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Distribution of Human Papillomavirus Types in Different Histological Subtypes of Cervical Adenocarcinoma

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A B S T R A C T

Little information is available regarding distribution of HPV types in different histological subtypes of adenocarcinoma (AC). Thus, in this study we examined the frequency of high-risk (hr) HPV types in AC, adenocarcinoma in situ (AIS) and adenosquamous carcinoma (ADSQ). A total of 102 cases of primary cervical adenocarcinoma (26 AIS and 76 invasive AC) obtained from pathology files from 1995–2006 were histologically subtyped. Our results demonstrated that endocervical type occupied the major subtype of AC (22/66) followed by ADSQ (17/66) where as in the group of AIS endocervical type (12/23) was followed by intestinal type of AIS (7/23). Successful DNA extraction was obtained in 89 samples; 81 out of 89 (91.0%) tested positive for HPV DNA. The prevalence of HPV DNA in AIS, AC and ADSQ was 91.3% (21/23), 90.9% (60/66) and 94.1% (16/17), respectively. We found HPV 18 type to be the most predominant type in AIS (11/21) and AC (17/60) followed by HPV of undeternmined type in AIS (3/21) and HPV 16 in AC (9/60) as the sole viral type. HPV 18 was most frequently detected type in all histological subtypes of AIS and AC. We have detected HPV DNA in all 5 samples of clear cell carcinoma (CCC), although other studies have reported a highly variable prevalence of HPV DNA in CCC. The most prevalent HPV type in ADSQ was HPV-16 followed by HPV 33 as single type. The observed overall predominance of HPV 18 in AIS ($\chi^2 = 6.109$, $p \leq 0.025$) and AC ($\chi^2 = 8.927$, $p \leq 0.01$) as well as of HPV 16 in ADSQ ($\chi^2 = 10.164$, $p \leq 0.01$) was statistically significant. Our data revealed statistically significant predominance of single hrHPV infections in AIS (16/21; $\chi^2 = 11.523$, $p \leq 0.001$) and AC (37/60; $\chi^2 = 6.533$, $p \leq 0.025$) whereas multiple hrHPV infections were more abundant in AC comparing to AIS (23/81and 5/81, respectively; $\chi^2 = 13.989$, $p \leq 0.001$).

Key words: *cervical adenocarcinoma, adenocarcinoma in situ, histological subtypes, HPV prevalence frequency and typing*

Introduction

There are two major histological types of invasive cervical cancer: squamous cell carcinoma (SCC) and adenocarcinoma (AC). Incidence rate of SCC has been declining in recent years[1] but unfortunately incidence of cervical AC is increasing in developed countries, despite their widespread screening programmes. Recent reports indicated that AC accounts for approximately 20–25% of uterine cervical cancer compared with only 5–15% in the past[2]. Many countries report steady increase in incidence rates especially among younger women, since early 1970s[2–6]. Although effective screening programmes contribute to decreasing incidence rates of SCC but neither improved surveillance or classification of ACs appears to account for all of the increase in ACs. There are more than 40 HPV types known to infect female genital tract, and a subset of at least 15 of these are known to have a strong oncogenic potential[11]. Therefore, HPV types have been classified according to their association with cervical cancer and precursor lesions into oncogenic or high-risk (hr) and low-risk (lr) HPV types[12]. Cervical squamous neoplasia has shown to be strongly associated with hrHPV infection with studies showing more than 90% of cancers containing HPV DNA[13,14]. Although, association of hrHPV with cervical AC has been studied less extensively, reports in the past decade indicate similar association, suggesting causal relationship between hrHPV and cervical

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AC[15,16]. Major limitation is that number of patients with cervical ACs involved in these studies was small. Another reason why causal relationship between HPV infection and cervical AC is further complicated is the fact that AC encompasses several heterogeneous histological subtypes. The majority of tumours are mucionus AC including endocervical and intestinal type, while minor component of cervical AC includes variety of histological subtypes such as endometrioid, clear cell serous, villoglandular, minimal deviation, mesonephric adenocarcinoma and mixture of those subtypes. Specific histological subtype is clear cell carcinoma (CCC) which accounts for 2–7% of cervical AC and if presenting in young patients usually involves association with diethylstilbestrol (DES) exposure *in utero*[17,18] and HPV DNA negativity. Other patients with CCC have no known risk factors and occur in an older age group[18].

