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ARTICLE

High incidence of human papillomavirus infection in cervical carcinoma patients in South Hungary

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ABSTRACT The aim of this study was to determine the incidence of human papillomavirus (HPV) in cervical carcinoma patients. A nested case-control study was performed to investigate the relationship between HPV infection and cervical carcinoma. A total of 347 women 169 of whom gave abnormal Pap smear tests; were recruited to participate in the study; 39 of them suffered from invasive carcinoma. The overall incidence of HPV infection in the cancer, positive cytology and normal cytology groups was 74% (29/39), 55% (72/130) and 4% (7/178), respectively ($p<0.001$). The risk for progression to cervical carcinoma when the HPV infection was associated with abnormal cytology was 2.16 (95%, CI: [1.01-4.69]). The incidence of HPV infection associated with abnormal cytology correlated significantly with the presence of cervical carcinoma.
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KEY WORDS

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Infection of the uterine cervix with human papillomavirus (HPV) usually occurs via sexual transmission; it can lead to malignant transformation. It is now believed that at least 17 types of HPV are associated with cervical cancer. The oncogenic virus type can be identified in nearly all the cervical cancers. They are not only associated with, but are also thought to be causative, of the cancer. Various mechanisms that contribute to the development of HPV-induced cancer have been described. The multistep process from HPV infection to carcinogenesis is not yet completely understood. HPV genetic sequences have been observed to be integrated into the host genome just as the cell develops invasive properties (Cullen et al. 1991). The E6 protein produced by high-risk HPV types 16 and 18 is known to be able to combine with the p53 protein and to cause the same functional consequence as a p53 gene mutation (Scheffner et al. 1990; Hoppe-Seyler and Butz 1993). Immunosuppression can also give rise to an increased risk of cervical neoplasia. Immunosuppression has been found to be associated with an increased rate of HPV infection in several studies (Sillman et al. 1984; Vermund et al. 1991) and, in consequence of the deficient host-regulatory mechanisms, allows neoplastic proliferation (Rock et al. 2000). HPV types 16, 18, 33, 31, 53 and 58 are most commonly associated with cervical oncogenesis. However, there is considerable heterogeneity in the geographic distribution of oncogenic HPV.

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Previous studies have investigated the prevalence and risk factors of HPV infection in Hungary, but not in association with cervical carcinoma (Deák et al. 1999; Nyári et al. 2004).

The aim of this study was to determine the incidence of HPV in cervical carcinoma patients, in order to facilitate the prediction of the possibility of development of cervical cancer in certain groups (high-risk HPV-infected patients).

Materials and Methods

During the period between January 2002 and September 2003, a nested case-control study was performed to investigate the relationship between HPV infection and cervical carcinoma at the Department of Obstetrics and Gynaecology of the University of Szeged. Cervical samples were collected for cytology and HPV testing from women attending the gynaecological outpatient clinic. Colposcopic and routine gynaecological examinations were performed in each case. Both the Papanicolau (Pap) and Bethesda classifications were used for cytology evaluation. Sampling, sample transport and HPV DNA determination via HPV hybrid capture assay were carried out in accordance with the instructions of the manufacturer of the kit (DIGENE HPV hybrid capture 2). Virus types were classified into two categories: high-risk HPV (including 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68), and low-risk (6, 11, 42, 43 and 44) types.

Data concerning age, occupation, lifestyle and health status were extracted from the patient register system.

Table 1. Distribution of HPV infections according to subtypes.

Group	No. of cases				p value
	Negative	Low-risk types	High-risk types	Total	
Normal Pap smear	171	4	3	178	<0.001
Abnormal Pap smear without cervical carcinoma	58	60	12	130	
Cervical carcinoma	10	4	25	39	

Statistical analyses were carried out with the STATA software package. The statistical methods used were the chi-square test and analysis of variance. To obtain an overview of the risk, logistic regression analysis was performed. A probability level of $p < 0.05$ was considered statistically significant.

Results

A total of 347 women with a mean of age of 42.9 years (SD 9.5) were recruited into the case-control study: 178 of them gave normal Pap smear test (these women served as control group) and 169 women gave abnormal Pap smear test (class III or higher), 39 of them were diagnosed with invasive carcinoma. This later group immediately underwent appropriate treatment.

The overall incidence of HPV infection in the cancer, positive cytology and normal cytology groups was 74% (29/39), 55% (72/130) and 4% (7/178), respectively ($p<0.001$). High-risk HPV subtypes were diagnosed in 86% (25/29 cases) of the HPV-infected cancer cases, 16% (12/72) of the HPV-infected cases of those who gave abnormal Pap smear test. The distribution of the HPV subtypes is shown in Table 1 and the age-specific distribution of HPV infection in Table 2. There were 46 and 5 low-grade squamous intraepithelial lesions cases in the abnormal Pap smear group and the control group, respectively.

HPV infection significantly increased the risk of abnormal cytology (odds ratio (OR) 30.5 95% confidence interval (CI) [13.3-70]) and the risk of cervical carcinoma (OR 68.8 95%, CI [24.2-195.6]). Further, the OR for progression to cervical carcinoma when the HPV infection was associated with abnormal cytology was 2.16 (95%, CI: [1.01-4.69]).

We did not find any significant difference in the incidence of HPV as a function of the place of residence or the previous obstetrical history of the women.

Discussion

The present study focused on the relationship between the incidence of HPV infection and that of cervical cancer. HPV infection associated with abnormal cytology correlated significantly with the development of cervical carcinoma.

In the 39 cancer cases, we found a rate of HPV infection of 74% (29 cases), 25 of these patients were infected by high-risk HPV, *i.e.* the proportion of high-risk HPV among the HPV-infected cancer patients was very high (86%). The corresponding proportion among the HPV-infected non-cancer patients was only 16% (12/72). The odds ratio for the progression to cervical carcinoma when the HPV infection was associated with abnormal cytology was 2.16 which represents significantly increased risk to develop cervical carcinoma (Branca et al. 2003).

In the second half of the 1990s, HPV testing was generally

Table 2. Age-specific distribution of HPV infection (n=347).

	Control group				Abnormal Pap smear group			
Age	Number of HPV-negative cases	Number of HPV-infected cases	Total	% of infected cases	Number of HPV-negative csaes	Number of HPV-infected csaes	Total	% of infected cases
20-29 years	0	0	0		10	30	40	75%
30-39 years	41	1	42	2%	10	21	31	68%
40-49 years	94	6	100	6%	25	15	40	38%
50-59 years	36	0	36	0%	9	6	15	40%
60-69 years	0	0	0		4	0	4	0%
Total	171	7	178	4%	58	72	130	55%

	Cervix carcinoma group			
Age	Number of HPV-negative cases	Number of HPV-infected cases	Total	% of infected cases
20-29 years	0	0	0	
30-39 years	2	4	6	67%
40-49 years	3	12	15	80%
50-59 years	4	5	9	56%
60-69 years	1	8	9	89%
Total	10	29	39	74%

applied for the clinical screening of women of fertile age in Hungary. However, with regard to the results of international studies on large numbers of patients, and from cost-benefit considerations this practice was later modified (Schafer et al. 1991). We currently perform HPV testing only when this is suggested by the results of cytological examinations carried out because of the possibility of HPV infection.

The regular clinical screening of HPV-infected patients and their treatment by conization has effectively reduced the development of cervical cancer (Rock et al. 2000; Tachezy et al. 2003). One result of our study was a knowledge of the incidence of HPV infection in cervical cancer in Hungary, which had previously not been well documented.

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