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Chlamydia trachomatis as a risk factor of cervical cancer: a facility based case-control study

Dr Bipul Kumar Biswas
Assistant Professor
Department of Obstetrics and Gynaecology
Kushtia Medical College

Dr Begum Maksuda Farida Akhtar
Associate Professor
Department of Obstetrics and Gynaecology
Sir Salimullah Medical College and Mitford Hospital

Dr Mahbuba Nargis
Consultant Gynaecologist
MCHTI, Azimpur Maternity Hospital Dhaka

Dr Dilip Kumar Bhowmick
Associate Professor
Department of Anaesthesia, Analgesia and Intensive Care Medicine
Bangabandhu Sheikh Mujib Medical University

Dr Bipul Kumar Biswas
Assistant Professor
Department of Obstetrics and Gynaecology
Kushtia Medical College

Abstract
Introduction
Despite being a potentially preventable cancer, almost five thousand deaths occur every year in Bangladesh due to cervical carcinoma. Studies suggests different infections organisms like human papilloma virus and Chlamydia trachomatis can play a carcinogenic role in this case. Hence the objective of the study is to explore the association between Chlamydia trachomatis infection and cervical carcinoma among Bangladeshi women.
Methods
This was a case-control study conducted in the department of Gynecology of Dhaka Medical College Hospital (DMCH), Dhaka from July to December, 2006. Histopathologically confirmed cases of cervical cancer admitted in above mentioned hospital were selected as cases and women admitted in the hospital for different cervical conditions without proven cervical cancer were selected as controls. Sociodemographic characteristics, clinical presentation and evidence of C. trachomatis infection were explored. Chi-square test was used to establish the association between chlamydial infection and cervical carcinoma.
Results
Average age (SD) of cervical carcinoma patients was 43 (8) years. Squamous cell carcinoma (SCC) was most prevalent type of carcinoma cervix (98%). Per-vaginal foul smelling discharge (96%) and bleeding (68%) were the most common clinical presentation of the patients. Among the risk factors of cervical cancer early age of marriage (86% in cases vs 34% in controls, p = 0.031) and use of oral contraceptive pills (46% in cases vs 22% in controls, p = 0.01) were more prevalent among the cases. Infection by C. trachomatis was identified as a significant risk factor of cervical carcinoma (p = 0.011).
Conclusions
Women with infection of C. trachomatis are at a higher risk of developing cervical carcinoma. Adequate screening and early management could potentially mitigate the burden of infection associated cervical carcinoma.

Keywords: *Cervical carcinoma, Chlamydia trachomatis, Risk factor, Bangladesh*

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I. Introduction

Cervical cancer is one of the most commonly diagnosed cancers among women worldwide (1). Despite the declining trend in the incidence and mortality rate of cervical cancer in developed countries by wide application of screening programs for early detection of precancerous lesions and vaccination (2–4), these remain high in most of the lower and middle income countries. In Bangladesh it is the second most prevalent female cancer with more than eight thousand new cases causing more than five thousand deaths every year (5). Multiple factors contribute to this higher prevalence and mortality in developing countries including Bangladesh. Among these, lack of awareness about cervical cancer among the people, health care providers, and policy makers, lack of prevention and early cervical screening programs, and limited resources and skilled personnel in healthcare facilities to sustain the programs etc. are the major contributing factors. (6).

A number of risk factors are attributable to cervical cancer including young age at first sexual intercourse, young age at first pregnancy, multiple male sexual partners, high parity, prolonged use of oral contraceptives etc. (7,8). Besides these some infective causes also attribute to the development of cervical carcinoma including Human papillomavirus (HPV) infection. It was reported that almost 70% of the global cervical cancer cases were associated with HPV genotype 16 and 18 infection (9,10). Among Bangladeshi women HPV-16 was most commonly detected high-risk HPV genotype, making them vulnerable to cervical cancer as well as its immediate precursor lesions (11). Other sexually transmitted infections such as bacterial vaginosis, *Chlamydia trachomatis*, herpes simplex virus, and human immunodeficiency virus have been identified as possible cofactors involved in cervical carcinogenesis (12). *C. trachomatis* is one of the most common sexually transmitted pathogens in women (13). Epidemiological studies have shown a higher rate of *C. trachomatis* infection in patients with cervical cancer (12,14–16). However, different studies reported ambiguous findings. For example, in a nested case–control study conducted in North-East Thailand indicated lack of significant effects of *C. trachomatis* infection on cervical cancer risk (17). Another study from Iran reported similar result where they found no significant association between cervical cancer and *C. trachomatis* (18).