While hrHPV infection appears to be required for the development of both SCC and AC, the distribution of hrHPV types seen in these two forms of disease varies from study to study. Whereas HPV 16 is the most frequently involved in the development of SCC, HPV 18 alone or in combination with HPV 16 is reported to be a predominant type in AC[19] and adenocarcinoma *in situ* (AIS). Little information is available regarding geographic variation of HPV types in different histological subtypes of AC. Herein we conducted a retrospective study in order to evaluate the frequency of HPV types in adenocarcinoma *in situ* (AIS), AC and adenosquamous carcinoma (ADSQ).

Materials and Methods

Case selection and histological subtyping

A total of 102 specimens of primary cervical adenocarcinoma were (26 AIS and 76 invasive AC) obtained from the Department of Pathology, University of Rijeka, Croatia, which were collected from 1995 to 2006. Paraffin embedded sections of cone or hysterectomy specimens were reviewed by two pathologists. Each case was histologically subtyped according to the standard histological criteria[20] and associated lesions of the squamous epithelium were recorded as well. Endocervical type was the most common invasive adenocarcinoma, found in 22 cases, followed by adenosquamous carcinoma (17 cases), intestinal (12 cases), and endometrioid type (8 cases). Five cases were diagnosed as clear cell carcinoma, 3 cases were signet-ring carcinoma, 3 cases as serous and one case as villoglandular and glassy cell carcinoma. Mixed mucinous adenocarcinoma was found in 4 cases. Associated CIN I–III lesions were found in 11 cases. According to morphological criteria 15 AIS were suptyped as endocervical, 7 cases as intestinal, 2 cases as endometrioid and one as adenoaquamous and mixed type. Depending on tissue availability, successful DNA extraction, defined by presence of β-globin gene sequence, was found in 89 samples, 3 cases of AIS and 10 cases of AC were excluded from further analysis.

DNA extraction and PCR analysis

Total DNA was isolated from formalin fixed, paraffin embedded samples. Great care was taken on sample sectioning to avoid any contamination between the samples. Depending on the amount of biopsy material embedded in paraffin, 4–10 sections (5 μm thick) were placed in a microcentrifuge tube. The sections were deparaffinized by adding 1 mL of xylene and heating at 55°C for 30 minutes, followed by centrifugation and subsequent removal of the supernatant. Upon dewaxing with three washes of xylene, 1 mL of 100% ethanol was added to remove residual xylene. The tissues were dried at 37°C for 30 minutes and DNA was isolated using NucleoSpin®Tissue kit (Macharey-Nagel, Duren, Germany) according to the manufacturer's instructions.

Detection of HPV DNA was performed using E6 and E7 consensus primers (Human Papillomavirus Typing Set, Takara Biomedicals, Japan). The HPV types in positive samples were further characterized by using type specific primers amplifying sequences of HPV 16, 18 and 33 within E6 and E7 open reading frame (ORF) (Human Papillomavirus Detection Set, Takara Biomedicals, Japan) and HPV 31, 45, 52, 59 and 68 in the E7 ORF[14].

Statistical analysis

HPV prevalence was expressed as percentage of all cases tested for HPV in different histological groups of AC (accounted only once). The overall prevalence of individual hrHPV types was determined as they appeared as either single or within multiple infections. Multiple hrHPV infection was defined as two or more hrHPV types. The differences of the means of the continuous variables were analyzed with the Student's *t*-test and the distribution of non-continuous histological variables *versus* HPV status was analyzed with the Chi-square test (χ^2). *P* values of <0.05 were used as the cut-off for statistical significance.

