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Human papillomavirus and other risk factors in Lithuanian cervical carcinoma patients

Živilė Gudlevičienė [1],

Alė Smilgevičiūtė-Ivshin [2, 4],

Aurelija Vaitkuvienė [3],

Agnė Šepetienė [3],

Janina Didžiapetrienė [1]

[1] *Cancer Research Center, Institute of Oncology, Vilnius University, Lithuania*

[2] *Central Outpatients Clinic, Vilnius, Lithuania*

[3] *Clinic of Obstetrics and Gynecology, Faculty of Medicine, Vilnius University, Lithuania*

[4] *Obstetrics and Gynecology Departament, Barzilai Medical Center, Ashkelon, Izrael*

Background. Cervical cancer is the second biggest cause of female cancer mortality worldwide and the most common cancer in women in Lithuania. The incidence of cervical cancer is strongly associated with HPV prevalence. However, not only HPV infection plays a crucial role in cervical cancer development; other risk factors which vary in different populations and geographical regions as well as HPV prevalence are important. The aim of this study was to detect the HPV, its type's prevalence and other cervical cancer risk factors for Lithuanian women.

Materials and methods. 191 women with primary diagnosed invasive cervical cancer (cases group) and 397 control women were invited to participate in the study. All women were interviewed and samples for HPV testing were taken.

Results. In the cases group, 92.7% of women and in the control group 26.7% were infected by HPV ($p < 0.0001$). HPV 16 was the most common type in both groups. HPV infection increases the risk of cervical cancer 75 times (OR = 75.39; 95% CI 33.61–192.98).

Women with lower education, workers, those who started sexual intercourses before 20 years of age, at older age of the first menstrual period, 3–5 or more childbirths, smokers and with a long ago or never performed Pap test are at a significantly higher risk of cervical cancer development. Other non-HPV risk factors were not associated with cervical cancer risk.

Conclusions. Data of our study show a high prevalence of HPV in Lithuanian population. It may have an impact on the biggest cervical cancer incidence. The other risk factors are similar as in other lower economic resource countries.

Key words: HPV, cervical cancer, risk factors

INTRODUCTION

Cervical cancer is the second biggest cause of female cancer mortality worldwide with approximately 500 000 new cases and 280 000 deaths yearly. In 2007, the age-standardized incidence rate reached 16.2 and the mortality rate 8.9 in the world (1). About 80% of cases of cervical cancer are reported from developing countries: 68 000 from Africa, 77 000 from Latin America and 245 000 from Asia (2). Cervical cancer is the most common cancer in women also in Lithuania (3). In Western Europe and the United States, the cervical cancer incidence rate was much lower in 2009. This lower rate is attributable to the success of the widespread use of the Papanicolaou (Pap) test, which detects changes in cervical tissue and is a major tool in screening for early identification of cervical cancer (4). The incidence is significantly higher in the developing countries where cervical screening is not provided.

There is no doubt that infection with high-risk human papillomaviruses (HPV) is the cause of certain types of human cancer and, in particular, cervical carcinoma. Extensive epidemiological evidence demonstrated an association of the persistent HR-HPV (high-risk human papillomaviruses) infection and the later development of cervical and others cancers (5). Present data support the existence of more than 120 HPV types. Over 100 different HPV genotypes have been isolated to date, and more than 40 of these types infect the epithelium and mucosa of the anogenital tract and other

Correspondence to: Zivile Gudleviciene, Cancer Research Center, Institute of Oncology, Vilnius University, P. Baublio 3b, Vilnius, Lithuania. E-mail: zivile.gudleviciene@gmail.com

areas (4, 5). IARC (the World Health Organization International Agency for Research on Cancer) formally considers the carcinogenicity of exposures to humans. Whereas human carcinogenicity might best be considered for some agents like HPV as a continuum of probabilities without a clear breaking point, IARC classifies carcinogens categorically as carcinogenic, probably carcinogenic, possibly not classifiable, or probably not carcinogenic. There has been very little experimental work on the carcinogenicity of HPV types, except for HPV16 and HPV18; thus, epidemiologic evidence has been unusually important (6). Fifteen HPV types have been classified as high-risk for the development of cervical cancer (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82), three have been classified as of probable high-risk (26, 53, 66), 12 as low-risk (6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81, CP6108), and three are considered to be of undetermined risk (34, 57, 83). HPV 16 is one of the most common types among cervical cancer patients, followed by HPV 18 which is more related to cervical adenocarcinoma (4, 6). Women with a persistent HPV infection are at a higher risk of cervical cancer if theyare left untreated.

However, not only HPV infection plays a crucial role in cervical cancer development. The other risk factors, such as an early age of sexual intercourse, the number of sexual partners, unprotected intercourse, the number of parities, smoking, infection with certain bacteria or viruses, previous sexually transmitted diseases, socioeconomic status, race, limited access to care, close relatives with cancer, senescence, low fruit and vegetable intake, use of oral contraceptives, etc. are very important in the development of this infection and cervical cancer as well (7). The incidence of cervical cancer has been found to vary among populations. Mortality from cervical cancer is also related to multiple factors, such as ethnicity, place of residence, income, and socio-economic status (8, 9). These non-HPV risk factors are specific in different populations. For example, poor hygiene, long time from the last Pap smear taking have been related to cervical cancer in some developing low resource regions like Latin America (10).

