Research in Molecular Medicine

Human Papillomavirus Testing and Disease Recurrence of Cervical Cancer

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Citation Aminimoghaddam S, Sajedi NAS. Human Papillomavirus Testing and Disease Recurrence of Cervical Cancer. Research in Molecular Medicine. 2023; 11(1):49-56. https://doi.org/10.32598/rmm.11.1.1274.1

https://doi.org/10.32598/rmm.11.1.1274.1

Article Type:
Research Paper

Article info:
Received: 20 Dec 2023
Revised: 15 Jan 2024
Accepted: 05 Feb 2024

Keywords:
Human papillomavirus (HPV), Recurrence, Cervical cancer, Chemotherapy, Radiotherapy

ABSTRACT

Background: Cervical cancer stands out as one of the most prevalent gynecological cancers. Cervical cancer's link to human papillomavirus (HPV) testing and recurrence is unclear despite previous studies. Investigating this relationship in Iranian patients is a pivotal aspect of this research.

Materials and Methods: This study encompassed all cervical cancer patients referred to Firoozgar Hospital, Tehran, Iran, between 2016 and 2018. Utilizing a census method, the patients' data, including their demographics and treatment details, were extracted from records. Follow-up samples were collected after vaginal cuff or cervix treatment (surgical or radiotherapy). A total of 124 patients were included in the study and categorized into two groups: Patients with recurrence and those without. INNO-LiPA standard test was employed to detect HPV presence. Comparative analysis of various variables, such as age at diagnosis, smoking history, multiple partners, sexually transmitted diseases history, body mass index, abnormal cervix, vaginal fornix involvement, cervical parameters involvement, tumor size, The International Federation of Gynaecology and Obstetrics (FIGO) staging, MRI staging, pathology, and treatment, was conducted between the recurrence and non-recurrence groups.

Results: A total of 124 patients were included in the study, with an average age of 45.95±7.45 years. Most patients had an 18-25 kg/m^2 body mass index. Based on MRI findings, the most common stage of cervical cancer was stage III, IIB. Squamous cell carcinoma pathology was the most prevalent, observed in 47 patients (37.9%). The most frequently performed treatment modality was radical trachelectomy and adjuvant chemoradiotherapy, accounting for 20 cases (16.1%). There were no significant differences in terms of age at disease diagnosis, smoking history, body mass index, histological type, and treatment type between patients with recurrent disease and those without recurrence. However, a significant difference was observed in terms of lymph node involvement. In addition, the HPV test was positive in 3 cases (2.4%) with recurrence and 11(8.9%) without. These results suggest no relationship between hrHPV (high-risk human papillomavirus) status and disease recurrence (P=0.196).

Conclusion: The result of our study showed no correlation between positive HPV test and cervical cancer recurrence. Consequently, HPV testing is not suitable as a reliable predictor for the recurrence of cervical cancer.

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Introduction

Cervical cancer is a significant global health concern, ranking as the fourth most prevalent cancer among women worldwide, particularly affecting those under the age of 45 [1-4]. Predominantly occurring in less developed regions, it accounted for approximately 604000 new cases and 342000 deaths in 2020 in 36 countries, highlighting a pressing need for improved treatment strategies [5]. Survival rates vary dramatically with the disease stage, from over 90% in localized cases to below 20% in metastatic stages, underscoring the importance of early detection and effective treatment modalities, including surgery, chemotherapy, and radiation therapy [6, 7]. Radiotherapy, when combined with surgery, represents one of the most effective treatment modalities for cervical cancer [8, 9]. Despite advancements, treatment failures, and disease recurrences remain challenges, particularly in advanced stages. Hence, alternative options such as hysterectomy or chemotherapy are recommended [10]. In general, treatment options for early and locally invasive stages of cervical cancer include radical hysterectomy or radical trachelectomy with pelvic lymphadenectomy, accompanied by concurrent chemotherapy and radiation therapy. In contrast, metastatic cervical cancer necessitates systemic therapies for treatment. Systemic treatment options include chemotherapy, targeted therapies, and immunotherapy, which have low cure rates for advanced stages and undesirable side effects [11, 12]. Moreover, recent clinical trials advocate cisplatin-based chemotherapy-radiotherapy regimens as the standard treatment approach [13, 14]. Despite these therapeutic advances, we still need to improve treatment methods and especially prognosis to prevent cervical cancer recurrence.

Human papillomavirus (HPV) is a significant contributing factor in cervical cancer, typically cleared by the immune system. Of over 200 HPV types identified, 15 pose a high risk for cervical cancer. While the body often overcomes HPV naturally, certain genetic and lifestyle factors can influence the progression to cancer in those with high-risk HPV types [15, 16]. Despite the abundance of studies exploring the link between HPV and cervical cancer recurrence, limited research has delved into this association among patients who underwent surgery and radiotherapy.