Results

As shown in Table 1. endocervical type represented the major subtype of AC (22/66) followed by ADSQ (17/66) where as in the group of AIS endocervical type (12/23) was followed by intestinal type of AIS (7/23). The average age of patients with AIS, AC and ADSQ was 41.82, 48.9 and 44, respectively. Statistical analysis revealed that average age of the patients with AIS and AC (41.82 years *versus* 48.9 years) was significantly different (Student's t-test; $t=2.55$, degrees of freedom 87, $p\leq0.05$). Looking at different histological subtypes the average age of patients with intestinal AC and AIS was the youngest (35.8 and 39.28 years respectively). Cervical intraepithelial neoplasia (CIN), ranging from CIN I to CIN III accompanied AIS and AC in 27 cases (16/23 and 11/66, respectively).

We were able to successfully extract DNA from 89 samples and 81 (91.0%) tested positive for HPV DNA. HPV DNA prevalence according to different histological subtypes of AC, AIS and ADSQ is presented in Table 1.

TABLE 1
VARIOUS HISTOLOGICAL SUBTYPES OF CERVICAL ADENOCARCINOMA AND HIGH RISK HPV PREVALENCE

Diagnosis	n	Age range years	Average age years	CIN component		HPV negative		HPV positive		Single HPV infection		Multiple HPV infections*	
				n	%	n	%	n	%	n	%	n	%
Endocervical	22	26–74	48.59	6	27.3	2	9.1	20	90.9	15	75	5	25
Intestinal	5	30–40	35.8	1	20	1	20	4	80	2	50	2	50
Endometrioid	8	29–82	54.37	–	–	–	–	8	100	4	50	4	50
Clear cell	5	42–73	63.8	–	–	–	–	5	100	4	80	1	20
Serous	3	38–78	55.67	1	33.3	2	66.7	1	33.3	1	100	–	–
Villoglandular	1	40	40	–	–	–	–	1	100	1	100	–	–
Mixed	4	37–69	48.75	1	25	–	–	4	100	2	50	2	50
Glassy cell	1	65	65	–	–	–	–	1	100	–	–	1	100
Adenosqumaous	17	21–73	44	2	11.8	1	5.9	16	94.1	8	50	8	50
All invasive adenocarcinoma	66	21–82	48.9	1	116.7	6	9.1	60	90.9	37	61.7	23	38.3
Endocervical	12	26–56	45.5	10	83.3	1	8.3	11	91.7	7	58.3	4	33.3
Intestinal	7	30–46	39.28	5	71.4	–	–	7	100	6	85.7	1	14.3
Mixed	1	40	40	1	100	–	–	1	100	1	100	–	–
Adenosqumaous	1	47	47	–	–	–	–	1	100	1	100	–	–
Endometrioid	2	43	43	–	–	1	16.7	1	50	1	100	–	–
All adenocarcinoma *in situ*	23	26–56	41.82	16	69.6	2	8.7	21	91.3	16	76.2	5	23.8

CIN – cervical intraepithelial neoplasia, HPV – human papillomavirus, *Multiple HPV infections: positive for > 1 high risk HPV

The prevalence of HPV DNA in AIS, AC and ADSQ was 91.3% (21/23), 90.9% (60/66) and 94.1% (16/17), respectively. We have detected HPV DNA in all 5 samples of CCC although other studies have reported a highly variable prevalence of HPV DNA in CCC[17,18,21]. Also, patients with CCC belong to oldest age group (63.8 years) compared to all other histological subtypes of AC (Table 1).

While HPV types 16, 18, 31 and 33 were detected in single or multiple infections we did not detect HPV types 45, 52, 59 and 68 in any tested samples. All samples that were HPV DNA positive but were not typed as HPV 16, 18, 31, 33, 45, 52, 59 or 68 were marked as HPV X. We found HPV 18 type to be the most predominant type in AIS (11/21) and AC (17/60) followed by HPV X in AIS (3/21) and HPV 16 in AC (9/60) as the sole viral type (Table 2). Also, HPV 18 was most frequently detected type in all histological subtypes of AIS and AC. On the other hand the most prevalent HPV type in ADSQ was HPV 16 followed by HPV 33 as single type. The observed overall predominance of HPV 18 in AIS (χ^2= 6.109, p≤ 0.025) and AC (χ^2=8.927, p≤0.01) and of HPV 16 in ADSQ (χ^2=10.164, p≤0.01) was statistically significant (Table 3).