The incidence of cervical cancer is strongly associated with the prevalence of HPV: in the developing countries, the prevalence of HPV is high and the rates of cervical cancer incidence and mortality are the highest as well. On the other hand, the large HPV and cancer burden may be explained by the highly prevalent HPV variants of HPV types 16 and 18 which have an increased oncogenic potential. Given the major mode of transmission of genital HPV, certain patterns of sexual behaviour (early age at the first sexual intercourse, the number of sexual partners and the sexual behaviour of the partner) are associated with an increased risk of HPV genital acquisition. Although HPV infection is the trigger of carcinogenesis, certain co-factors (high parity, long-term use of oral contraceptives, smoking and co-infection with the human immunodeficiency virus (HIV) enhance the progression from infection to cancer (11, 12).

The first study on HPV prevalence was conducted in Lithuania in 1999 (13). The authors showed a very high prevalence of high-risk HPV in young Lithuanian women (25.1%), with a higher prevalence in younger women. In urban women, change of sexual partners and smoking were the strongest risk factors associated with high-risk HPV; in rural women, these were cervical cytology changes and change of sexual partners. The high prevalence of HPV and the absence of a cervical cancer screening program seem to be strongly associated with the high cervical cancer incidence and mortality rates in Lithuania. The cervical cancer screening program was started in Lithuania in July 2004.

In 2000–2003, a hospital-based case-control study of cervical cancer risk factors was conducted at the Institute of Oncology, Vilnius University (Lithuania). The aim of this study was to detect the HPV, its prevailing type and other cervical cancer risk factors for Lithuanian women. The results of this study will be important for selecting the group of women with the highest risk of cervical cancer development.

MATERIALS AND METHODS

Study population

The study was performed in 2002–2004 at the Institute of Oncology, Vilnius University, Lithuania. The study protocol was confirmed by the Ethical Committee of the Ministry of Health (2002-10-01, Protocol No. 64). The study cohort comprised 191 women with primary diagnosed invasive cervical cancer. The diagnosis of cancer was confirmed histologically at the State Pathology Center (Vilnius, Lithuania). In the study group, 174 patients (91%) were diagnosed with squamous cell carcinoma (SCC) and 17 (9.0%) with cervical adenocarcinoma (AD). All women were interviewed, and samples for HPV testing were taken before treatment. The inclusion criteria were 18–70 years of age, primary diagnosed invasive cervical cancer, good physical and mental condition, not diagnosed cancer of other localization, signed Patients Information and Agreement form. The mean age of the study participants was 45.8 years (range, 20–69).

As the control group, 397 women were recruited in the nearby outpatient clinics (Vilnius, Lithuania). The exclusion criteria were age beyond the range 18–70 years, poor physical or mental condition, history of previous hysterectomy or conization, cancer of other localizations. Cytological abnormalities in the Pap smear were not the exclusion criteria. In the control group, in 65 women (17.7%) squamous intraepithelial lesions (SILs) were diagnosed. All women signed the Patients Information and Agreement form. The mean age in the control group was 36.5 years (range, 18–65).

HPV DNA detection and typing

For HPV detection, DNA was extracted from cervical cells. Brush swabs were used to obtain cervical samples. Cellular material from the brush was collected in 1 ml of transport medium. The cells were stored at – 20 °C until HPV DNA testing.

Table 1. **HPV and HPV types prevalence in study and control group women**

Study groups		n	HPV negative	HPV positive	HPV types																			
					6	16	6/16	18	16/18	31	33	35	45	51	52	53	54	58	61	66	67	68	70	X*
Case		191																						
	SCC		10 (5.8%)	164 (94.2%)	1	97	3	9	2	5	4	1	2		1			2		1		1		35
	AD		4 (23.5%)	13 (76.5%)		6		3																4
Control		397																						
	No lesions		261 (78.5%)	71 (21.4%)	7	11	1			1	4		1	1		3	1	1	1	2				37
	ASC		16 (76.2%)	5 (23.8%)		2																1		2
	LSIL		8 (53.3%)	7 (46.7%)		1					3							1						2
	HSIL		6 (20.7%)	23 (79.3%)		13		1	1					1				1			1			5

*X – undetermined HPV type.

For HPV DNA detection, polymerase chain reaction (PCR) with general primer pairs MY09 / MY11 was used. The HPV types 16 and 18 were identified following the type-specific polymerase chain reaction (TS-PCR). Other HPV types were identified using HPV DNA sequencing. PCR was performed in 40 cycles. Each cycle consisted of the denaturation step at 95 °C for 1 min, primer annealing step at 55 °C for 1 min 30 sec, and the chain elongation step at 72 °C for 1 min. The final extension of 10 min at 72 °C was performed. Each PCR experiment was performed with positive and negative PCR controls. As a positive control, DNA from HeLa and SiHa cells was used. Negative control samples contained no DNA. All samples were tested for β globine gene. PCR products were analyzed by electrophoresis in 2% of agarose gel stained with ethidium bromide. HPV detection was performed at the Institute of Oncology, Vilnius University (Lithuania). HPV DNA sequencing was performed at the Invitek Seguencing Centre (Berlin, Germany).

Evaluation of other (not HPV) risk factors

Other risk factors (not HPV) were analyzed using a questionnaire. The questionnaire was compiled according to International Agency for Research of Cancer (IARC) case-control studies. Our questionnaire consist of 15 questions regarding socioeconomic, educational, marital status of the women, sexual behaviour of women and their partners, age at first intercourse, first menstruation, number of parities and abortions, use of hormonal and other contraception, smoking and the time from taking the last Pap smear. Women answered the questions and filled the questionnaire by themselves.

