

THE INFLUENCE OF VARIOUS RISK FACTORS ON THE CORRELATION BETWEEN HPV INFECTION AND THE ADVANCEMENT OF CERVICAL CARCINOMA

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(Received, 07th May 2024, Revised 20th June 2024, Published 25th June 2024)

Abstract: Cervical cancer is a significant global health challenge, disproportionately impacting women in developing nations, where approximately 85% of incidence and mortality occur. The primary etiological agent is the human papillomavirus (HPV), with high-risk types HPV 16 and 18 accounting for over 90% of cases. Despite the high prevalence of HPV, most infected women do not develop cervical cancer, indicating the role of additional risk factors. **Objective:** This study aims to investigate the association between various sociodemographic and behavioral factors, HPV infection, and the progression of cervical cancer. **Methods:** This case-control study was conducted at the Cancer Care Hospital and Research Center in Pakistan from April 2024 to April 2024. It involved 200 consecutive subjects, with 100 cases diagnosed with precancerous lesions (HSIL/LSIL) or invasive carcinoma of the uterine cervix, and 100 age and ethnicity-matched controls with normal cervical cytology. Data were collected through structured personal interviews and analyzed using descriptive and inferential statistical methods. The significance level was set at $p < 0.05$. **Results:** Significant differences between cases and controls were observed in dietary habits, gravidity, parity, age, menopausal status, residential setup, tobacco chewing, smoking, and age at marriage. Non-vegetarian diet, higher gravidity and parity, older age, postmenopausal status, rural residence, tobacco use, and early marriage were significantly associated with increased cervical cancer risk ($p < 0.0001$). No significant difference was found in literacy rates ($p = 0.68$). **Conclusion:** The study highlights the multifactorial etiology of cervical cancer, emphasizing the need for targeted interventions addressing specific risk factors. Early detection, HPV vaccination, and public health education, particularly in rural areas, are crucial for reducing cervical cancer burden.

Keywords: Cervical cancer, HPV, Risk factors, Gravidity, Parity, Tobacco use, Rural residence, Early marriage, Case-control study

Introduction

Cervical cancer is a significant global health challenge, particularly impacting women in developing nations, where approximately 85% of its incidence and mortality are concentrated, leading to an alarming annual toll of 529,800 cases and 275,000 deaths (1). This imbalance is starkly evident in low-income countries like India, where cervical cancer ranks as the leading cause of cancer-related deaths among women (2). The primary culprit behind this disease is the human papillomavirus (HPV), with over 90% of cases linked to HPV infection, notably the high-risk types HPV 16 and 18 (3).

Surprisingly, despite the widespread prevalence of HPV, the majority of infected women (~80%) do not progress to cervical cancer, indicating the involvement of additional factors beyond viral presence (4). These factors, classified

as either internal (inherited mutations, hormonal fluctuations, immune conditions) or external (tobacco use, dietary habits, radiation exposure, other infectious agents), play pivotal roles in the initiation and progression of cervical malignancies (5).

Various demographic and behavioral characteristics have been identified as risk factors for invasive cervical cancer, including early sexual debut, multiple sexual partners, low socio-economic status, high parity, tobacco exposure, and a history of sexually transmitted diseases (6). The interaction between these factors and HPV infection synergistically increases the risk of cervical cancer development and progression (7).

The focal point of numerous studies is to unravel the intricate relationship between demographic variables, HPV infection, and cervical cancer. By elucidating these

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synergistic effects, researchers aim to refine risk assessment strategies, optimize screening protocols, and develop targeted interventions for vulnerable populations (8). Understanding the multifactorial nature of cervical carcinogenesis is crucial for advancing prevention efforts and improving clinical outcomes worldwide (9). Ultimately, while HPV infection serves as the primary trigger for cervical cancer, a multitude of demographic and environmental factors contribute to its pathogenesis. Through thorough research, we aim to unravel this complexity, leading to more effective prevention and management strategies to combat this disease and reduce its global impact.

Methodology

This study employed a case-control design involving a total of 200 consecutive subjects. The case group consisted of 100 individuals diagnosed with precancerous lesions (high or low-grade squamous intraepithelial lesion - HSIL/LSIL) or invasive carcinoma of the uterine cervix. Participants were recruited from Cancer Care Hospital and Research Center in Pakistan, based on histologically confirmed diagnoses. Lesion classification and grading followed the World Health Organization criteria, while tumor staging and histological grading adhered to the International Federation of Obstetrics and Gynecology (FIGO) guidelines.