When we analysed the distribution of HPV 16 and 18 in endocervical AIS and AC together we found statistically significant prevalence of HPV 18 (21/31; χ^2=6.458, p≤0.025). Also, prevalence of HPV 18 in intestinal AIS and AC was statistically significant (9/11; χ^2=4.701, p≤ 0.05) (Table 3). However, there is no statistically significant prevalence of HPV 18 in remaining histological subtypes of AIS and AC.

Combining together single and multiple HPV infections, HPV 18 was detected in 68.2% of AC (30/44) and 66.7% of all AIS (14/21) cases whereas HPV 16 in 36.4% (16/44) and 28.6% (6/21), respectively. Single HPV type infections were statistically significant in AIS (16/21; χ^2=11.523, p≤0.001) and AC (37/60; χ^2=6.533, p≤0.025) while equal number of single and multiple HPV infections was detected in ADSQ (8/16). However we found statistically significant higher number of multiple infections in AC compared to AIS (23/81and 5/81, respectively; χ^2=13.989, p≤0.001).

Discussion

When we examined the number of AC cases diagnosed at our Department of pathology (which covers large region of Rijeka county), we noticed increasing trend of glandular cervical carcinomas during 1995–2006 period of time with predominant number of cases in women 29–49 years of age (data not shown). These data are in accordance with increasing trend of this neoplasia seen in developed countries[2,6].

It is well established that hrHPV is causal factor in development of SCC and its precursor lesions[22] with studies reporting almost 100% prevalence of HPV in SCC[11,13,23]. However, causal linkage of HPV infection to the cervical AC has not been considered as strong as it is for SCC due to more variable and generally lower HPV prevalence rates (60%–96%)[18,19,22,24–26]. Recent more sensitive extraction and detection techniques have made it possible to identify the higher rate of HPV infection in

TABLE 2
HIGH-RISK HPV TYPES DISTRIBUTION ACCORDING TO HISTOLOGICAL SUBTYPES

Diagnosis	HPV positive	HPV 16		HPV 18		HPV 31		HPV 33		HPV X*		HPV 16 & 18		HPV 18 & 31		HPV 18 & 33		HPV 16 & 31		HPV 16 & 33		> 2 hr-HPV**	
	n	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Endocervical	20	3	15	10	50	1	5	–	–	1	5	2	10	1	5	–	–	–	–	–	–	2	10
Intestinal	4	–		2	50	–	–	–	–	–	–	2	50	–	–	–	–	–	–	–	–	–	–
Endometrioid	8	–		2	25	–	–	–	–	2	25	1	12.5	1	12.5	–	–	–	–	–	–	2	25
Clear cell	5	–		2	40	–	–	1	20	1	20	–	–	–	–	–	–	–	–	–	–	1	20
Serous	1	–		–	–	1	100	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Villoglandular	1	–		1	100	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Mixed	4	1	25	–	–	–	–	–	–	1	25	1	25	–	–	–	–	–	–	–	–	1	25
Glassy cell	1	–		–	–	–	–	–	–	–	–	–	–	–	–	1	100	–	–	–	–	–	–
Adenosqumaous	16	5	31.3	–	–	–	–	3	18.7	–	–	1	6.3	–	–	–	–	1	6.3	3	18.7	3	18.7
All invasiveadeno-carcinoma	60	9	15	17	28.3	2	3.3	4	6.7	5	8.3	7	11.7	2	3.3	1	1.7	1	1.7	3	5	9	15
Endocervical	11	1	9.1	4	36.3	–	–	–	–	2	18.2	1	9.1	1	9.1	–	–	1	9.1	–	–	1	9.1
Intestinal	7	1	14.3	4	57.1	–	–	–	–	1	14.3	–	–	–	–	–	–	–	–	–	–	1	14.3
Mixed	1	–		1	100	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Adenosqumaous	1	–		1	100	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Endometrioid	1	–		1	100	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
All adenocarcinoma *in situ*	21	2	9.5	11	52.3	–	–	–	–	3	14.3	1	4.8	1	4.8	–	–	1	4.8	–	–	2	9.5