This study aims to investigate the association between HPV and cervical cancer recurrence in the Iranian population, a research area that remains underexplored. By focusing on this linkage, we aim to contribute to understanding HPV as a potential prognostic factor in cervical cancer, offering new insights for clinical decision-making and highlighting the need for further research in this vital area.

Materials and Methods

Study population

The present study employed a cross-sectional design, encompassing all patients diagnosed with cervical cancer who were referred to Firoozgar Hospital, Tehran City, Iran, between 2016 and 2018. The sampling procedure utilized a census method, covering the entire population of interest. Demographic and treatment information was obtained from patients' records during routine follow-up visits after vaginal cuff treatment (for patients who underwent surgical treatment) or cervix treatment (for patients who received radiotherapy). Data including age, body mass index (BMI), smoking, multiple partners, previous pap smear, vaccination against HPV, and so on were evaluated at the time of diagnosis. Patients were divided into two groups based on the presence or absence of recurrence. Subsequently, samples were collected and examined using the INNO-LiPA standard test to determine the presence or absence of HPV. Data analysis was performed using the SPSS software, version 26. A single designated individual carried out all sampling procedures to minimize technical errors.

Statistical analysis

Quantitative variables were presented as Mean±SD, while qualitative variables were expressed as numbers and percentages. The normality of variable distributions was assessed using the K-S test. The student's t-test was utilized for normally distributed variables, whereas the Mann-Whitney U test was employed for non-normally distributed variables. The chi-square test was applied to compare qualitative variables. Additionally, logistic regression analysis was conducted to assess the predictive value of HPV test results for cancer recurrence. Statistical significance was defined as a $P<0.05$.

Results

A total of 124 patients were included in the study, with an Mean±SD age of 45.95±7.45 years. The highest frequency of diagnoses was observed in the age range of 35 to 49 years. Most patients had a body mass index of 18-25 kg/m^2. Based on MRI findings, the most common stage of cervical cancer was stage III, IIB. Squamous cell carcinoma pathology was the most prevalent, observed

in 47 patients (37.9%). The most frequently performed treatment modality was radical trachelectomy and adjuvant chemoradiotherapy, accounting for 20 cases (16.1%). There were no significant differences in terms of age at disease diagnosis, smoking history, body mass index, histological type, and treatment type between patients with recurrent disease and those without recurrence. However, a significant difference was observed in terms of lymph node involvement (Table 1). Additionally, the HPV test yielded positive results in 3 patients (2.4%) with recurrent disease and 11 patients (8.9%) without recurrence, indicating no association between high-risk HPV status and disease recurrence (P=0.196) (Figure 1).

Table 2 presents data collected for the 14 patients who tested positive for HPV, including the time interval between completion of initial treatment and positive HPV diagnosis, diagnosis of recurrence, and additional procedures performed following a positive high-risk HPV result. Among these patients, only 3 were diagnosed with recurrence based on HPV positivity. Further details are provided in Table 2.

The logistic regression analysis results, as shown in Table 3, indicate no significant relationship between recurrence and HPV status.

Discussion

Our study findings indicated that only 3 individuals (21.43%) diagnosed with cervical cancer recurrence tested positive for HPV. Therefore, the results of the regression analysis indicated that the HPV test cannot serve as a reliable factor for predicting cervical cancer recurrence in patients. This finding contrasts with a study conducted by Yu et al. [17], where high-risk cervicovaginal human papillomavirus (hrHPV) testing proved valuable in predicting cervical cancer recurrence. Their research identified hrHPV persistence as a risk factor for disease recurrence, emphasizing the need to consider hrHPV testing in the follow-up period for monitoring cervical cancer. Similarly, Aryasomayajula et al. [18] investigated the role of hrHPV testing in cervical cancer surveillance. Their study encompassed 262 eligible patients, revealing that 58 cases (22%) experienced recurrence. Of the 169 patients subjected to hrHPV during the surveillance period, 41(24%) had positive results. Notably, recurrent disease was diagnosed in 24 individuals (14%), of whom 5(21%) had at least one positive HPV test during follow-up, compared to 36(24%) of the 145 patients without recurrent disease (P=0.67). No association was observed between HPV testing and recurrence detection. Although their findings align with ours, their overall conclusion suggested that routine HPV testing for evaluating cervical cancer recurrence is not supported by their study. They further emphasized the lack of guidelines regarding the management of positive HPV results, which may result in unnecessary additional tests and procedures. Additionally, a study conducted by de Lucena et al. [19] investigated the frequency and viral load of hrHPV in cervical and vaginal samples during the initial follow-up of patients treated for invasive cervical cancer. Their results indicated a higher prevalence of cytological abnormalities in samples with HPV compared to those without HPV. Furthermore, samples with cytological abnormalities exhibited significantly higher viral loads than those without. This study suggests that HPV detection methods may serve as a useful adjunct to conventional cytology during early follow-up for detecting residual cervical cancer following radiotherapy. However, overall, the findings did not support the routine use of HPV testing for detecting recurrence in patients with a history of cervical cancer.