The control group comprised 100 age and ethnicity-matched individuals with normal cervical cytology and no history of cancer. Control samples were obtained from women visiting the hospital for other gynecological reasons, including endometrial biopsy or cervical tissue biopsy. Prior to participation, all subjects provided written consent, and the study protocol adhered strictly to the principles outlined in the Helsinki Declaration. Ethical approval for the study was obtained from the ethics committee of the institute (ICPO-ICMR/IEC/2009/P-004).

Structured personal interviews were conducted with all enrolled subjects to gather demographic characteristics, including age, ethnicity, and relevant medical history. Data analysis was performed using appropriate statistical methods. Descriptive statistics summarized demographic characteristics, while inferential statistics, such as t-tests or

chi-square tests, assessed associations between demographic variables and cervical cancer risk. The significance level was set at $p < 0.05$.

Results

This study examines the association between sociodemographic and behavioral factors and the progression of cervical cancer. Significant differences between cases and controls were found in several areas. Dietary habits showed a strong association with cervical cancer risk, with 38% of cases being vegetarians compared to 62% of controls, and 62% of cases being non-vegetarians compared to 38% of controls ($p < 0.0001$).

Gravidity and parity also displayed significant differences. Only 25% of cases had three or fewer pregnancies compared to 96% of controls, while 75% of cases had more than three pregnancies compared to 4% of controls ($p < 0.0001$). Similarly, 36% of cases had three or fewer live births compared to 99% of controls, whereas 64% of cases had more than three live births compared to 1% of controls ($p < 0.0001$).

The mean age of cases was 44.5 years (SD = 8.7 years) compared to 40.5 years (SD = 7.5 years) for controls, indicating that cervical cancer patients tend to be older ($p < 0.0001$). Menopausal status showed 70% of cases were premenopausal compared to 80% of controls, while 30% of cases were postmenopausal compared to 20% of controls ($p < 0.0001$).

Residential setup showed 10% of cases were from urban areas compared to 30% of controls, and 90% of cases were from rural areas compared to 70% of controls ($p < 0.0001$). Tobacco chewing and smoking were more prevalent among cases, with 20% being tobacco chewers compared to 5% of controls, and 30% being smokers compared to 2.5% of controls ($p < 0.0001$ for both).

Literacy rates showed no significant difference, with 40% of cases being literate compared to 50% of controls ($p = 0.68$). Age at marriage indicated 60% of cases were married below 21 compared to 35% of controls, suggesting an increased risk of cervical cancer with earlier marriage ($p = 0.004$). (Table 1)

Table 1: Sociodemographic and Behavioural Factors Among Cases and Controls

Factor	Group	Cases (%)	Controls (%)	p-value
Dietary Habits	Vegetarians	38% (38)	62% (62)	< 0.0001
	Non-Vegetarians	62% (62)	38% (38)	
Gravidity	≤3 Pregnancies	25% (25)	96% (96)	< 0.0001
	>3 Pregnancies	75% (75)	4% (4)	
Parity	≤3 Live Births	36% (36)	99% (99)	< 0.0001
	>3 Live Births	64% (64)	1% (1)	
Age Distribution	Mean Age (Years)	44.5	40.5	< 0.0001
	Standard Deviation (Years)	8.7	7.5	

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Menopausal Status	Premenopausal	70% (70)	80% (80)	< 0.0001
	Postmenopausal	30% (30)	20% (20)	
Residential Setup	Urban	10% (10)	30% (30)	< 0.0001
	Rural	90% (90)	70% (70)	
Tobacco Chewing	Chewers	20% (20)	5% (5)	< 0.0001
	Non-Chewers	80% (80)	95% (95)	
Smoking	Smokers	30% (30)	2.5% (2.5)	< 0.0001
	Non-Smokers	70% (70)	97.5% (97.5)	
Literacy Rates	Literate	40% (40)	50% (50)	0.68
	Illiterate	60% (60)	50% (50)	
Age at Marriage	<21 Years	60% (60)	35% (35)	0.004
	≥21 Years	40% (40)	65% (65)	

Table 2: Clinical Stages of Cervical Cancer Cases

Clinical Stage	Cases (%)
Pre-cancerous	9% (9)
Stage I	11% (11)
Stage II	33% (33)
Stage III	38% (38)
Stage IV	9% (9)

Table 2 shows the distribution of clinical stages among cervical cancer cases. In the case group, 9% (9 patients) were pre-cancerous, with 80% (7/9) having low-grade squamous intraepithelial lesions (LSIL) and 20% (2/9) having high-grade squamous intraepithelial lesions (HSIL).