Statistical analysis

To estimate the risk of cervical cancer associated with various HPV types and the other risk factors, odds ratios (OR) and 95% confidence intervals (CI) were calculated, the logistic regression model was used. The OR for HPV were adjusted for age (categorized into five age groups: <30 years, 30–39 years, 40–49 years, 50–59 years and >60 years). OR for other risk factors were adjusted for age and HPV positivity. Various risk factors according to the questionnaire were examined. A result of $p < 0.05$ was considered significant. Statistical analysis was performed using SAS Analytical Software at the Vilnius University Institute of Mathematics and Informatics.

RESULTS

Role of HPV and its types in cervical cancer risk

HPV prevalence. All study women were tested for HPV by PCR. In the study group, 92.7% of women were infected by HPV and in the control group 26.7% ($p < 0.0001$). HPV 16 was the most common type in cases in and control women (53.9% and 25.0%, respectively). Other types most frequently detected in cervical cancer patients were the high-risk types HPV 18, 31 and 33 (together comprising 11.0%). In the control group, low-risk HPV types 6, 54, 61 and 70 were detected in 10 patients. The other most frequent types (HPV 33, 53 and 58) detected in control women were considered as high-risk types. In Table 1, the prevalence of HPV and its types is shown according to histological cancer diagnosis or cytological and histological findings in control women.

Risk assesment of HPV and its types. Data of our study show that HPV infection increases the risk of cervical cancer 75 times (OR = 75.39; 95% CI 33.61–192.98) (Table 2). The risk grows up to several hundred times if a woman is infected with high-risk HPV types. HPV type 16 is predomi-

Table 2. **Risk of HPV and its types for cervical cancer development**

HPV status	Case		Control		Age-adjusted OR and 95% CI
	n	%	n	%	
HPV negative	14	7.3	291	73.3	1.0 (ref)
HPV positive	177	92.7	106	26.7	42.4 (22.5–85.8)
Total	191	100.0	397	100.0	
HPV 6	1	0.5	7	2.0	3.2 (0.1–29.9)
HPV 16	103	53.9	27	25.0	74.2 (35.3–168.2)
HPV 16/06	3	1.6	1	0.2	93.2 (7.0–>999.9)
HPV 16/18	2	1.0	1	0.2	14.9 (1.2–347.7)
HPV 18	12	6.3	1	0.2	619.2 (88.9–>999.9)
HPV 31	5	2.6	1	0.2	97.5 (8.4–>999.9)
HPV 33	4	2.1	7	2.0	16.6 (3.1–82.8)
HPV 45	2	1.0	1	0.2	129.1 (7.9–>999.9)
HPV 58	2	1.0	3	0.8	8.8 (0.9–86.8)
HPV 66	1	0.5	2	0.5	16.4 (0.5–295.6)
HPV X	39	20.3	46	11.5	18.7 (8.5–43.6)

* – undetermined HPV type.

nantly associated with cervical carcinoma (OR = 100.30; 95% CI 46.05–238.59). Women infected with HPV 16 are at a 100-fold higher risk of developing cervical cancer than women infected with other HPV types. It must be noted that the increased risk of cervical cancer is also associated with a double HPV infection – HPV types 16 and 6 (OR = 57.81; 95% CI 3.15–∞) or with undetermined HPV type infection (HPV-X) (OR = 22.54; 95% CI 10.07–53.62).

Role of other than HPV risk factors

Other than HPV cervical cancer risk factors were analyzed using multivariate logistic regression analysis. In the study group, 145 women from 191 filled up the questionnaire; the response rate was 76%. In the control group, 337 women from 397 were interviewed, the response rate being 85%. The overall response rate in both groups was 82%.

In Table 3, the other (not HPV) risk factors associated with cervical cancer risk are presented. Data in the table are calculated in two categories: age-adjusted (*) and age- and HPV-adjusted (**).

Socioeconomic factors. The majority of women that participated in the study were of Lithuanian nationality (106 in the study and 269 in the control group). Some of them were of Russian, Polish and other nationalities. In our study, nationality was not a statistically significant risk factor for cervical cancer development.

In the study group, the majority of women had a special (intermediate) education (68), contrary to the control group in which most of women had a higher education (169). The calculation of the OR revealed a lower education was to be a factor for cervical cancer development; women with primary education were at the highest risk. The situation was similar as regards social status: workers were at a higher risk of cervical cancer development in comparison with employees (OR* = 4.3, 95% CI 2.2–8.6; OR** = 2.5, 95% CI 1.0–6.5). Both risk factors (social status and education) could be interdependent, but in this study OR was not calculated after adjustment for these two variables.

Family and sexual history. The majority of women in the study and control groups were married (122 and 209, respectively). The marital status was not associated with the risk of cervical cancer. Age at the first intercourse was a statistically significant factor associated with an increased of risk cervical cancer. Women who start sexual intercourses at a younger age (in our study younger than 20 years) are at a 2–3 times higher risk (OR* = 2.1, 95% CI 1.3–3.5; OR** = 2.8, 95% CI 1.4–5.9). The number of sexual partners, other sexual intercourses of the partner, the intensity of intercourse (sexually active or not) were not associated with an increased risk of cervical cancer.

Gynecological and maternal history. Women's gynecological history is significant in the development of cervical cancer. Our study has shown that in cases of a late first menstrual period (later than at 15 years of age), the risk of cervical cancer increases 2–5 times (OR* = 2.1, 95% CI 1.1–4.1; OR* = 5.0, 95% CI 1.8–14.8).