Therefore, the question of whether *C. trachomatis* infection increases the risk of cervical cancer has so far not been answered and is still a matter of debate. Hence, we conducted a study to examine the association between *C. trachomatis* infection and cervical cancer risk specifically among Bangladeshi women.

II. Methods

This was a case-control study conducted in the department of Gynecology of Dhaka Medical College Hospital (DMCH), Dhaka from July to December, 2006. Histopathologically diagnosed patients of cervical cancer admitted in above mentioned hospital were selected as cases and patients admitted in the hospital for different cervical conditions without proven cervical cancer were selected as controls. Inclusion criteria were: (i) diagnosed cases of cervical cancers irrespective of histological type and age (cases), (ii) women admitted in the hospitals in gynecological unit other than cervical neoplasia (controls). Exclusion criteria were (i) patients of carcinoma of cervix treated by chemotherapy and radiotherapy, (ii) pregnant patients with carcinoma of cervix. For the purpose of the study a total of 50 cases and 50 controls were selected.

Diagnosis of cervical cancer

Following enrollment with informed written consent, all patients underwent colposcopy, and a second cervical smear with endocervical sampling was carried out at the first study visit. Punch biopsy was performed whenever a suspicious colposcopic image with complete visualization was identified. Women with a diagnosis of cervical intraepithelial neoplasia 2 or 3 were submitted to cervical conization and those with a diagnosis of cervical cancer were referred for specialized treatment. Women with a suspicious image penetrating the cervical canal and those in whom colposcopy findings were unsatisfactory and in addition had an abnormal second cervical smear were also submitted to cervical conization.

Histopathology

Biopsy specimens were stained with hematoxylin and eosin (HE) reviewed according to the World Health Organization (WHO) criteria (19) and classified as: cervical intraepithelial neoplasia grade 1, 2, 3, invasive squamous cell carcinoma or invasive cervical adenocarcinoma. All the histological tests were carried out in a pathology laboratory and in all cases diagnosis was made by the same pathologist.

Serology for *C. trachomatis*

The following laboratory tests were performed to find the past or present evidences of Chlamydial infection (1) Immuno-chromatographic test (ICT) of the endocervical swab, (2) Chlamydia lgG enzyme linked immunosorbent Assay (ELISA).

Serum IgG antibody responses to *C. trachomatis* were determined by a ELISA, using synthetic peptides derived from the major outer membrane protein (MOMP) variable domain. This feature allows the screening and diagnosis of *C. trachomatis* infections to be performed without interference from the antibodies against Chlamydia pneumoniae. The assay was carried out according to the manufacturer's instructions. The results were based on optical density (OD) measurements and the cut-off OD value. Absorbance was determined using a bichromatic spectrophotometer set at 450 nm, calibrated with a blank solution at the wavelength range of 620–630 nm. All measurements were performed within 10 min of calibration. Samples with index values 1.1 were considered positive, while sample index values <0.9 were considered negative. Samples with index values between 0.9 and 1.1 were considered inconclusive and in these cases the tests were repeated.

Statistical Analysis

All statistical analyses were performed using the SPSS version 24.0. Data were expressed as percentages of the total or as a frequency of *C. trachomatis*-seropositive cases. The prevalence of *C. trachomatis* was compared in each group of cervical neoplasia diagnoses using the chi-square test. P-value <0.05 was interpreted as statistically significant.

III. Results

Cervical carcinoma patients were comparatively older than the controls (average age of cases was 43 years and that of controls was 39 years). Majority of the patients were illiterate and belonged to low income families (Table 1). Squamous cell carcinoma (SCC) was most prevalent carcinoma of cervix (well differentiated SCC 48%, moderately differentiated SCC 46% and undifferentiated SCC 4%) (Figure 1).