Clinically, 11% (11 patients) of the cancer cases were at stage I, 33% (33 patients) were at stage II, 38% (38 patients) were at stage III, and 9% (9 patients) were at stage IV.(Figure 1)

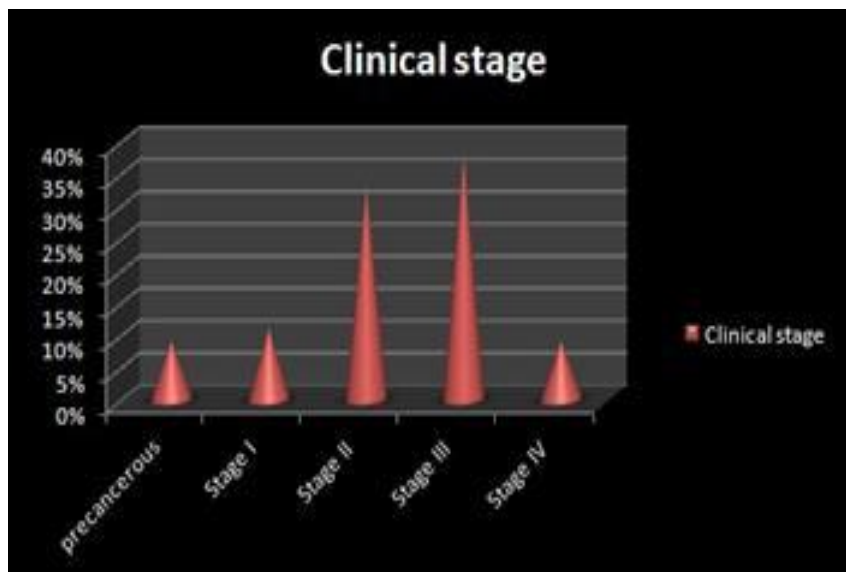


Figure 1: Distribution of cervical cancer patients according to the clinical stage of the disease

Table 3: Histopathological Grades of Cervical Cancer Cases

Histopathological Grade	Cases (%)
WDSCC	42% (42)

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MDSCC	40% (40)
PDSCC	9% (9)

Table 2 shows the distribution of histopathological grades among cervical cancer cases. In the case group, 42% (42 patients) were diagnosed with well-differentiated squamous cell carcinoma (WDSCC), 40% (40 patients) with moderately differentiated squamous cell carcinoma

(MDSCC), and 9% (9 patients) with poorly differentiated squamous cell carcinoma (PDSCC). This indicates that the majority of cervical cancer cases were either well-differentiated or moderately differentiated squamous cell carcinomas. (Figure 2)

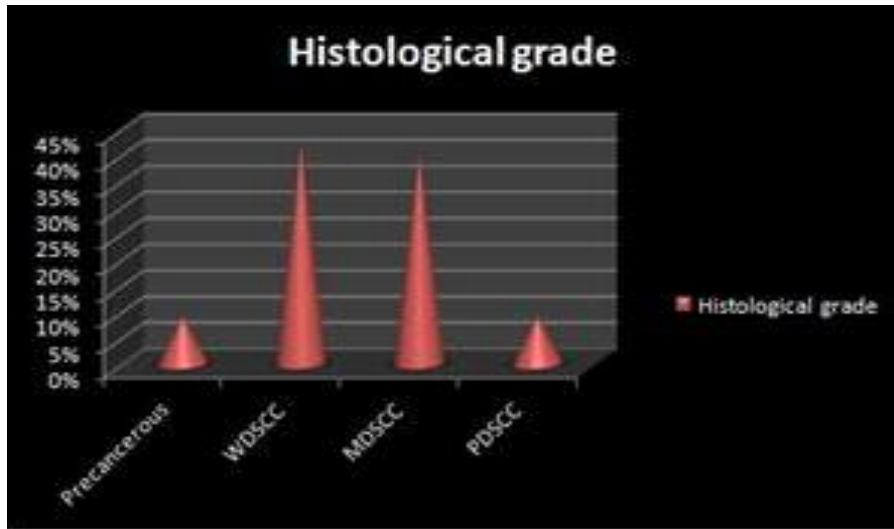


Figure 2: Distribution of cervical cancer patients according to histological grade of the disease