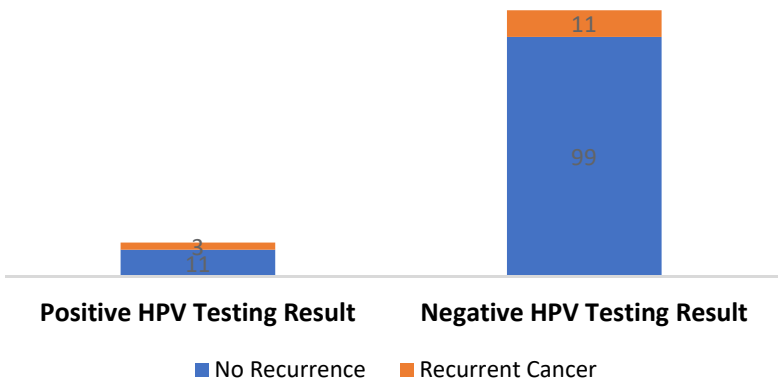

Figure 1. Relationship between high-risk HPV status and disease recurrence (P=0.196)

Table 1. Demographic and clinical characteristics of patients who tested for high-risk cervico-vaginal HPVby cervical cancer recurrence status

Variables			No. (%)		P
			No Recurrence	Recurrent Cancer	
Age at diagnosis (y)	<35		11(8.9)	1(0.8)	0.871
	35-39		43(34.7)	5(4)	
	40-45		30(24.2)	3(2.4)	
	45-50		8(6.5)	2(1.6)	
	>50		18(14.5)	3(2.4)	
Smoker history	Yes		100(80.6)	14(11.3)	0.287
	No		10(8.1)	0(0)	
Multi-partner	Yes		13(10.5)	2(1.6)	0.530
	No		97(87.2)	12(9.7)	
Sexually transmitted diseases history	Yes	Repeated	18(15.4)	4(3.7)	0.384
		Non repeated	32(27.4)	5(4.3)	
	No		53(45.3)	5(4.3)	
BMI (kg/m^2)	>18		12(9.7)	4(3.2)	0.323
	18-25		47(37.9)	5(4)	
	25-30		28(22.6)	2(1.6)	
	<30		23(18.5)	3(2.4)	
Abnormal cervix	Yes		39(31.5)	7(5.6)	0.219
	No		71(57.3)	7(5.6)	
Involvement of the vaginal fornix	Yes		17(13.7)	3(2.4)	0.698
	No		93(75)	11(8.9)	
Involvement of cervical parameters	Yes		23(18.7)	3(3.3)	0.368
	No		86(69.9)	10(8.1)	
Lymph node involvement	Yes		3(2.4)	8(6.5)	0.000
	No		107(86.3)	6(4.8)	
Tumor size (cm)	2		65(52.4)	9(7.3)	0.907
	2-4		37(29.8)	4(3.3)	
	> 4		8(6.5)	1(0.8)	

Variables		No. (%)		P
		No Recurrence	Recurrent Cancer	
FIGO leveling surgery	IV	7(5.6)	0(0)	0.198
	III	31(25)	5(4)	
	IIB	22(17.7)	1(0.8)	
	IIA2	11(8.9)	1(0.8)	
	IIA1	0(0)	1(0.8)	
	IB3	1(0.8)	1(0.8)	
	IB2	22(17.7)	2(1.6)	
	IB1	7(5.6)	1(0.8)	
	IA2	8(6.5)	2(1.6)	
	IA1	1(0.8)	0(0)	
MRI staging	IV	5(4)	1(0.8)	0.682
	III	24(19.4)	4(3.2)	
	IIB	24(19.4)	2(1.6)	
	IIA2	16(12.9)	2(1.6)	
	IIA1	17(13.7)	1(0.8)	
	IB3	5(4)	1(0.8)	
	IB2	4(3.2)	2(1.6)	
	IB1	4(3.2)	1(0.8)	
	IA1	8(6.5)	0(0)	
	ND	1(0.8)	0(0)	
	IIIB	1(0.8)	0(0)	
	A1	1(0.8)	0(0)	
Pathology	Adenocarcinoma	3(2.4)	2(1.6)	0.169
	Sarcoma	5(4)	1(0.8)	
	Malignant melanoma	13(10.5)	1(0.8)	
	Neuroendocrine carcinoma	15(12.1)	3(2.4)	
	Aden squamous	14(11.3)	4(3.2)	
	Cervical intraepithelial neoplasia (CIN) I neoplasia CIN I	7(5.6)	0(0)	
	CIN II	9(7.3)	0(0)	
	Squamous cell carcinoma	44(35.5)	3(2.4)	

