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RESEARCH ARTICLE

Risk Factors that Cause Cervical Intraepithelial Lesion Development: A Single Center Cross-sectional Study in Turkey

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Abstract

Backgrounds: Studies have been conducted in many regions to identify major and minor risk factors that play a role in the development of cervical intraepithelial lesions (CIN), which are precursors of cervical cancer. The aim of this study is to determine the major and minor risk factors for the development of CIN in a single center. **Methodology:** This study is a cross-sectional study involving 2003 patients who applied to the gynecology clinic of Adıyaman University Training and Research Hospital between January 2016 and December 2019. The relationship between cytology results and Human Papilloma Virus (HPV) presence, wart, infection presence, educational status, choice of contraceptive method, body mass index (BMI) and smoking were statistically analyzed. Binary logistic regression test was used to analyze the data. $p < 0.05$ value was considered significant. **Results:** The presence of HPV is the most important variable with 55.6% in explaining the variables on the result of colposcopy. However, HPV 16-18 positivity is 46 times, other HrHPV 5.1 times, the presence of infection in vaginal cytology 4.8 times, using combine oral contraceptive pills COC as a contraceptive method 2 times, Copper intrauterine device (Cu-IUD) use 3 times, education level 2.3 times, smoking 4.4 times and thirty and above BMI increases positivity by colposcopy 0.6 times. **Conclusions:** HPV positivity is still a major risk factor for CIN development. Contraceptive method selection, presence of vaginal infection, smoking and obesity are other risk factors that increase the risk of developing CIN.

Keywords: Copper releasing IUDs- Cervical Intraepithelial Neoplasia risk- Oral contraceptives- Human papilloma virus

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Introduction

Cervical cancer is a preventable cause of cancer with more than half a million women newly diagnosed each year [1]. It is known that cytology (Pap test) test used in cervical cancer screening decreases mortality and incidence [2]. Presence of persistent infection with Human Papilloma Virus (HPV) is associated with precancerous cervical intraepithelial neoplasia (CIN) and is a risk factor for cervical cancer [3]. Low-grade lesions are usually caused by transmission with low risk HPV types; however, persistent infections with higher risk HPV types (HRHPV) lead to high grade lesions [4]. Although persistent infection with HrHPV is an effective cause of cervical cancer; smoking, infection with other sexually transmitted diseases (Clamidya trochomatis, etc.) and hormonal contraception and hormonal imbalances are defined as cofactors that increase the development of cervical cancer when combined with high-grade cervical lesions and HPV infection for the development of cervical cancer [3]. Although there are studies showing the relationship between hormonal contraceptive methods and cervical cancer [5-6], there are conflicting publications on the use of Cooper intrauterine device (Cu-IUD) [7-8].

The aim of this study is to determine the major and minor risk factors for the development of cervical intraepithelial neoplasia in a single center.

Materials and Methods

Study Population

This study is a cross-sectional study involving patients who applied to the gynecology outpatient clinic of Adıyaman University Training and Research Hospital

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between January 2016 and December 2019. Approval was obtained for this study from the non-interventional regional ethics board committee. The study included 2003 married and monogamous patients with examination data, cervical cytology results, HPV test, colposcopy results, vaginal cytological evaluations and treatment information in the hospital database.

Exclusion criteria were the age of 18, pregnancy, a history of cervical conization, a history of previous malignancy or hematological disease, a history of chemotherapy / radiotherapy, a patient with diabetes mellitus, a history of autoimmune disease, and immunosuppressive medication.

A questionnaire was created for the patients included in the study. In the questionnaire, the patients' obstetric history (gravida, parity, abortion rates), educational status, smoking history, height and weight information, types of contraceptive methods they used and how long they used were questioned by reaching the patients. Body mass index (BMI) was calculated from height and weight data. Examination findings, vaginal cytology evaluation results, cervical cytology, colposcopic biopsy and LEEP conization results and HPV test results recorded in the database of the hospital were noted.

Statistical Analysis

SPSS 22 program was used in the analysis of the data. In the analysis of qualitative data, Chi-square test and binary logistic regression analysis were used. The group whose negative cytology result was accepted as the reference to the logistic regression model established to estimate the cytology result; HPV presence, wart, presence of infection, educational status, contraceptive method selection, BMI and cigarette use are included. The model was found compatible. Forward Stepwise method was used. Independent variables are included in the model in order. $p < 0.05$ is considered important.