The risk of cervical cancer is also associated with the number of parities. In case of 3–5 childbirths, a woman's risk of developing cervical cancer increases 2.6–2.7 times (OR* = 2.6, 95% CI 1.3–5.2; OR** = 2.7, 95% CI 1.0–7.6), and it increases even more if the number of childbirths is more than 5 (OR* = 21.3, 95% CI 3.7–179.1; OR** = 21.9, 95% CI 2.9–238.7).

In our study, abortions showed no association with an increased risk of cervical cancer development (p = 0.1816–0.5516).

The results of our study in which the risk was calculated without considering the histological type of tumour, hormonal contraceptives did not increase the risk of cervical cancer (OR* = 0.4, 95% CI 0.2–0.7; OR** = 0.3, 95% CI 0.1–0.6). Other types of contraceptives, such as condoms and other barrier contraceptive devices, had no influence on the development of cervical cancer in our patients, either.

Smoking status. The influence of smoking on the cervical cancer carcinogenesis is being widely discussed, and researchers indicate different types of risks associated with this factor. Our study has shown that the risk of cancer increases two times among smoking women in comparison with non-smoking ones when calculating OR adjusted by the age (OR* = 2.0, 95% CI 1.2–3.5). However, when calculating OR after adjustment by age and HPV positivity, smoking did not increase the risk of cervical cancer, i. e. it is possible to assume that the factor of smoking is independent from the risk of HPV caused cevical cancer.

Last Pap smear taking. The fact that most women do not seek routine screening for cervical pathology also influences the development of cervical cancer. The never or very rarely performed Pap smear taking increases the risk 2–3 times in comparison with those who are screened with Pap test once a year (OR* = 2.0, 95% CI 1.2–3.7; OR** = 2.9, 95% CI 1.4–6.2).

Table 3. **Cervical cancer risk associated with other than HPV risk factors**

No.	Risk factor	Case (n = 145)	Control (n = 337)	**Age- and HPV-adjusted OR and 95% CI	p for trend	*Age-adjusted OR and 95% CI	p for trend
1	Nationality				0.6211		0.3568
	other	7	15	1.0 (ref)		1.0 (ref)	
	Lithuanian	106	269	2.1 (0.5–8.4)		0.9 (0.4–2.9)	
	Russian	19	23	2.9 (0.6–14.5)		1.9 (0.6–6.8)	
	Polish	13	30	2.6 (0.5–13.9)		1.1 (0.3–3.9)	
2	Education				**<.0001**		**<.0001**
	higher	20	169	1.0 (ref)		1.0 (ref)	
	special	68	103	6.1 (2.7–14.6)		6.1 (3.3–11.7)	
	secondary	29	53	4.2 (1.5–12.6)		6.9 (3.2–15.6)	
	primary	28	12	43.8 (9.0–258.7)		43.2 (12.9–170.5)	
3	Social status				**0.0014**		**<.0001**
	other	42	139	1.0 (ref)		1.0 (ref)	
	worker	52	31	2.5 (1.0–6.5)		4.3 (2.2–8.6)	
	employee	51	167	0.5 (0.2–0.9)		0.5 (0.3–0.9)	
4	Marital status				**0.0249**		0.0607
	married	122	209	1.0 (ref)		1.0 (ref)	
	unmarried	5	74	0.3 (0.1–0.9)		0.4 (0.1–1.1)	
	divorced	16	36	0.4 (0.1–1.0)		0.7 (0.3–1.4)	
	living without marriage	2	18	0.2 (0.01–1.0)		0.2 (0.02–0.8)	
5	Age at first intercourse				**0.0063**		**0.0050**
	>20 years	53	118	1.0 (ref)		1.0 (ref)2	
	<20 years	92	219	2.8 (1.4–5.9)		2.1 (1.3–3.5)	
6	Number of sexual partners				0.4783		0.7553
	1	68	130	1.0 (ref)		1.0 (ref)	
	2	38	81	0.6 (0.2–1.3)		1.1 (0.6–1.9)	
	3–5	32	86	0.6 (0.3–1.4)		1.1 (0.6–1.9)	
	>5	7	40	0.5 (0.2–1.8)		0.6 (0.2–1.6)	
7	Any sexual intercourse of partners				**0.0053**		**0.0006**
	never	62	86	1.0 (ref)		1.0 (ref)	
	don't know	29	122	0.2 (0.1–0.5)		0.3 (0.2–0.6)	
	ever	54	129	0.5 (0.2–1.1)		0.9 (0.5–1.5)	
8	The last sexual intercourse				0.2308		**<.0001**
	>2 years ago	67	25	1.0 (ref)		1.0 (ref)	
	<2 years ago	18	34	0.5 (0.1–1.6)		0.4 (0.2–0.9)	
	sexually active	60	278	0.4 (0.1–1.2)		0.2 (0.1–0.4)	
9	Age at first menstruation				**0.0004**		**0.0108**
	12–15 years	112	281	1.0 (ref)		1.0 (ref)	
	<12 years	2	27	0.1 (0.01–0.5)		0.2 (0.02–0.8)	
	>15 years	31	28	5.0 (1.8–14.8)		2.1 (1.1–4.1)	
10	Number of deliveries				**0.0013**		**0.0002**
	1–2	91	211	1.0 (ref)		1.0 (ref)	
	0	14	104	0.1 (0.2–1.2)		0.7 (0.3–1.6)	
	3–5	34	20	2.7 (1.0–7.6)		2.6 (1.3–5.2)	
	>5	6	2	21.9 (2.9–238.7)		21.3 (3.7–179.1)	
11	Number of abortions				0.5516		0.1861
	0	54	189	1.0 (ref)		1.0 (ref)	
	1–2	68	118	1.5 (0.7–2.9)		1.6 (0.9–2.7)	
	≥ 3	23	20	1.2 (0.4–3.3)		1.2 (0.6–2.4)	
12	Use of oral contraceptives				**0.0008**		**0.0025**
	never	125	191	1.0 (ref)		1.0 (ref)	
	ever	20	146	0.3 (0.1–0.6)		0.4 (0.2–0.7)	
13	Use of other contraceptives				0.3088		0.5131
	never	101	182	1.0 (ref)		1.0 (ref)	
	ever	44	155	0.7 (0.4–1.4)		0.9 (0.5–1.4)	
14	Smoking				0.9719		**0.0105**
	never	105	257	1.0 (ref)		1.0 (ref)	
	ever	40	80	0.9 (0.5–2.0)		2.0 (1.2–3.5)	
15	PAP test				**0.0049**		**0.0132**
	1–2 year ago	23	118	1.0 (ref)		1.0 (ref)	
	never	122	218	2.9 (1.4–6.2)		2.0 (1.2–3.7)	