Table 1: Sociodemographic characteristics of the patients

Characteristics	Case (women with ca cervix)	Control (women other than ca cervix)	p-value
Age (years)			
Mean (SD)	42.78 (8.01)	39.32 (5.44)	0.013
30-40	12 (24.0)	25 (50.0)	0.014
41-45	27 (54.0)	22 (44.0)	
46-50	7 (14.0)	3 (6.0)	
>50	4 (8.0)	0 (0.0)	
Educational status			
Illiterate	29 (58.0)	28 (56.0)	0.656
Primary	16 (32.0)	14 (28.0)	
Secondary	5 (10.0)	8 (16.0)	
Income			
<Tk. 3000	38 (76.0)	39 (78.0)	0.500
≥Tk. 3000	12 (24.0)	11 (22.0)	

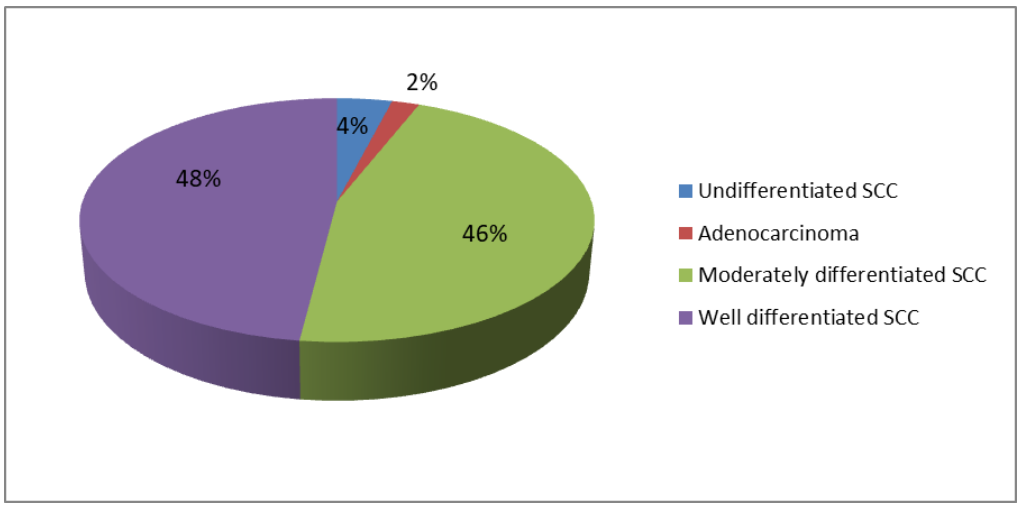

Figure 1: Classification of cervical cancer among the patients (n = 50)

Per-vaginal discharge was the most common clinical presentation of cervical cancer (96%), followed by abnormal per-vaginal bleeding (68%), foul smelling discharge (64%) and post-coital bleeding (50%). Among the risk factors of cervical cancer early age of marriage and use of oral contraceptive pills were more prevalent among the cases. Infection by *C. trachomatis* was identified as a significant risk factor of cervical carcinoma.

Table 2: Clinical presentation and risk factors of cervical cancer of the patients

Characteristics	Case	Control	p-value
Clinical presentation			
History of abnormal PV bleeding	34 (68.0)	14 (28.0)	0.001
History P/V discharge	48 (96.0)	24 (48.0)	0.001
History of foul smelling discharge	32 (64.0)	0 (0.0)	0.001
Post coital bleeding	25 (50.0)	0 (0.0)	0.001
Age of marriage			
<15	43 (86.0)	17 (34.0)	0.031
>15	7 (14.0)	33 (66.0)	
Number of sexual partner			
Single	49 (98.0)	50 (100.0)	0.245
Multiple	1 (2.0)	0 (0.0)	
OCP			
Yes	23 (46.0)	11 (22.0)	0.010
No	27 (54.0)	39 (78.0)	
History of STD			
Yes	1 (2.0)	2 (4.0)	0.558
No	49 (98.0)	48 (96.0)	
Smoking			
Yes	1 (2.0)	0 (0.0)	0.482
No	49 (98.0)	50 (100.0)	
Cervical smear for *C. trachomatis* (ICT)			
Negative	21 (42.0)	34 (68.0)	0.012
Positive	24 (48.0)	10 (20.0)	
Equivocal	5 (10.0)	6 (12.0)	
Serological evidence for *C. trachomatis*			
Negative	18 (36.0)	32 (64.0)	0.011
Positive	27 (54.0)	13 (26.0)	
Equivocal	5 (10.0)	5 (10.0)	

IV. Discussion

Cervical carcinoma is one of the most prevalent gynecological cancers which is mostly preventable as it is associated with a number of infectious organism including Human Papilloma Virus, *Chlamydia trachomatis*, herpes simplex virus etc. are involved in this carcinogenesis (12). As a result, identifying the risk factors could potentially guide the further prevention programs. The present study provides an insight on the association of *Chlamydia trachomatis* infection with cervical cancer.

