)	3.0(0.31-83.0)	0.36
	No	57(95.0%)	59(98.3%)	1	
History of Other STDs	Yes	32(53.3%)	5(8.2%)	12.2(4.5-39.0)	<0.00
	No	28(46.7%)	55(91.8%)	1	

Table no.05: Estimated relative risks (OR) of cervical cancer in relation to diet/habits.

Diet/Habits		Cases (n=60)	Controls (n=60)	OR(95%CI)	P-value
Frequency of fruit consumption (per week)	≤ 2 times	54(90%)	39(65%)	4.7(1.81-14.05)	0.001
	> 2 times	6(10%)	21(35%)	1	
Frequency of green vegetable consumption (per week)	≤ 3 times	34(56.6%)	27(45%)	1.59(0.77-3.3)	0.203
	> 3 times	26(43.4%)	33(55%)		
History of tobacco consumption					
<i>Smoking</i>	Yes	0	0	-	-
	No	60(100%)	60(100%)		
<i>Chewing</i>	Yes	42(70%)	35(58.3%)	1.65(0.77-3.57)	0.184
	No	18(30%)	25(41.6%)	1	

In both cases and controls there was no reported tobacco smoking, however women who chewed tobacco [OR 1.65, 95% CI 0.77– 3.57] had slightly higher risk of developing cervical cancer which was not statistically significant.

DISCUSSION

Sexual behavioural variables:

Most women who develop cervical cancer tend to have one or more identifiable factors that increase the risk of disease development. Human papillomavirus (HPV) infection has been well established as one of the important risk factor. [5] However not all women infected with HPV develops cancer cervix, which suggests that there are other additional factors like reproductive factors, sexual behavioural factors, nutritional factors, socio-demographic factors and other sexually transmitted infections which facilitate the onset and progression of the disease in conjunction with HPV. [6,9,10]

The association between sexual history and cervical cancer is well established. In our study women with early age of coitus and extramarital relationships were the important risk factors which are consistent with previous epidemiological studies conducted elsewhere. [11-22]

In most other studies [23,15,14,17] showed that the increased number of sexual partners increased cervical cancer risk compared with less number of sexual partners. However the number of sexual partners was not studied in our study. It has been suggested that male promiscuity as one of the important determinant for viral transmission and thereby contributing to the onset of cancer cervix. A significant association was seen in our study between husband's extramarital sexual relationship and cervical cancer among the cases which was inconsonance with other studies. [11,24-26]

The role of male circumcision as a protective factor for cancer cervix was not

established in our study as only a small proportion of the husbands were circumcised; however the protective role of male circumcision was shown in some of the previous studies.

Reproductive variables:

In our study and some of the other studies conducted elsewhere [27-31] did not find any statistically significant relationship between cervical cancer and the age at menarche and menopause.

Parity:

The role of multi parity has also been explored in the development of cervical cancer. In our study, a statistically significant relationship was found where women with higher parity (>3) had higher risk of cervical cancer. Our study results were in consonance with the study conducted in Chennai which showed that high parity (>4 vs. ≤ 2 births) was associated with invasive cervical cancer (OR=7.3) after restricting the analysis to HPV positive women. [11] And another study showed that birth interval or the rapidity of multiple pregnancies also as an independent risk factor for cervical cancer. [32] Further the influence of parity was studied in a pooled analysis of 10 case-control studies which revealed that women who had 5–6 or 7 or more full-term pregnancies compared to nulliparous women showed, ORs of 5.0 and 8.3, respectively. [33] A similar, although apparently weaker, association with parity was reported in developed countries. [34,35]

Genital Hygiene/Menstrual hygiene:

A direct role of poor hygienic conditions on risk of HPV infection and cervical cancer has been reported. [36] In our study, women who used homemade napkins with poor genital/menstrual hygiene showed a higher risk of developing cancer cervix. A study in Kerala, India confirmed the importance of genital hygiene in the fight against infections that have a role in the development of cervical dysplasia and

cancer. [37] Another Indian study revealed that use of unclean cloth as compared to the use of clean cloth or use of sanitary napkins had 2.5 fold higher risks for the development of CIN III and malignancy. The factor remained statistically significant even after adjustment with other factors such as age, age at marriage, promiscuity and education, thus highlighting the importance of menstrual hygiene. [38]

A study in Mali also showed that use of homemade napkins as a statistically significant risk factor in the development of cervical cancer and that poor hygiene was observed to be a co factor for cervical cancer with prevalent HPV infection. [36] A WHO report also suggests that genital hygiene to be an important component associated with cervical neoplasia. [39] It has been speculated that women with poor hygienic practices or living in poor hygienic conditions might have increased risk of HPV infection or cervical cancer. [40,11]

Infective risk factors:

Some of the case-control studies have reported positive associations between history of genital infection such as Neisseria Gonorrhoeae, Chlamydia Trachomatis and cervical cancer. [41-44,13]

The same finding was revealed in our study where women who had previous history suggestive of sexually transmitted diseases [OR 8.8, 95% CI 3.2 – 28.0] had significantly higher risk of cervical cancer. HIV positive women and women with history of suggestive of HPV infection had more risk of cervical cancer however it was not found to be statistically significant. But in other study, [45] self-reported history of sexually transmitted diseases (STDs) other than HPV were not associated with high-grade squamous intraepithelial lesions (HSIL) and cervical cancer.

HIV infected women are more likely to be infected with high risk HPV types and thereby more prone to develop precancerous

lesions than HIV negative women in the same age category. [46-48]

Tobacco Consumption:

Tobacco smoking is one of the important environmental determinants which has been consistently identified to influence the risk of cervical cancer where in studies show at least a twofold risk for current smokers compared to non-smokers. [45,49,50]

In our study tobacco smoking was not reported among both cases and controls. We did not find any statistically significant association between tobacco chewing and cervical cancer. But in some of the studies tobacco chewing/pan chewing had significant relationship with cervical cancer where in 2-fold increased risk of ICC was found after adjustment for education, occupation and other major risk factors. [51]

Diet:

Some of the studies have suggested that a diet high in carotenoids, vegetables and fruits, and high intake of vitamin C and E may reduce the risk and considered as the protective agents against cervical cancer. [52,53]

In our study we found a statistically significant association between increased frequency of fruit consumption (> 2 times in a week) and the cervical cancer. However we could not find the same with frequency of vegetable consumption. But in a study from China showed the protective role of intake of green vegetables for cancer cervix. [54] And in similar study revealed a relation between the risk of both cervical cancer and in situ disease and intake of carotenoids, vitamin C, folate, fruits and vegetables. Vitamin A was not found to be statistically protective factor. [55] However there is lack of information available with regard to studies dealing with the dietary aspects of cervical cancer from the developing countries including India. There is a need to take up the research on this important aspect

for considering this important component of diet for primary prevention strategy.

Awareness of Pap smear:

In our study none of the cases and controls was aware of Pap smear examination.

Some of the studies report that there is lack of awareness about important risk factors of cervical cancer among educated young women of India which points out that the larger population of less educated women is in greater lack of awareness. [56,57]

CONCLUSION

In our study we studied some of the known risk factors of cancer cervix and to conclude among the sexual behavioural variables like age at first coitus, history of extra marital sex in husband & wife, latency period, reproductive variables like parity, genital and menstrual hygiene, along with previous history of sexually transmitted diseases and lastly dietary factors like frequency of fruit consumption had a significant association with cancer cervix.

Limitations:

The results from the current study must be considered in light of certain limitations. Firstly, the study was carried out in a small group of 60 cases and 60 controls for a period of six months. Another limitation of the study is that most of the data was obtained from the women's self-reports wherein some of the information pertaining to age of menarche, age at the first sexual intercourse and history of HPV and other STDs were difficult for them to remember.

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