Variables		No. (%)		P
		No Recurrence	Recurrent Cancer	
Treatment	Surgery	2(1.6)	0(0)	0.337
	Conization	16(12.9)	1(0.8)	
	Total hysterectomy	14(11.3)	3(2.4)	
	Trachelectomy radical	10(8.1)	0(0)	
	RTAH	8(6.5)	4(3.2)	
	Chemoradiotherapy	20(16.1)	2(1.6)	
	Adjuvant radiotherapy	4(3.2)	1(0.8)	
	RTAH and adjuvant radiotherapy	18(14.5)	1(0.8)	
	RTAH and adjuvant chemoradio-therapy	18(14.5)	2(1.6)	

Additionally, our investigation into demographic factors revealed the absence of significant differences in various parameters, such as age at diagnosis, smoking history, body mass index, histological type, and treatment type, between patients with and without recurrence, underscoring the complexity of predicting disease relapse in cervical cancer. However, numerous papers suggest a noteworthy relationship between demographic data and cervical cancer recurrence. For instance, Das discovered that demographic factors such as early marriage, illiteracy, and high parity were associated with cervical cancer development [20]. identified patient age, tumor appearance, and tumor size as risk factors for early recurrence of cervical cancer [21]. Ward observed changes in the cervical cancer population over time, noting an increase in pre-menopausal patients and those with non-squamous histology [22]. Thulaseedharan (2012) found that increasing age, a higher number of pregnancies, and lack of education were associated with an elevated risk of cervical cancer [23].

Furthermore, a notable distinction was observed concerning lymph node involvement, emphasizing its potential role as a prognostic indicator. However, findings regarding the role of lymph node involvement as a prognostic indicator for cervical cancer recurrence are mixed. Noventa et al. suggest that the presence of HPV-DNA in pelvic lymph nodes may be a potential risk factor

Table 2. Follow-up of patients with HPV positive (n=14)

Variables	Yes/No	No. (%)
Did HPV positivity lead to a diagnosis of recurrence?	Yes	3(21.43)
	No	11(78.57)
Were additional measures taken because of HPV positive?	Yes	8(57.14)
	No	6(42.86)
Average time from completion of initial treatment to HPV-positive diagnosis (y)	1.76±0.64	

Table 3. Logistic regression analysis for predicting cervical cancer recurrence

Variable	B	SE	Wald	P	Odds Ratio
HPV test result positive (versus negative)	0.898	0.725	1.53	0.215	(10.16-0.59)2.45

for recurrence and poor prognosis in early-stage cervical cancer [24]. In contrast, Creasman suspects using lymph vascular space involvement (LVSI) as the sole determining factor for post-hysterectomy radiotherapy [25]. Üreyen found that lymph node involvement did not significantly affect the site of recurrence, but distant recurrence was more common in the lymph node-positive group [26]. Overall, the literature presents conflicting evidence, highlighting the need for further research to establish the significance of lymph node involvement as a prognostic indicator for cervical cancer recurrence.

Additionally, a limitation of the study was the loss of follow-up with some patients, leading to their exclusion from the final analysis. This attrition could have introduced bias and affected the study's outcomes, emphasizing the importance of consistent patient follow-up in research.

Conclusion

In summary, our study enriches the understanding of the role of HPV testing in predicting cervical cancer recurrence. Our results underscore that only a minority of individuals with recurrent cervical cancer tested positive for HPV, challenging the notion that HPV testing alone is not a reliable predictor of recurrence. The divergent findings from related studies emphasize the imperative for further research to precisely define the role of HPV testing in cervical cancer surveillance. Additionally, the conflicting evidence surrounding the significance of lymph node involvement as a prognostic indicator highlights the need for continued research in this crucial area. Consequently, while HPV testing may offer valuable supplementary information alongside conventional cytology during early follow-up, its routine adoption for recurrence detection requires meticulous consideration. This caution is underscored by the potential risk of triggering unnecessary additional tests and procedures, particularly in the absence of well-defined management guidelines for positive HPV results.

Ethical Considerations

Compliance with ethical guidelines

Patients' information was collected in accordance with the ethical principles established by the Research Ethics Committees of Iran University of Medical Sciences, following the assigned ethical (Code: IR.IUMS.FMD.REC.1399.774).

Funding

This research did not receive any grant from funding agencies in the public, commercial, or non-profit sectors.

Authors contribution's

Conceptualization, review and editing: All authors; Methodology, investigation, writing the original draft: Soheila Aminimoghaddam; Funding acquisition, resources, and supervision: Noor Al Sadat Sajedi.

Conflict of interest

The authors declared no conflict of interest.

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