HPV – human papillomavirus, *Includes HPV types other than 16, 18, 31, 33, 45, 52, 59, 68; **Includes multiple high risk HPV infections (HPV 18, 16 &31, HPV 18, 16 & 33, HPV 16, 31 &33, HPV 16, 18, 31 &33)

AC with frequencies reaching 85% or more[18,27]. Although DNA extractions from older (>10 years) paraffin embedded tissue blocks can be sometimes cumbersome we were able to detect HPV DNA in large majority of cases (91%) consistent with previous findings[18,28]. We screened our samples for only 8 hrHPV types because combined together, as we showed previously[29], they cover almost 90% of overall HPV type found in cervical carcinoma.

TABLE 3
OVERALL PREVALENCE OF HIGH-RISK HPV TYPES IN VARIOUS HISTOLOGICAL SUBTYPES OF CERVICAL ADENOCARCINOMA

Diagnosis	HPV positive	HPV 16		HPV 18		HPV 31		HPV 33		HPV X*	
	n	n	%	n	%	n	%	n	%	n	%
Endocervical	20	7	35	15	75	3	15	2	10	1	5
Intestinal	4	2	50	4	100	–	–	–	–	–	–
Endometrioid	8	3	37.5	5	62.5	3	37.5	2	25	2	25
Clear cell	5	1	20	3	60	–	–	2	40	1	20
Serous	1	–	–	–	–	1	100	–	–	–	–
Villoglandular	1	–	–	1	100	–	–	–	–	–	–
Mixed	4	3	75	1	25	1	25	1	25	1	25
Glassy cell	1	–	–	1	100	–	–	1	100	–	–
All invasive adenocarcinoma	44	16	36.4	30	68.2	8	18.2	8	18.2	5	11.4
Adenosquamous	16	13	81.3	4	25	3	18.7	8	50	–	–
Endocervical	11	4	36.4	6	54.5	2	18.2	1	9.1	2	18.2
Intestinal	7	2	28.6	5	71.4	1	14.3	1	14.3	1	14.3
Mixed	1	–	–	1	100	–	–	–	–	–	–
Adenosquamous	1	–	–	1	100	–	–	–	–	–	–
Endometrioid	1	–	–	1	100	–	–	–	–	–	–
All adenocarcinoma *in situ*	21	6	28.6	14	66.7	3	14.3	2	9.5	3	14.3

HPV – human papillomavirus, *Includes HPV types other than types 16, 18, 31, 33, 45, 52, 59 & 68

HPV infection is required for the development of both SCC and AC, however, distribution of HPV types seen in these two forms of the diseases differ. HPV 16 type is the most frequently involved in the development of SCC[30] of the cervix where as studies describing HPV type prevalence in AC are in disagreement. Some report HPV 16 and HPV 18 type to have equal prevalence[30,18], while others show predominance of HPV 18 in AC[26]. In this study we found that, in overall, HPV 18 statistically significantly prevails in AIS and AC, while in ADSQ HPV 16 is the most frequent type. We found HPV 18 predominantly in endocervical and intestinal AIS and AC, however there is no statistically significant prevalence of HPV 18 in remaining histological subtypes of AIS and AC. Large meta-analysis study[16] showed that the highest risks of developing AC were associated with HPV 18 (OR=410) followed by HPV 16 (OD=164). In context of these findings our results support the hypothesis of HPV 18 being the most important risk factor in developing of cervical AC. Existing data on the HPV DNA detection in cervical CCCs are opposing, with some studies indicating HPV DNA presence[17,21,28], while others were unable to identify HPV DNA[18,31]. In our study we found all 5 CCC cases to be HPV DNA positive. Therefore our results are in line with those that reported positive findings but exact cause for the discrepancy in the HPV DNA detection from CCCs is still unclear.