* age-adjusted; ** age- and HPV-adjusted.

DISCUSSION

In a worldwide study by a PCR-based method for HPV detection, approximately 100% of cervical cancers are HPV-positive versus 5–20% in control women (2, 4, 5). Our hospital-based case control study showed that 92.7% of cervical cancer patients and 26.7% of control women were HPV-positive. However, this prevalence was different when women were analyzed according to cancer histology. Almost all women with SCC were HPV-positive, and women with AD were positive in 76.5% of cases. The situation with HPV prevalence was different also in control group women according to cytology. The highest HPV prevalence was among women with the HSIL diagnosis (79.3%); women without any cytological lesions were infected with HPV at a lower frequency (21.4%) ($p < 0.05$) (Table 1). It seems that in Lithuania the prevalence of HPV infection is high among healthy women. Due to the high HPV prevalence, the incidence of cervical cancer in Lithuania is highest in Europe.

Geographical differences in the prevalence of HPV types had been reported among countries (14). The IARC pooled analysis of 11 case-control studies from 9 countries (Brazil, Morocco, Paraguay, the Philippines, Thailand, Peru, Mali, Spain, and Columbia) reports the HPV prevalence among cervical cancer patients at 90.7%, with the most frequently detected HPV type 16 (54.6%); HPV 18 was detected in 11.0% of cases. A slightly higher HPV prevalence was found in Mali, Morocco and Philippines (96.9%, 94.6% and 93.8%, respectively). In our study, like in other studies from Europe and the world, the most prevalent types were HPV 16 and 18, 55.8% of infections were detected in SCC and 35.3% in AD; however, the prevalence of HPV 18 (6.7%) was less common than in other countries. In cervix AD, HPV 18 was identified more frequently than in SCC (17.7% and 5.2%, respectively). It should be noted that HPV 16 was also detected in 19.0% of the control group women. These women should be under gynecological supervision as their cervical cancer risk is higher.

Worldwide, other types important in SCC are as follows: HPV 33 (4.3%), HPV 45 (4.2%), HPV 31 (4.2%), HPV 58 (3.0%), HPV 52 (2.5%) and HPV 35 (1.0%) (15). In our study, the other types of HPV were as follows: most of the cervical cancer patients were diagnosed with HPV 31 and 33 and the control group women – with HPV 33,53 and 58. Consequently, the results are similar to those reported by other authors, showing that HPV types 31 and 33 are fairly frequently identified in various populations. In our study group women, HPV type 45 was detected less frequently than in the studies of other countries. The low-risk group type HPV 6 was detected only in 7.6% of control women.

As mentioned above, virus infection alone is not sufficient for the development of cervical cancer. Other risk factors are also involved in this process. Therefore, a lot of research has been done on the exploration of these factors. IARC has announced the data of a multicentric research (16). Risk factors for cervical cancer are divided into two groups. The factors that enhance HPV infection in women, its prevalence and persistence belong to the first group. The second group comprises the factors that may have some influence on carcinogenesis caused by HPV, i. e. may re-enforce the viruses, and sometimes they may even start to act independently. The first group contains such factors as early start of sexual intercourse, variety of sexual partners, lack of personal hygiene, poor socioeconomic status; in the second group includes smoking, hormonal contraceptives, other viruses (human immunity system suppressing virus – HIV). Suppression of the immunity system fosters the growth of tumours of any kind. It is concluded that the most important risk factors for cervical cancer development are the socioeconomic status and sexual history of women.

The role of socioeconomic differences in cervical carcinogenesis had been analyzed by comparing two countries – Spain and Columbia (17). Both are Spanish-speaking countries, although their economic status and conditions of life are rather different. In Columbia, the level of cervical cancer prevalence is high (standardized rate 42.2 / 100 000), while in Spain it is low (7.7 / 100 000). In both countries, women of a lower social level are 3-fold more often exposed to diseases than women of a higher social class. According to other authors, the estimates are influenced by the prevalence of infection among underclass women and also by the tendency of male spouses to request the services of prostitution (10). Vietnamese researchers consider the low level of education as a risk factor for developing the disease (18). In Venezuelan urban areas of women 38.5% had a low educational level: 89.7% of them knew that Pap smear is used to screen cervical cancer: 92.0% of women who did not complete elementary school had the knowledge of the purpose of vaginal cytology (19).