Results

Sociodemographic data and clinical features of study populations

According to the use of contraceptive methods, 2003 patients who participated in the study were grouped as patients using copper IUD (Cu-IUD), those who used combined oral contraceptives (COC) and those who did not use medical contraceptives. The number of patients using Cu-IUD was 765 (38.2%), the number of patients using COC was 580 (29%) and the number of patients not using medical contraceptive method was 658 (32.9%).

The mean age of patients using Cu-IUD was measured as 39.21 ± 7.83. The mean age of patients using COC was 35.51 ± 6.64.

The levels of education, BMI, smoking, application symptoms, vaginal cytology results, presence of wart, cervical cytology results, colposcopic biopsy results, conization results and HPV positivity and positive HPV types belonging to both groups are shown in Table 1.

Table 1. Age Averages, Obstetric data, Educational Status, Symptoms, Vaginal Cytology, Cervical Cytology, Colposcopic Biopsy, Conization Results, HPV Positivity and HPV Types, BMIs and Smoking were Given

	None*	COC†	Cu-IUD‡
Age	40,29±9,79	35,51±6,64	39,21±7,83
Obstetrics			
Gravida	3,19±1,90	2,34±2,00	3,66±1,91
Parity	2,56±1,54	1,67±1,35	2,88±1,42
Abortus	0,62±0,71	0,67±0,91	0,83±1,23
Educational Status			
Middle School and Below	77 (% 11,7)	39 (% 6,8)	45 (% 5,9)
Middle School or Above	512 (% 77,8)	366 (% 63,3)	598 (% 78,2)
License	48 (% 7,3)	123 (% 19,3)	42 (% 29,9)
Master	21 (% 2,3)	50 (% 8,7)	80 (% 10,5)
Symptoms			
Discharge	315 (47,8)	260 (% 44,9)	325 (42,5)
Lower abdominal pain	70 (% 10,7)	110 (% 18,9)	140 (% 18,2)
Iching	119 (% 18,1)	70 (% 12)	160 (% 21)
Dyspareunia	14 (% 2,2)	40 (% 6,9)	60 (% 7,8)
Dysmenorrhea	140 (% 21,2)	100 (% 17,3)	80 (% 10,5)
Vaginal Cytological Diagnosis			
Normal Vaginal Flora	301 (% 47,3)	250 (% 45,4)	175 (% 24,1)
Active Inflammation	49 (% 7,7)	30 (% 5,5)	10 (% 1,4)
Candidiasis	91 (14,3)	120 (% 21,8)	160 (% 22,1)
Bacterial Vaginosis	189 (% 29,7)	120 (% 21,8)	375 (% 51,7)
Trichomonas Vaginalis	7 (% 1,1)	30 (% 5,5)	0 (% 0,0)
Chronic Cervicitis	0 (% 0,0)	0 (% 0,0)	5 (% 0,7)
Wart			
Positive	42 (% 6,4)	140 (% 24,1)	100 (% 13,1)
Negative	616 (% 93,6)	440 (% 75,9)	665 (% 86,9)
Cervical Cytology			
Negative	420 (% 63,8)	180 (% 31)	320 (% 41,8)
ASCUS§	126 (% 19,1)	160 (% 27,6)	190 (% 24,8)
LG-SIL**	70 (% 10,6)	150 (% 25,9)	150 (% 19,6)
HG-SIL (CIN II+)††	42 (%6,4)	90 (% 15,5)	105 (% 13,7)
Colposcopic Biopsy Results			
Negative	7 (% 3,8)	10 (% 2,4)	0 (% 0,0)
Chronic Cervicitis	56 (% 30,8)	20 (% 4,9)	135 (% 28,1)
LG-SIL	63 (% 34,6)	200 (% 48,8)	230 (% 47,9)
HG-SIL CINII ††	56 (% 30,8)	170 (% 41,5)	90 (% 18,8)
HG-SIL CINIII §§	0 (% 0,0)	10 (% 2,4)	25 (% 5,2)
Conization Biopsy Results			
Chronic Cervicitis	7 (7,7%)	10 (% 4,2)	25 (% 13,1)
LG-SIL	42 (% 46,2)	60 (% 25)	85 (% 44,7)
HG-SIL CINII	21 (% 23,1)	50 (% 20,8)	25 (% 13,2)
HG-SIL CINIII	21 (% 23,1)	120 (% 50)	55 (% 28,9)
HPV#			
Negative	476 (% 72,3)	140 (% 24,1)	335 (% 43,8)
Positive	182 (% 27,7)	440 (% 75,9)	430 (% 56,2)

Continued Table 1.