Our data revealed statistically significant predominance of single hrHPV infections in AIS and AC, however, other studies showed similar results only for AC[18,27]. Presented results support hypothesis of Zielinski et al.[27] that invasive growth of glandular epithelial cells is triggered by the action of a single HPV type rather than a potentially synergistic action of multiple HPVs. However, in our study we found rather high prevalence of multiple HPV infections in AIS and invasive AC, 23.8% and 38.2% cases respectively (Table 1), that can not be overlooked. The fact that multiple infections are even more abundant in invasive AC than in the precursor lesion, might indicate that multiple infection could contribute to cancer development in a more aggressive way than a single infection with hrHPV.

Conclusion

Our study revealed that the most prevalent hrHPV type in AIS and AC is HPV 18 while HPV 16 is predominant type in ADSQ. Analysis of various histological subtypes of AIS and AC demonstrate that in endocervical and intestinal carcinoma HPV 18 is predominant type, whereas in remaining histological subtypes such predominance was not detected. We have detected HPV DNA in all 5 samples of CCC although other studies have reported a highly variable prevalence of HPV DNA in CCC. Our data revealed statistically significant predominance of single hrHPV infections in AIS and AC whereas multiple hrHPV infections were more abundant in AC comparing to AIS.

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RASPODJELA TIPOVA HUMANOG PAPILOMAVIRUSA U RAZLIČITIM HISTOLOŠKIM SUPTIPOVIM ADENOKARCINOMA VRATA MATERNICE

S A Ž E T A K

Budući da su podaci u svijetu o prevalenciji HPV tipova u različitim histološkim suptipovma adenokarcinoma (AC) vrlo oskudni, proveli smo ovu studiju s ciljem da ispitamo prevalencije HPV tipova u AC, adenokarcinomu *in situ* (AIS) i adenoskvamoznom karcinomu (ADSQ) u Hrvatskoj. Ukupno 102 arhivska uzoraka primarnog adenokarcinoma vrata maternice (26 AIS i 76 AC), prikupljeno je na patologiji tijekom 1995–2006, i histološki suptipizirano. Dobiveni podaci su pokazali da je najzastupljeniji suptip AC endocervikalni (22/66), zatim ADSQ (17/66), dok je u AIS-u endocervikalni suptip utvrđen u 12/23, a intestinalni u 7/23 AIS-a. DNK je uspješno izolirana iz 89 uzoraka. U 81 uzorku (91%) dokazana je HPV DNK. Utvrđena je HPV DNK prevalencija u AIS-u 91,3%, u AC 90,9 % i ADSQ 94,1%. U slučajevima infekcije samo jednim tipom utvrdili smo da je HPV 18 najučestaliji u AIS-u (11/21) i AC (17/60), a slijede ih grupa neodređenog tipa HPV-a u AIS-u (3/21) te HPV 16 u AC (9/60). HPV 18 je i najučestaliji genotip u svim histološkim suptipovima AIS-a i AC. Također smo dokazali HPV DNK u svih 5 uzoraka karcinoma svjetlih stanica (CCC) iako su druge studije pokazale različite podatke o prevalenciji HPV DNK u CCC. Najučestaliji pojedinačni HPV tipovi u ADSQ su HPV 16 i HPV 33. Dokazano je da je ukupna prevalencija HPV 18 u AIS-u i AC, te HPV 16 u ADSQ statistički značajna; HPV 18 u AIS-u ($\chi^2 = 6.109$, $p \leq 0.025$) i AC ($\chi^2 = 8.927$, $p \leq 0.01$) i HPV 16 u ADSQ ($\chi^2 = 10.164$, $p \leq 0.01$). Infekcija s jednim HPV tipom je statistički značajno učestalija u AIS-u (16/21; $\chi^2 = 11.523$, $p \leq 0.001$) i AC (37/60; $\chi^2 = 6.533$, $p \leq 0.025$), dok je višestruka HPV infekcija učestalija u AC-u u odnosu na AIS (23/81 i 5/81, $\chi^2 = 13.989$, $p \leq 0.001$).