The American (USA) researchers also mark the lack of education as one of the important risk factors (20). They are of the opinion that women with a lower educational level start their sexual life earlier and have more parities, attend gynecologists more rarely, have more intimate partners or choose partners who have more other intimate partners. Similar results were obtained in Peru (21). Immigrant women also show a tendency to develop cervical cancer. Low literacy is associated with a low income and poor health status. It disproportionately affects ethnic minorities, including immigrants who often arrive in the USA with low levels of education, less income, low English proficiency, and conflicting models of cultural knowledge about disease and prevention as compared with the USA models. Health literacy influences preventive behaviour and has been shown to be a better predictor of cervical cancer screening than ethnicity or education (22).

Our results support the opinion that women with a lower educational level are at a higher risk of developing cervical cancer. The data of our study have shown that the risk of cervical cancer for women with incomplete secondary education is considerably higher (OR* = 43.2, 95% CI 12.9–170.5; OR** = 43.8, 95% CI 9.0–258.7). The risk of developing cervical cancer is also increased for women with a lower social

status: women workers are at a 2.5–4 times higher risk in comparison with other women (OR* = 4.3, 95% CI 2.2–8.6; OR** = 2.5, 95% CI 1.0–6.5).

The next group of most important cervical cancer risk factors is sexual behaviour: age at the first intercourse, the number of sexual partners, sexual intensity, etc. The risk of HPV infection and HPV-associated cervical cancer increases with the number of sexual partners: the possibility of HPV infection grows from 17% for women with one sexual partner up to 83% for those with 5 and more sexual partners. Such results demonstrate the enhancing risk of acquiring HPV infection for adolescents and young women with each new sexual partner. The increasing risk of cervical carcinoma is associated with the lifetime number of sexual partners as the effect of increased exposure to HPV infection; cervical cancer risk may increase with the duration of HPV infection. It is likely that women who have earlier the first sexual intercourse are also exposed to HPV earlier and this exposition lasts longer. However, in many of the study populations, as also in our study, most women reported only one sexual partner. For these women, the risk of exposure to HPV and, consequently, of developing cervical cancer chiefly depends on the lifetime number of sexual partners of their husband. However, these answers are usually not correct. Many of the study women answer "don't know" the question about sexual partners of their husbands. On the other hand, the large differences in these unmeasured variables may contribute to the heterogeneity among the studies. Each additional sexual partner was lower in hospital-based than in population-based case-control studies and in studies carried out in developing countries. This suggests a possible variation in the quality of the information available (15). Nevertheless, our study results suggest that the risk of cervical cancer is not associated with the number of sexual partners, the patner's extramarital sexual relations and the frequency of sexual intercourse, possibly because the majority of women in our study answered that they had only one sexual partner in their life. However, early sexual experience was a risk factor in our study: the risk of cancer increased 2–3 times if the first sexual intercourse occurred at the age under 20 years (OR* = 2.1, 95% CI 1.3–3.5; OR** = 2.8, 95% CI 1.4–5.9).

On the other hand, the number of screened men for HPV infection prevalence is very low. Due to the fact that HPV is a sexually transmitted disease, several studies have shown that circumcision protects men from infection persistence and their partners from cervical cancer development (23, 24). It also protects men and women from other sexually transmitted diseases (25).

One of the important and discussed in the literature risk factors for cervical cancer is the use of steroid hormones contraceptive purposes (11, 26). Most studies indicate that the use of these hormones, especially for a longer period, induces the acquisition of cervical cancer among HPV-positive women. HPV-positive women who had used oral contraceptives (OC) were at a higher risk of cervical cancer (OR = 1.47 [1.02–2.12]). According to literature data, the usage of OC for less than 5 years is not associated with the risk of cancer (OR = 0.77 [0.46–1.29]). If they have been used for a longer period, the risk grows substantially: OR = 2.72 [1.36–5.46] if used for 5 to 9 years, and OR = 4.48 [2.24–9.36] if used for more than 10 years (27). The finding of hormone receptors in cervical epithelial tissue also supports a possible role of steroids. Some reports indicate that progression of dysplasia to carcinoma *in situ* is faster if a woman has been taking hormonal contraceptives for more than 6 years. To evaluate the relationship between the use of oral contraceptives and the risk of invasive cervical cancer, a case-control study involving 479 patients and 789 population controls was undertaken in five geographic regions of the USA. Initially, the relationship was obscured by confounding variables, particularly the interval since the last Pap smear. Control for this variable as well as for sexual and sociodemographic factors revealed a RR (relative risk) of 1.5 overall, with long-term users (5 or more years) being at a 2-fold higher risk than non-users (28). Steroid hormones (estrogen and progesterone) are thought to play a role in the establishment and / or progression of this disease. The high-risk, HPV-infected women taking estradiol (E2) develop HSIL lesions that progress to invasive ones at the transformation zone (estrogen-sensitive region), which is the location implicated in the genesis of cervical cancer. Estrogen also affects the type of immune response, which can affect the persistence of HPV infection and the anti-tumour response (29). A recent meta-analysis has evaluated the association between OC use, duration of use and the number of years after ending their consumption (15). Among current users of OC, the risk of cervical cancer increased with the duration of use (five or more years of use versus never use, RR 1.90, 95% CI 1.69–2.13). The risk declined once women stopped using OC, and after 10 years or more of cessation the risk returned to that of never-users. Cervical cancer is caused by HPV infection, and exposure to genital HPV is not independent of OC use. Women using OC are more likely to be exposed to HPV than those using barrier methods or who have no sexual intercourse, and the use of barrier methods is associated with a moderate reduction of the risk of HSIL and cancer. Furthermore, cervical neoplasia is more likely to regress and HPV infection is more likely to clear in women whose partners use condoms during sexual intercourse than in those who do not. Therefore, even if OCs are not causally associated with cervical cancer, HPV-positive women who use them instead of barrier methods might be at an increased risk (30). Other controversial results were reported in the literature as well. The research undertaken in New Mexico (USA) denied the role of oral contraceptives in the stimulation of cervical dysplasia. On the contrary, their protective effect was determined. However, some of the authors believe that the women studied used different hormonal contraceptives. In our study, the risk of cervical cancer development was calculated irrespective of the histological type of tumour (insufficient number of adenocarcinomas), and exposure to

