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Original article ■

The Influence of HPV16, Smoking and Coitarche in the Development of Cervical Dysplasia in the Stage where Conization is the Treatment of Choice

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SUMMARY

The high incidence of premalignant lesions of the cervix in our country and worldwide was the primary aim for conducting this study so as to establish whether HPV16, smoking and coitarche (first intercourse) are significant factors in the developmental stages of cervical dysplasia in the case of which the conization is a surgical treatment of choice.

In the period of three years, one hundred and thirty-six women from the Republic of Macedonia with histologically confirmed CIN were examined as well as 50 control cases with normal cytology and colposcopic findings. The aforesaid epidemiologic factors examined in this study were obtained through special questionnaires. The resulting material was statistically processed to determine whether these factors are risk factors for development of higher stages of cervical dysplasia.

The obtained statistical analysis showed that HPV16, smoking and coitarche under the age of 18 are very important factors in the development of higher stages of CIN where conization is indicated as a treatment of choice.

Our study demonstrated that coitarche under the age of 18, smoking and infection with HPV16 as the most common high risk HPV in our country are the most important factors in causing and development of high grade CIN, where conization is necessary as a treatment of choice. Thus, socially-based organized screening can be of great benefit in early diagnosis and adequate treatment of this highly prevalent disease.

Key words: conization, HPV, CIN, smoking, coitarche

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INTRODUCTION

According to IARC GLOBOCAN 2008 and WHO 2010 (1, 2), the world female population over 15 years of age who is at risk for developing cervical cancer reaches 2.337 million. Current statistics show that each year around 530.000 new cases of cervical cancer are diagnosed and about 275.000 die from this disease. According to these data, cervical cancer is the third most common type of cancer among the female population worldwide, and takes the second place among women between 15-44 years of age.

According to the WHO in 2010 (2), the prevalence of HPV16 in the world for higher stages of cervical dysplasia (CIN2, CIN3) is 51.1% and for cervical cancer 70.9%.

The high incidence of premalignant lesions of the cervix in our country and the world was the primary motive for conducting this study so as to establish whether HPV16, smoking and coitarche are important factors in the developmental stages of cervical dysplasia, in the cases of which it is necessary to perform conization as a surgical treatment of choice.

MATERIAL AND METHODS

In this study, 136 women from the Republic of Macedonia with histologically confirmed CIN as well as 50 control cases with normal cytology and colposcopic findings were examined in the period of three years. In both groups, the following material was taken: the liquid-based smear for cytological evaluation, and biopsy and endocervical curettage for histological evaluation. Material for HPV analysis was also obtained by exfoliative cervical smear, and cervical biopsy was analyzed with the tests that use the polymerase chain reaction (PCR) method. To prove HPV16, the oligohybridization method was used.

The previously mentioned epidemiological factors (smoking and coitarche) were investigated through specially designed questionnaires that were filled by all patients during this study.

The resulting material was statistically processed by multiple methods of descriptive and analytical statistics. Analyses were conducted using the statistical package BMDP (3). Univariate statistical analysis of the data was performed using tables of contingency and estimation of relative risk (RR). The statistical significance of the factors was calculated with χ^2 test (Fisher exact test) and the Mantel Haentzel's test. As uncategorized variables, the t-test and F-test were used for the calculation of significance. For the multivariate analysis adjusted for the age under 18, an unconditional logistic regression model was used to estimate a relative risk in the genesis of CIN. The study complies with the declaration of Helsinki.

RESULTS

Univariate statistical analysis showed that out of 136 women with histologically confirmed CIN, 51 had CIN1, 43 had CIN2 and 42 CIN3. The prevalence of HPV among the studied cases was 56,6% (RR (relative risk) =3.9178; and significance (p)<0,00001), of which HPV16 was found in 13,2% (RR=7,4243 p<0,025), represented WITH 14% in CIN2, and 26,2% in CIN3. In the control group, the prevalence of HPV was 18%, of which HPV16 was represented with 2% (Table 1).

