Risk Management and Healthcare Policy

Dovepress

open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Assessment of High-Risk Human Papillomavirus Infection Characteristics in Cervical Squamous Cell Carcinoma and Adenocarcinoma in China

Lijuan Zhuang*, Xiaoyan Xie*, Lihua Wang, Xiulan Weng, Yingling Xiu, Dabin Liu, Liying Zhong

Department of Obstetrics and Gynecology, Fujian Maternity and Child Health Hospital, College of Clinical Medicine for Obstetrics & Gynecology and Pediatrics, Fujian Medical University, Fuzhou, 350001, People's Republic of China

*These authors contributed equally to this work

Correspondence: Liying Zhong; Dabin Liu, Department of Obstetrics and Gynecology, Fujian Maternity and Child Health Hospital, College of Clinical Medicine for Obstetrics & Gynecology and Pediatrics, Fujian Medical University, 18 Daoshan Road, Fuzhou, 350001, People's Republic of China, Tel +86-13860610354; +86-13489997701, Fax +86-591-87551247, Email zhongliying@fjmu.edu.cn; 15968250@qq.com

Background: The characteristics of high-risk human papillomavirus (HR-HPV) infection in different pathological types of cervical cancer in China are unclear. The aim of this study was to evaluate HR-HPV genotypes and age stratification with cervical squamous cell carcinoma (SCC) and adenocarcinoma (ADC) in China.

Materials and Methods: Patients diagnosed with cervical cancer by histopathology in Fujian Maternity and Child Health Hospital from January 1, 2014, to December 31, 2017, were included in this study. The HR-HPV genotype was analyzed in cervical specimens. Logistic regression was used to calculate odds ratios (ORs). All tests of statistical significance were two-sided, and the P value<0.05.

Results: A total of 1,590,476 women were screened for cervical cancer, and 688 cervical cancers were detected, including 554 SCC and 93 ADC. The overall HR-HPV infection rate in SCC was higher than that in ADC (91.2% vs 81.7%, P=0.005). HPV-16 was the most prevalent genotype in SCC (70.0%) but was only 31.2% in ADC (P<0.001). However, the prevalence of HPV-18 in ADC was significantly higher than that in SCC (45.2% vs 7.0%; P<0.001). In SCC, the prevalence of HPV-16 was consistently much higher than that of HPV-18 regardless of age group. Among ADC, the prevalence of HPV-18 was higher than that of HPV-16 in women aged ≥45 years. Interestingly, in those aged <35 years, the highest prevalence was observed for HPV-16. HPV-18 infection has the highest risk of ADC (OR= 12.109; P< 0.001), and HPV-45 and HPV-51 were also found to be associated with the occurrence of ADC. However, HPV-16 infection greatly increased the risk of having histological SCC.

Conclusion: HPV-16 and HPV-18 infections are key risk factors for SCC and ADC. The use of HR-HPV genotyping tests in cervical cancer screening and vaccination against major HPV genotypes could reduce the incidence of cervical cancer.

Keywords: cervical squamous cell carcinoma, cervical adenocarcinoma, high-risk human papillomavirus

Introduction

Cervical cancer is the fourth most common cancer among women in the world, causing approximately 266,000 deaths globally each year, and approximately 88% of the disease burden occurs in developing countries.[1] As a cancer closely associated with socioeconomic development, cervical cancer remains one of the main public health burdens, especially in developing countries.[2] As reported, China contributed the highest number of cases (106 000) in 2018, resulting in a great global cervical burden.[3]

Squamous cell carcinoma (SCC) of the cervix is an epithelial invasive cancer that affects the squamous cells that coat the outer surface of the cervix, the outer layer of the cervix,[4] which most commonly occurs at the squamocolumnar junction between the nonkeratinizing stratified squamous epithelium of the outer layer of the cervix and the nonciliated simple columnar epithelium of the inner cervical canal and is the most common pathological type of cervical cancer, accounting for 80–85%.[4] In contrast, cervical adenocarcinoma (ADC) mainly originates from cervical glandular