hormonal contraceptives did not increase the risk of cervical cancer development (OR* = 0.4, 95% CI 0.2–0.7; OR** = 0.3 95%, CI 0.1–0.6). Neither did other kinds of contraceptives (such as condoms, barrier contraceptives) increase the rate of cervix cancer development.

A recent pooled analysis of 25 epidemiological studies from across the world analyzed the association between reproductive factors and cervical carcinoma. Women with seven or more full-term pregnancies (FTP) were at a higher risk of developing cervical carcinoma than those who had one or two FTPs. Early age at first FTP (17 years *versus* 25 years) was also associated with the risk of both CIN3 / carcinoma *in situ* (RR 1.78; 95% CI 1.26–2.51) and invasive carcinoma (RR 1.71; 95% CI .42–2.23) [10]. Since long ago, a higher parity rate has been considered to be a risk factor for cervical cancer. However, until recently no tests have been performed to evaluate the influence of parities on HPV-positive women. IACR summarized the results from 10 epidemiological case-control studies accomplished in different (mostly developing) countries (14). Munoz and other authors have revealed that parity enhances the morbidity of both invasive (squamous) cervical cancer and carcinoma *in situ*. The risk of cervical cancer development among HPV-positive women correlates directly with parity. HPV-infected women who had 7 and more pregnancies with labour outcome are at a 4-fold higher risk of developing cervical cancer (OR = 3.8 [2.7–5.5]) than HPV-infected nulliparous women or those with 1–2 pregnancies. Similar data have been reported in studies from Puerto Rico and the Caribbean (10). In studies restricted to HPV-positive women, high parity has been consistently associated with an increased risk of cervical cancer rather than in populations with low parity. In the US population, some evidence of a relationship between multiparity and HPV exposure was found. The risk of cervical cancer could be explored by the high regenerative ability of the injured cervix after childbirth, and new recuperating cells are highly prone to various carcinogenic factors. Our study also proved an increasing risk of cervical cancer with the growing number of parities. With 3–5 deliveries, the risk of cervical cancer in a woman increases 2.6–2.7 times (OR* = 2.6, 95% CI 1.3–5.2; OR** = 2.7, 95% CI 1.0–7.6), and with over 5 deliveries it increases even more (OR* = 21.3, 95% CI 3.7–179.1; OR** = 21.9, 95% CI 2.9–238.7).

A recent pooled analyses of epidemiological studies has shown that women who reported a history of abortion were at an increased risk (odds ratio 1.7) (13). In our study, this risk was not confirmed.

Some facts presented in the literature show that in smokers tobacco metabolites penetrate into the discharge of cervix tissue and might affect it directly. It has been stated that in the women-smokers that developed cervical carcinoma *in situ*, the main metabolite of nicotine – cotinine – and nicotine itself are found in cervical tissue discharge in greater amounts than in their blood serum. Nicotine and cotinine are not inherently carcinogenic, but their presence in cervical tissue proves that they reach the cervix and might induce malignant processes. Recently, it has been proven that the discharge of cervical tissue of smokers contains NNK, a tobacco-specific N-nitrosamine. Later, cervix cells were found to metabolize NNK. As a result of the metabolism, genotoxins and carcinogenic metabolites are produced, implying the carcinogenic influence of tobacco smoking on the malignant transformation of cervical cells (31). Most of the epidemiological studies prove the disastrous effect of smoking on the development of cervical carcinoma. Women-smokers develop the disease 3-fold more often than non-smokers. A dose-response effect was also observed in cases of precancerous processes as well as in carcinoma. Moreover, many researchers believe that smoking enhances the risk of squamous cell carcinomas, more rarely – adenocarcinomas (15). Smoking has been independently associated with an increased risk of cervical cancer. A recent pooled analysis of twelve studies worldwide found that current smoking was associated with a significantly increased risk of squamous cell carcinoma (RR 1.50; 95% CI 0.70–1.05). The existence of a dose–response effect of cigarettes per day and duration of smoking is still controversial. In a pooled analysis of 10 IARC case-control studies, there was an excess risk of squamous cell carcinoma for ever smoking HPV-positive women (OR = 2.08; 95% CI 1.33–3.27), but among ever smokers, there was no evidence of increasing risk with the years of smoking, the number of cigarettes per day or age at starting smoking. Smoking cessation has also been associated with regression of CIN. In a longitudinal study, 82 women with CIN1 or less were encouraged to quit smoking. After six months of follow-up, lesions in 50% of those who stopped smoking disappeared, while lesions grew in those who did not stop (31, 32). Young women are more likely to be exposed to HPV; if also smokers, they might be at an increased risk of cervical cancer. New research confirms that smoking is an independent risk factor for cervical cancer in women with oncogenic HPV types, and the risk of SCC of the cervix was found to be associated with smoking among heavy smokers in the HPV16 / HPV18 seropositive group (OR = 2.7; 95% CI 1.7–4.3). The IARC revised all research data and in 2002 draw a conclusion that tobacco smoking still acts as an independent risk factor (16). In our study, the influence of tobacco smoking was medium, and the risk of cervical carcinoma was 2-fold higher in smoking women in comparison with non-smoking ones, calculating OR by the age (OR* = 2.0, 95% CI 1.2–3.5). However, calculating OR in both case-control groups by the age and HPV prevalence, smoking did not increase the risk of cervical cancer.