The age of the first sexual intercourse (coitarche) was divided into three groups: under the age of 18; from 18 to 20; and over the age of 20. In the examined cases under 18 there were 47,8% (RR=2,0556 p<0,008); from 18 to 20 there were 49% (RR=0,9402 p<0,81) and over 20 there were 16,2% (RR=1 p /). In control cases under 18 there were 26%, from 18 to 20 38% and above 20 there were 36%. In terms of smoking, the patients were divided into 2 groups: non-smokers and current smokers. The second group was divided into two subgroups: current smokers - 10 cigarettes and over and under 10 cigarettes per day. In the examined cases, the first group was represented by 41,2% (RR=1), and the second by 44,1% (RR=1,8387; p<0,03). The second group was divided into two subgroups, of which the first subgroup included 25% (RR=2,3878 p<0,02), and the second subgroup 19,1% (RR=1,1743; p<0,63). In the control cases, the first group was represented with 74% and the second with 26%, of which the first subgroup was represented with 10%, and the second with 16% (Table 2). Conization was performed in 45.59% of the examined cases.

Multivariate statistical analysis was adjusted for the age under 18, since this group was the one with the highest risk, with p<0,25; from the aforesaid risk factors it was shown that HPV contributed to RR with 6.398; smoking contributed with RR with 2.501 and coitarche with 1.718 (Table 3). The relative risk of these epidemiological factors, presented by 95% confidence interval and compared in several different studies, is given in Table 4.

Table 1. Distribution of HPV, especially HPV16, in patients with CIN

	N	HPV+	HPV -	HPV16
Control gr.	50	18%	82%	2%
Examined gr.	136	56,6% RR=3,9178 p<0,00001	43,4% RR=1	13,2% RR=7,4243 p<0,025
CIN 1	51	39,2%	60,8%	2%
CIN 2	43	55,8%	44,2%	14%
CIN 3	42	78,6%	21,4%	26,2%

Legend: N-number of patients; RR-relative risk; p-significance

Table 2. Univariate statistical analysis of epidemiological risk factors: HPV, HPV16, smoking and coitarche

Risk factors for CIN	Control group (N=50)	Examined group (N=136)	Relative risk (RR)	95% Confidence interval (CI)	Significance (p)	
Coitarche	<18	26%	47,8%	2,0556	1,1732-3,601	<0,008
	18-20	38%	49%	0,9402	0,5778-1,53	<0,81
	>20	36%	16,2%	1	/	/
Smoking	never	44%	41,2%	1	/	/
	current smoker <10 cig./day	16%	19,1%	1,1743	0,608-2,268	<0,63
	current smoker >10 cig./day	10%	25%	2,3878	1,017-5,608	<0,02
HPV+	18%	56,6%	3,9178	2,0221-7,5907	<0,00001	
HPV-	82%	43,4%	1	/	/	
HPV16	2%	13,2%	7,4243	1,2959-160,37	<0,025	

Legend: N-number of patients

Table 3. Multivariant statistical analysis of epidemiological risk factors: HPV, coitarche and smoking, adjusted for the age under 18

Risk factor $p < 0,25$	Relative risk (RR)	Confidence interval (CI)	Significance (p)
HPV (+/-)	6,398	2,787-14,684	<0,00001
Coitarche	2,501	1,135-5,510	<0,025
Smoking	1,718	1,080-2,734	<0,025

Table 4. The relative risk with 95% confidence interval of the epidemiological risk factors: HPV; smoking and coitarche, adjusted for the age under 18 and compared with several studies conducted by different authors

Author	Control group	Examined group	HPV (+/-)	Smoking >10 cig./day	Coitarche <18
Schiffman MH&al., 1993 [4]	N=500	N=500	RR=20,06	RR=1,7	RR=1,3
Toshiyuki S&al., 1997 [21]	N=778	N=92	RR=9,4 (CIN 1) RR=77 (CIN 2,3)	RR=2,5	RR=1,3
Dimitrov Go. et al., 2012	N=50	N=136	RR=6,398	RR=2,501	RR=1,718

Legend: N-number of patients; RR-relative risk

DISCUSSION

The molecular epidemiological studies clearly show that certain types of HPV are the most important cause of cervical cancer (4, 5).