	None*	COC†	Cu-IUD‡
HPV Types			
HPV 16	77 (% 11,7)	160 (% 27,6)	185 (% 24,2)
HPV 18	14 (% 2,1)	40 (% 6,9)	30 (% 3,9)
OTHER HPV	91 (% 14,3)	240 (% 35,8)	215 (% 27,6)
BMI***			
<25	175 (% 26,6)	200 (% 34,5)	240 (% 31,4)
25-29,99	343 (% 52,1)	270 (% 46,6)	440 (% 57,5)
>30	140 (% 21,3)	110 (% 19)	85 (% 11,1)
Smoking			
Positive	100 (% 13,07)	80 (% 13,8)	8 (% 1,2)
Negative	665 (% 86,93)	500 (% 86,2)	650 (% 98,8)

* None, Patient group not using medical contraceptive method; †COC, Group of women using combined oral contraceptives; ‡Cu-IUD, Group of women driving intrauterine device with copper; §Atypical Squamous Cells Of Undetermined (ASCUS); **Low Grade Squamous Intraepithelial Lesion (LGSIL); ††High Grade Intraepithelial Lesion Cervical Intraepithelial Neoplasia grade II-III (HGSIL CINII-III); ‡‡High Grade Intraepithelial Lesion Cervical Intraepithelial Neoplasia grade III (HGSIL CINII); §§High Grade Intraepithelial Lesion Cervical Intraepithelial Neoplasia grade III (HGSIL CINIII); #Human Papilloma Virus; ***Body Mass Index

Analysis of CIN risk factors for groups

HPV positivity was significantly higher in women using COC (p <0.001). Wart incidence was also low in women using Cu-IUD (p <0.001). When the cervical cytology findings of women using COC and Cu-IUD were compared, it was found that the incidence of abnormal cervical cytology in both groups increased compared to the patient group who did not use medical contraceptive method (p <0.001) (Table 2).

When colposcopic biopsy results were compared, the incidence of LGSIL, HGSIL CIN II lesions was higher in patients using COC compared to the patients using Cu-IUD. In the patient group using Cu-IUD, the rate of chronic cervicitis was higher than the patient group using COC. In both patient groups using COC and using Cu-IUD; HGSIL CIN III result rates were higher than the patients who did not use medical contraceptive method (p <0.001) (Table 2).

When conization results are evaluated; While chronic cervicitis and LG-SIL rates were high in patients using Cu-IUD, HGSIL CIN II and CIN III rates were higher in those using COC(p<0.001).

Bacterial vaginosis was more common in women using Cu-IUD, while bacterial vaginosis was lower in women using COC. Trichomonas vaginalis infection was more common in women using COC (p <0.001) (Table 2).

Multivariate analysis of potential risk factors for CIN

To the logistic regression model established to estimate the result of colposcopy; HPV 16-18 Positivity, Ot HrHPV positivity, contraceptive methods and duration of use, BMI is between 25-29.99, BMI is above 30, educational status and smoking are included. Model fit was found to be good. Forward Stepwise method was used. Independent variables were included in the model in order. Those with BMI 25-29.99 and duration of contraceptive method had no significant contribution to the model.

The presence of HPV explains 55.6% of the change in colposcopy result. The effect of other variables on the change in colposcopy is 7%. HPV 16-18 presence 46 times, Ot HrHPV positivity 5.1 times, presence of infection in vaginal cytology 4.8 times, using COC as a contraceptive method 2 times and using Cu-IUD as a contraceptive method 3 times, education level 2.3 times, smoking 4.4 times and 30 BMI greater than, was found to increase the risk of colposcopy result to be positive 0.6 times (Table 3).

Discussion

This study is a cross-sectional study of data analysis retrospectively, but supported by one-to-one surveys. In addition, while determining the epidemiological factors of patients, a questionnaire was conducted to prevent bias.