The risk of other contagious factors is reported in the literature. If *Herpes simplex* virus type 2 (HSV-2) (35) or *Chlamydia trachomatis* (CT) (34) antibodies are found in HPV-positive women, they are at a higher risk of cervical cancer development. However, not many studies have been done on this issue so far. We did not study the influence of other possible contagious risk factors on the development of cervical carcinoma in our research, either.

In summary, in our age-adjusted analysis, women with special (OR = 6.1, 95% CI 3.3–11.7), secondary (OR = 6.9, 95% CI 3.2–15.6) or primary (OR = 43.2, 95% CI 12.9–170.5) education, workers (OR = 4.3, 95% CI 2.2–8.6), those who started sexual intercourse before 20 years of age (OR = 2.1, 95% CI 1.3–3.5), age at the first menstrual period >15 years (OR = 2.1, 95% CI 1.1–4.1), 3–5 childbirths (OR = 2.6, 95% CI 1.3–5.2) or more than 5 (OR = 21.3, 95% CI 3.7–179.1), smokers (OR = 2.0, 95% CI 1.2–3.5) and rare or no Pap tests (OR = 2.0, 95% CI 1.2–3.7) were at a significantly higher risk of cervical cancer development. All these determinants, except smoking, were statistically significant after adjustment for both age and the status of HPV infection.

Other non-HPV risk factors (marital status, number of sexual partners, sexual intercourse of partners, sexual activity, use of oral or other contraceptives) in our study were not associated with cervical cancer risk or this association was not statistically significant (nationality, number of abortions).

CONCLUSIONS

- A high prevalence of HPV infection (92.7%) was detected among Lithuanian women diagnosed with cervical carcinoma of cases; among healthy women it was 26.7% ($p < 0.0001$); HPV type 16 was most frequent among both cervical cancer patients and healthy women.
- Other than HPV risk factors associated with cervical cancer risk in Lithuanian patients are the following: lower education, lower social status, younger age at the first intercourse, late age of the first menstrual period, high number of parities, no or rare Pap smear taking.

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Živilė Gudlevičienė, Alė Smilgevičiūtė-Ivshin, Aurelija Vaitkuvienė, Agnė Šepetienė, Janina Didžiapetrienė

ŽMOGAUS PAPILOMOS VIRUSO PAPLITIMAS IR KITI RIZIKOS VEIKSNIAI TARP LIETUVOS MOTERŲ, SERGANČIŲ GIMDOS KAKLELIO VĖŽIU

Santrauka

Įvadas. Gimdos kaklelio vėžys užima antrą vietą moterų sergamumo onkologinėmis ligomis struktūroje ir yra viena pagrindinių moterų mirties priežasčių pasaulyje. Tai taip pat viena dažniausių onkologinių moterų ligų Lietuvoje. Sergamumo gimdos kaklelio vėžiu rodikliai yra susiję su žmogaus papilomos viruso paplitimo dažniu, tačiau vien virusinės infekcijos nepakanka, kad formuotųsi gimdos kaklelio vėžys, veikia ir kiti rizikos veiksniai. Tiek ŽPV paplitimas, tiek ir kiti rizikos veiksniai skiriasi priklausomai nuo tiriamosios populiacijos ar geografinės zonos. Šio tyrimo tikslas – nustatyti ŽPV, jo tipų paplitimą bei kitus gimdos kaklelio vėžio rizikos veiksnius tarp Lietuvos moterų.

Medžiaga ir metodai. Į tyrimą įtraukta 191 moteris su pirmą kartą diagnozuotu gimdos kaklelio vėžiu (atvejų grupė) ir 397 sveikos moterys (kontrolinė grupė). Visos moterys užpildė klausimyną apie rizikos veiksnius, iš jų buvo paimta medžiaga ŽPV bei jo tipams nustatyti.

Rezultatai. Atvejų grupėje 92,7 % moterų rasta ŽPV infekcija, kontrolinėje grupėje – 26,7 % ($p < 0,0001$). Dažniausiai nustatytas 16-o tipo ŽPV. Ši infekcija didina riziką susirgti gimdos kaklelio vėžiu 75 kartus (OR = 75,39; 95 % CI 33,61–192,98). Didesnę riziką susirgti gimdos kaklelio vėžiu Lietuvoje turi žemesnio išsilavinimo moterys; darbininkės; pradėjusios lytinį gyvenimą iki 20 metų amžiaus; tos, kurioms vėlesniame amžiuje prasidėjo mėnesinės; gimdžiusios 3–5 kartus; rūkančios ar ilgą laiką neatlikusios Pap tyrimo.

Išvada. Lietuvoje nustatytas didelis ŽPV infekcijos paplitimas turi įtakos ir padidėjusiam sergamumui gimdos kaklelio vėžiu. Kiti rizikos veiksniai, nulemiantys šios ligos formavimąsi, panašūs kaip ir kitose žemesnio ekonominio lygio šalyse.

Raktažodžiai: ŽPV, gimdos kaklelio vėžys, rizikos veiksniai