The aim of our study was to determine the relative risk of developing higher grade of cervical dysplasia, caused by HPV16, smoking and early coitarche (under the age of 18), where conization is indicated as a treatment of choice. This study, conducted as a clinical "case control" study, was performed in Skopje, the Republic of Macedonia, in a period of three years.

In our population, HPV and especially HPV16, are the most significant risk factors, strongly associated with the occurrence and development of cervical dysplasia. The presence of HPV, and especially HPV16, grows as the stage of CIN is increasing (Table 1). These results coincide with the results of the world literature where HPV16 has proved to be the most significant factor responsible for the occurrence of cervical premalignant and malignant lesions (6, 7). Early coitarche below the age of 18 proved to be an important co-factor in the genesis and development of cervical premalignant and malignant lesions. In our study, it accounts for 47,8%, RR=2,0556 and $p < 0,008$ in the tested cases is almost as twice (26%) as high compared to the control group.

Numerous authors have recognized the independent effect of coitarche below the age of 18 in various studies (Munoz 1989 (8); Apgar 2002 (9); Bosch 1992 (10)).

It seems evident that smoking is a significant risk factor in the etiology of cervical intraepithelial neoplasia, as shown in numerous epidemiological studies worldwide (11). Our study presented that the relative risk for the occurrence of cervical intraepithelial neoplasia among current smokers is almost as twice as high compared to those who have never smoked. These facts coincide with a number of studies where the RR ranges from 1.5 to 2.9 (12, 13). The findings in our study for all three epidemiological factors are in consent with numerous studies conducted by different authors (4, 14, 15).

CONCLUSION

From the presented above, it can be concluded that the coitarche under the age of 18, smoking and infection with HPV16, as the most common high risk HPV in our country, are the most important factors in causing and development of high grade CIN, in the case of which it is necessary to perform the conization as a treatment of choice.

Therefore, the organization of a society-based screening can be of great benefit in early diagnosis and adequate

treatment of this highly prevalent disease.

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UTICAJ HPV16, PUŠENJA I PRVOG SEKSUALNOG ODNOSA U RAZVOJU CERVICALNE DISPLAZIJE U STADIJUMU U KOME JE KONIZACIJA HIRURŠKI TRETMAN IZBORA

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Sažetak

Visoka incidenca premalignih lezija grla materice, kod nas i u svetu, bili su primaran motiv izvođenja ove studije kako bi se utvrdilo da li su HPV16, pušenje i prvi seksualni odnos značajni faktori u razvoju stadijuma cervikalne displazije, kada je neophodna konizacija kao hirurški tretman izbora.

Ispitivano je 136 žena sa histopatološki potvrđenim CIN-om i 50 kontrolnih slučajeva sa normalnim citološkim i kolposkopskim nalazom, iz Republike Makedonije, u periodu od tri godine. Prethodno navedeni epidemiološki faktori koji su ispitivani u ovoj studiji bili su dobijeni pomoću specijalno pripremljenih upitnika. Dobijeni materijal je bio statistički obrađen kako bi se utvrdilo da li su ovo faktori rizika za prelaz u viši stadijum cervikalne displazije.

Statističke analize su pokazale da su HPV16, pušenje i prvi seksualni odnos pre 18. godine veoma važni faktori razvoja viših stadijuma CIN-a, kada je indikovana konizacija kao tretman izbora.

U našoj studiji se pokazalo da su prvi seksualni odnos pre 18. godine, pušenje i infekcija HPV-om 16, kao najčešći visoko rizični HPV u našoj zemlji, najznačajniji faktori uzroka i razvoja visokog stepena CIN-a, kada je neophodan tretman izbora konizacija, pa stoga društveno baziran organizovani skrining može biti veoma koristan za ranu dijagnozu i adekvatnu terapiju ovog veoma čestog oboljenja.

Ključne reči: konizacija, HPV, CIN, pušenje, prvi seksualni odnos