These findings highlight significant associations between various risk factors and the progression of cervical cancer. Early age at marriage, tobacco use, and rural residence emerged as critical factors linked to increased susceptibility to HPV infection and cervical cancer development. These insights emphasize the need for targeted interventions and comprehensive prevention strategies to address the multifaceted etiology of cervical cancer.

Discussion

This study highlights significant associations between sociodemographic and behavioral factors and the progression of cervical cancer, providing crucial insights into its multifactorial etiology. Our findings align with previous research, underscoring the importance of these factors in the development and progression of cervical cancer.

The association between dietary habits and cervical cancer risk is evident, with a higher prevalence of non-vegetarians among the cases (62%) compared to controls (38%). This finding is consistent with previous studies suggesting that dietary patterns may influence the risk of cervical cancer, potentially through mechanisms involving inflammation and immune response modulation (10).

Gravidity and parity emerged as significant factors, with a higher proportion of cases having more than three pregnancies and live births. Specifically, 75% of cases had more than three pregnancies compared to 4% of controls, and 64% of cases had more than three live births compared to 1% of controls. These results corroborate previous research indicating that high parity and gravidity are

associated with an increased risk of cervical cancer due to prolonged hormonal exposure and potential immunosuppression during pregnancy (11).

The age distribution showed that cervical cancer patients were generally older, with a mean age of 44.5 years compared to 40.5 years for controls. This finding is in line with other studies that have identified age as a significant risk factor, with older women having a higher likelihood of developing cervical cancer due to cumulative exposure to HPV and other risk factors over time (12).

Menopausal status also showed a significant association, with 30% of cases being postmenopausal compared to 20% of controls. This aligns with the understanding that hormonal changes during menopause can affect the cervical epithelium and potentially contribute to cancer development (13).

Our study also found that rural residence is a significant risk factor, with 90% of cases residing in rural areas compared to 70% of controls. This supports previous findings that women in rural areas may have limited access to healthcare services, including cervical cancer screening and HPV vaccination, which increases their risk (1).

Behavioral factors such as tobacco chewing and smoking were more prevalent among cases, with 20% of cases being tobacco chewers compared to 5% of controls, and 30% of cases being smokers compared to 2.5% of controls. These behaviors are well-documented risk factors for cervical cancer, likely due to their carcinogenic effects and their role in weakening the immune system's ability to clear HPV infections (14).

Interestingly, literacy rates did not show a significant difference between cases and controls, suggesting that factors other than education level may be more critical in

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this population. However, early age at marriage was significantly associated with cervical cancer risk, with 60% of cases married before the age of 21 compared to 35% of controls. This finding highlights the role of early marriage and associated early sexual activity in increasing the risk of HPV infection and subsequent cervical cancer (15). The clinical staging of cervical cancer patients showed that a significant proportion were diagnosed at advanced stages (stage III and IV), underscoring the need for early detection and intervention. Histopathological grading revealed that most cases were well-differentiated or moderately differentiated squamous cell carcinomas, consistent with the typical histological presentation of cervical cancer (9). The study had certain limitations, including potential selection bias due to the hospital-based recruitment method and the possibility of recall bias during the collection of demographic data through personal interviews. Additionally, the generalizability of the findings may be limited to the study population and may not extend to other geographic or demographic groups.

Conclusion

In conclusion, our study reinforces the critical need for targeted interventions addressing the identified risk factors, including dietary habits, reproductive history, residential setup, and behavioral factors. Enhancing access to cervical cancer screening, HPV vaccination, and public health education, particularly in rural areas, is essential for reducing the burden of cervical cancer. Further research should continue to explore these associations and develop comprehensive prevention strategies tailored to high-risk populations.

Declarations

Data Availability statement

All data generated or analyzed during the study are included in the manuscript.

Ethics approval and consent to participate.

Approved by the department Concerned.

Consent for publication

Approved

Funding

Not applicable

Conflict of interest

The authors declared an absence of conflict of interest.

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Final Approval of version

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