The selection of contraceptive methods and the effect of the selected contraceptive methods on the development of CIN and potential risk factors that may affect the development of CIN were investigated in patients who applied to our center. This study, conducted in a large population of Turkish women, is a featured study comparing the effect of contraceptive methods on CIN development and other risk factors causing cervical cancer development.

It is a major factor in HPV CIN development and invasive cervical cancer development [9]. It has been reported that HPV 16 and 18 types cause CIN III development more frequently than HPV 16 than Ot HrHPV types [10]. In our study, HPV positivity, especially HPV 16-18 positivity, has been shown to increase the risk of CIN compared to Ot Hr HPV types.

In a recent metaanalysis, it has been reported that the use of Cu-IUD increases HPV clearance and prevents persistent infection [11]. In our study, HPV positivity was more common in patients using COC.

In a recent study by Loopik et al (2020); reported that there was an increased risk of developing CIN III lesions compared to non-users with both COC use and Cu-IUD use. They also reported that this risk is higher in women using COC compared to women using Cu-IUD [12]. These findings support our study. As a result of colposcopic biopsy in our study, it was found that the frequency of LG-SIL and HG-SIL CIN II lesions were more common in those using COC. In contrast, in the patient group using both COC and Cu-IUD, the rate of HG-SIL CIN III lesion detection was higher than the group not using a medical contraceptive method. In addition, while the frequency of incidence of HGSIL CIN II and CIN III lesions was higher in the patient group using COC in patients with conization compared to those using Cu-IUD; LG-SIL rates were higher in the patient group using Cu-IUD.

In a cross-sectional study examining patients in the California health system; No increase in frequency of HG-SIL CIN II and CIN III lesions was reported in those using Cu-IUD; however, there was an increase in the frequency of HG-SIL CIN II lesions in users of levonorgesterone Intrauterine Device (LNG-IUD). In our

Table 2. HPV Positivity, Presence of Wart, Cervical Cytology, Colposcopic Biopsy, Conization Results, and Frequency of Vaginal Cytology Results were Shown in Women Using Cu-IUD, Women Using COC, and Women not Using Medical Contraceptives.

	None	COC	Cu-IUD	
HPV#				
Positive	182	440	430	
	(% 27,7)	(% 75,9)	(% 56,2)	P<0,001
Negative	476	140	335	
	(% 72,3)	(% 24,1)	(% 43,8)	
Wart				
Negative	616	440	665	
	93,6 %	75,9 %	86,9 %	P<0,001
Positive	42	140	100	
	6,4 %	24,1 %	13,1 %	
Cervical Cytology				
Negative	420	180	320	
	63,8	31,0	41,8	
ASCUS†	126	160	190	
	19,1	27,6	24,8	<0,001
LG-SIL‡	70	150	150	
	10,6	25,9	19,6	
HG-SIL (CINII+)§	42	90	105	
	6,4	15,5	13,7	
Colposcopy Results				
Negative	7	10	0	
	3,8 %	2,4 %	0,0 %	
Chronic Cervicitis	56	20	135	
	30,8 %	4,9 %	28,1 %	
LG-SIL	63	200	230	<0,001
	34,6 %	48,8 %	47,9 %	
HG-SIL CINII**	56	170	90	
	30,8 %	41,5 %	18,8 %	
HG-SIL CINIII*	0	10	25	
	0,0 %	2,4 %	5,2 %	
Conization Results				
Chronic Cervicitis	7	10	25	
	7,7 %	4,2 %	13,1 %	
LG-SIL	42	60	85	
	46,2 %	25,0 %	44,7 %	
HG-SIL CINII	21a	50a	25a	
	23,1 %	20,8 %	13,2 %	P<0,001
HG-SIL CINIII	21	120	55	
	23,1 %	50 %	28,9 %	
Vaginal Cytology				
Normal vaginal flora	301	250	175	
	(% 47,3)	(% 45,4)	(% 24,1)	
Active Inflamation	49	30	10	
	(% 7,7)	(% 5,5)	(% 1,4)	
Candidiyasis	91	120	160	
	(14,3)	(% 21,8)	(% 22,1)	
Bacterial Vaginosis	189	120	375	
	(% 29,7)	(% 21,8)	(% 51,7)	

Continued Table 2.