Received: 30 July 2022
Accepted: 23 October 2022
Published: 2 November 2022

precursor lesions that develop from mucus-producing gland cells in the cervical canal,[5] and the incidence in China is much lower than that of SCC. However, the epidemiology of ICC appears to have changed over the past few years. As screening for cervical cancer and cervical precancerous lesions is widely carried out, the proportion of invasive cervical cancer attributable to SCC has increased from 95% to 67–84% in the past two years, while the proportion of ADC has increased from approximately 5% to 27%.[6–8] The increase is especially obvious in young women. Compared with SCC in the same period, ADC has a poor prognosis.[9] It is generally believed that the sensitivity of ADC to radiotherapy is lower than that of SCC. In addition, cervical adenocarcinoma screening is less effective than cervical squamous cell carcinoma. The abnormal performance of ADC in gynecological examination is more insidious than that of SCC. Therefore, improving the early diagnosis rate of cervical adenocarcinoma is of great significance for improving the curative effect of cervical adenocarcinoma.

Infection with high-risk HPV plays a causative role in the development of cervical cancer. Different HPV genotypes presented different carcinogenics. According to the IARC Monograph Working Group, HPV types were classified categorically as carcinogenic (Group 1), probably carcinogenic (Group 2A), possibly carcinogenic (Group 2B), not classifiable (Group 3), or probably not carcinogenic (Group 4). The HR-HPV species A7 (HPV 18, 39, 45, 59 and 68) and A9 (HPV 16, 31, 33, 35, 52 and 58) were included in Group 1 and Group 2A.[10] There are also different correlations between carcinogenic HPV types and different histological manifestations of cervical cancer. Globally, SCC is closely related to HPV16 and its relatives (HPV31, 35 and 52, species A9), while ADC is more closely related to HPV18 and its relatives (HPV39, 45 and 59, species A7).[11,12] In addition, HPV 16, 18, 31, 33, 45, 52, and 58 are mainly associated with SCC and ADC worldwide.[13] In addition to HPV 16 and 18, it is especially worth noting that HPV 31, 33, 52, and 58 have a higher frequency in Chinese women,[14,15] indicating geographical differences in the distribution of HPV types. A large sample of HPV infection status and genotype research in SCC and ADC is of great significance for the prevention of cervical adenocarcinoma and vaccine development in Chinese women. In China, where cervical cancer screening has not yet been widely adopted, it is also of great significance to further analyze HPV as species A7 and A9 in SCC and ADC.

Therefore, the aim of this retrospective study was to conduct a large-scale analysis of the clinicopathological characteristics and HPV infection characteristics of SCC and ADC. Age stratification was also conducted to provide a useful reference for the diagnosis and management of SCC and ADC.

Methods

Study Design and Population

Patients with cervical squamous cell carcinoma and cervical adenocarcinoma diagnosed by histopathology in Fujian Provincial Maternity and Child Health Hospital from January 1, 2014, to December 31, 2017, were included in this study. Pathology reports, hematoxylin-and-eosin (H&E), and immunohistochemically stained slides of eligible patients were reviewed by two expert pathologists to confirm the initial histologic diagnoses. All participants met the following criteria: (1) the presence of histologically proven cervical squamous cell carcinoma or adenocarcinoma; (2) no history of severe immunodeficiency disease; and (3) no combined malignancy. Subsequent participants were also excluded according to the following criteria: (1) no HPV genotyping results; (2) previous malignancy of other sites. Clinicopathologic information was collected from medical records.

HR-HPV Genotype Test

Polymerase chain reaction-reverse dot blot (PCR-RDB) was used for the analysis of HR-HPV of patients, including 14 HR-HPV genotypes (HPV-16, −18, −31, −33, −35, −39, −45, −51, −52, −56, −58, −59, −66, and −68), in cervical exfoliated cells (Yaneng® Biosciences, ShenZhen, China). The L1 consensus HPV PGMY09/PGMY11 primer set [10] was used to amplify 5 μL of the extracted HPV DNA or control (positive or negative) in the 24-μL reaction system. HPV was amplified in a thermal cycler as follows: 50°C for 15 minutes, 95°C for 10 minutes, followed by denaturation at 94°C for 10 seconds, annealing at 45°C for 90 seconds, and extension at 72°C for 30 seconds for a total of 40 cycles. After amplification, hybridization and RDB on the strips fixed with 23 different type-specific probes were conducted. Positivity could be judged with the naked eye as the blue spots on the strip.