Our findings suggest that *C. trachomatis* infection, whether evidenced by positive ICT of the cervical cancer or presence of anti-Chlamydial IgG antibody was significantly associated with increased risk of cervical cancer. In the existing evidence, the finding that the presence of chlamydial infection was associated with an increased cervical cancer risk also supports our finding of the correlation between persistent *C. trachomatis* infection and cervical neoplasia cancer (12,14–16). However, a few studies reported contradictory findings of no association of *C. trachomatis* infection with cervical cancer (17,18).

A plausible mechanism for chlamydial infection to increase cervical cancer risk is the infection-associated inflammatory response which leads to production of reactive oxidative species, increased expression of cytokines, chemokines, and growth and angiogenic factors, decreased cell-mediated immunity, and the generation of free radicals, all of which can cause damages to DNA and impair DNA repair function resulting in genetic instability (20). *C. trachomatis* infection triggers the production of supernumerary centrosomes and chromosome segregation defects, facilitates multipolar mitosis, actively promotes chromosome instability, causes multinucleation, and thereby leads to transformation and tumor development (21). In the same line of evidence it was shown that infection of mice with *C. trachomatis* resulted in significantly increased cell proliferation, within the cervix, and in evidence of cervical dysplasia (22).

Besides chlamydial infection, other established sociodemographic and behavioral risk factors were found to be associated with cervical carcinoma among our patients. Among those, early age of marriage and sexual intercourse and use of oral contraceptive use were associated with cervical cancer in our study. These risk factors were also evidenced in previous studies (7,8). The sociodemographic characteristics of our patients are also consistent with the previously reported patient cohorts. The average of diagnosis of cervical cancer of our study was 43 years and majority of the patients were from lower socioeconomic class. Similar group of people were also reported as vulnerable in previous studies (15,16).

Majority of our patients were suffering from squamous cell carcinoma (SCC). Findings from several previous studies suggested the role of *C. trachomatis* as a carcinogenetic cofactor may be restricted to cervical SCC (15,23). However, some studies reported that *C. trachomatis* infection is associated with a higher risk in both SCC and adenocarcinoma of the cervix (14).

Infection with HPV is established as a major cause of cervical cancer (9,10). Several studies suggest that *C. trachomatis* infection may increase the risk of HPV acquisition as well as HPV persistence and ultimately increase the risk of cervical carcinoma (24,25). Moreover, it was evidenced that coinfection of HPV and *C. trachomatis* was related to a higher risk of uterine cervical cancer, further strengthening this relationship (14). However, the infections both of HPV and *C. trachomatis* are sexually transmitted. They have similar behavioral risk factors, such as younger age and higher numbers of sexual partners. As a result, these two infections could occur concurrently, rather than *C. trachomatis* infection directly affecting HPV acquisition.

Our study demonstrated that there is an association between *C. trachomatis* infection and cervical carcinoma. Our study, nonetheless, has some limitations. Firstly, our study was a case–control study where data on prevalence of *C. trachomatis* and cervical cancers were acquired simultaneously, rather than longitudinally. The underlying interaction between *C. trachomatis* and cervical cancer risk could be confirmed in longitudinal studies. Secondly, our study did not take into account the association between the duration of *C. trachomatis* infection and the risk of cervical cancer. Moreover, inadequate control for confounders may bias the results in overestimation or underestimation of risk estimates. Finally, the study sample size was not large enough to draw a robust inference at population level. The present study calls for further investigation in more prospective studies to provide more definitive evidence concerning the role of this pathogen as a promoter cervical carcinogenesis.

V. Conclusion

Our study suggests that infection with *C. trachomatis* could be one of the risk factors of cervical cancer. Therefore, it is necessary to expand the screening and treatment program for the women with *C. trachomatis* infection timely. This approach will not only protect against pelvic inflammatory disease and infertility, but potentially also prevent cervical cancer and reduce the incidence of cervical cancer.

Declarations:
Ethics approval and consent to participate
Approval of the study protocol was obtained from the ethical committee of Dhaka Medical College. Informed written consent was obtained from each participants before enrollment.
Consent for publication: Not applicable.
Availability of data and materials: Patient-level data will be available on request from the corresponding author.
Conflict of interest: The authors declare that they have no competing interests.
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Author Contributions
Conceptualization:
Formal analysis:
Investigation:
Methodology:
Resources:
Supervision:
Writing – original draft:
Writing – review & editing:

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