	None	COC	Cu-IUD	
Vaginal Cytology				
Trichomonas Vaginalis	7	30	0	
	(% 1,1)	(% 5,5)	(% 0,0)	

#HPV, Human Papilloma Virus; †ASCUS, Atypical Squamous Cells of Undetermined; ‡LGSIL, Low Grade Squamous İntraepithelial Lesion; §HGSIL CINII+, High Grade İntraepithelial Lesion Cervical İntraepithelial Neoplasia grade II-III;**HGSIL CINII, High Grade İntraepithelial Lesion Cervical İntraepithelial Neoplasia grade II; *HGSIL CIN III, High Grade İntraepithelial Lesion Cervical İntraepithelial Neoplasia grade III

study, there was no patient group using LNG-IUD, but contrary to this study, the rate of HG SIL CIN III lesion detection increased in patients using Cu-IUD compared to the group that did not use a medical contraceptive method. In contrast, in our study, the risk of developing CIN in women using Cu-IUD has been shown to be higher than women who use COC. It may be wrong to link it only to HPV positivity. According to the author; multifactorial evaluation is effective in this result.

Previous studies have shown that the use of Cu-IUD causes acute / chronic vaginal and cervical infections, and it has been shown that the vaginal flora changes with the use of Cu-IUD. Moreover, the frequency of bacterial vaginosis in these studies increased in women using Cu-IUD [13-15]. In our study, similar to these studies, there is an increase in the frequency of BV and other infectious agents except trichomonas vaginalis in patients using Cu-IUD. Also, in our study, the frequency of chronic cervicitis increased in both colposcopic biopsy results and conization results in the patient group using Cu-IUD.

In a recent study, the relationship between the presence of vaginal infection and CIN lesions has been investigated, and in these studies, it has been stated that the presence of vaginal infection may be a risk factor for cervical cancer by reducing HPV clearance [16]. In our study, the presence of vaginal infection in regression testing has been shown to play a role in the development of CIN. Given this effect of infection development on CIN, the increased risk for CIN in the patient group using Cu-IUD is not a surprise.

It has been reported that smoking is a cofactor that increases the development of CIN in patients using COC [3]. According to the results in our study, smoking increased the risk of developing CIN.

It has been stated that preventing obesity by creating BMI screening programs may decrease the development of cervical cancer [17]. It can be seen in this study that obesity has a minimal contribution to the development of CIN.

In our study, it was found that the level of education also contributed to the development of CIN. According to the author, this may also be related to the socioeconomic cultures of patients. Larger patient groups are needed to investigate this finding.

This study has some limitations. First, this study is a cross-sectional study conducted by examining retrospective data. Therefore, there may be bias in the data. However, this deficiency was tried to be eliminated with the questionnaires. Another limitation is that the

Table 3. Binary Logistic Regression Test Results for Determining Risk Factors for Cervical Intraepithelial Lesion Development

	B*	p	OR†	95% C.I. ‡ for OR	
				Lower	Upper
HPV§					
HPV 16-18 Positive	3,835	<0,001	46,271	33,517	63,878
Other HrHPV**	1,642	<0,001	5,166	3,201	8,338
Education Status	0,853	<0,001	2,346	1,558	3,533
Vaginal Infection	1,577	<0,001	4,841	2,796	8,383
Contraceptive Methods		<0,001			
COCs††	0,702	<0,001	2,017	1,432	2,841
Cu-IUDs‡‡	1,101	<0,001	3,007	2,185	4,140
BMI §§		0,004			
BMI(25-29,9)	0,193	0,226	1,213	0,887	1,658
BMI(>30)	-0,436	0,037	0,647	0,429	0,975
Smoking	1,494	<0,001	4,455	2,399	8,275
Constant	-1,045	<0,001	,352		

*β, coefficient; †O.R., Odds Ratio; ‡C.I., Confidence Interval; § HPV, Human Papilloma Virus;**Other High Risk HPV; †† COC, Group of women using combined oral contraceptives; ‡‡Cu-IUD, Group of women driving intrauterine device with copper; §§ BMI, Body Mass Index.

study was conducted in a single center. Studies on heterogeneous groups may be required. These limitations need to be considered before generalizing the data.

In conclusion; HPV positivity is still a major risk factor for CIN development. Contraceptive method selection, presence of vaginal infection, smoking and obesity are other risk factors that increase the risk of developing CIN.

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Conflict of interest

The authors declare no conflict of interest.

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