Ethical Considerations

Our study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki (1975, revised in 2013). The Ethics Committees of the Fujian Maternity and Child Health Hospital approved this study (approval number: 2020YJ239).

Statistical Analysis

Mean and standard deviation values were reported for continuous variables with statistical significance determined by *t*-test in invasive adenocarcinoma and invasive squamous cell carcinomas. Values and percentages were also reported. Logistic regression was used to calculate the odds ratio (OR) of different HPV genotypes and clinical characteristics in ADC and SCC. All data were processed using SPSS 22.0 (SPSS). All tests were two-sided with a significance level set to $P < 0.05$.

Results

Characteristics of Included Individuals

In this study, a total of 1,590,476 women were screened for cervical cancer, and 688 cervical cancers were detected, including 554 patients with SCC and 93 patients with ADC (Figure 1). Table 1 presents the general clinicopathological data of the included individuals. The average age of the ADC was 46.25±8.27 years and 47.84±8.76 years in SCC patients (P=0.103). A total of 91.4% (85/93) of patients with ADC were diagnosed with pathological stage IB1, while the rate was 78.2% (433/554) in patients with SCC (P=0.003). Lymphatic metastasis, vascular tumor thrombus and deep muscular layer invasion were more frequent in ADC than in SCC. Regarding tumor markers, SCC was more often abnormal in patients with ADC, but CA 125, CA 153 and CA 199 were more often abnormal among patients with SCC, with a significant difference. CEA showed no differences between SCC and ADC patients.

Infection Characteristics of Different HR-HPV Genotypes in SCC and ADC

Table 2 and Figure 2 show the characteristics of HR-HPV genotypes in the involved participants. The overall HR-HPV infection rate was 91.0% (504/554) in patients with SCC, which was significantly higher than that in patients with ADC (81.7%, 76/93) (P=0.007). Patients in the ADC group were more likely to have multiple infections than patients in the SCC group (31.3% vs 15.5%; P=0.006).

In the detected HR-HPV genotypes of SCC patients, HPV-16 was the most prevalent genotype, which was detected in 388 cases, accounting for 70.0% (388/554) of all SCC patients. The rate decreased to 31.2% (29/93) in patients with ADC (P<0.001). The top 5 prevalent HR-HPV genotypes were HPV-18, −58, −52, −33, and −31 in the SCC cases. For ADC patients, the detection HPV-18 rate was significantly higher than that in the SCC group (45.2% vs 7.0%; P<0.001). HPV-16, −51, −59, −45, −52, and −56 also showed leading prevalence in patients with ADC. When comparing the differences between HR-HPV genotypes in SCC and ADC, other than HPV-18, the proportion of HPV-51 also dropped from 6.5% (6/93) in ADC to 1.6% (9/554) in SCC (P<0.013). The difference in the proportion of HPV-33 and HPV-58 in SCC patients was also statistically significant compared with that in ADC and SCC patients (Figure 2 and Table 2).

A subgroup analysis was also conducted with different HPV species in ADC and SCC patients. α9 HR-HPV showed a high frequency in patients with SCC, accounting for 82.1% (455/554). The rate decreased to 33.3% (31/93) in ADC patients (P<0.001). However, ADC patients were more often infected with α 5/6 HR-HPV and α 7 HR-HPV, with prevalence rates of 10.8% (10/93) and 50.5% (47/93), respectively. (P=0.031; P<0.001).

Age Stratification Analysis of HR-HPV in ADC and SCC

Age correlation analysis was also carried out in this study (Figure 3). After age stratification, age between 35–44 (32.26%) and age between 45–54 years (48.39%) presented two onset age peaks in ADC (Figure 3A). In patients with SCC, the onset age peaks were 45–54 years (41.16%) (Figure 3B). The HR-HPV infection rates in ADC for different age groups were 83.3% (<35 years old), 81.0% (35–45 years old), 83.3% (45–54 years old), and 77.8% (≥55 years old)

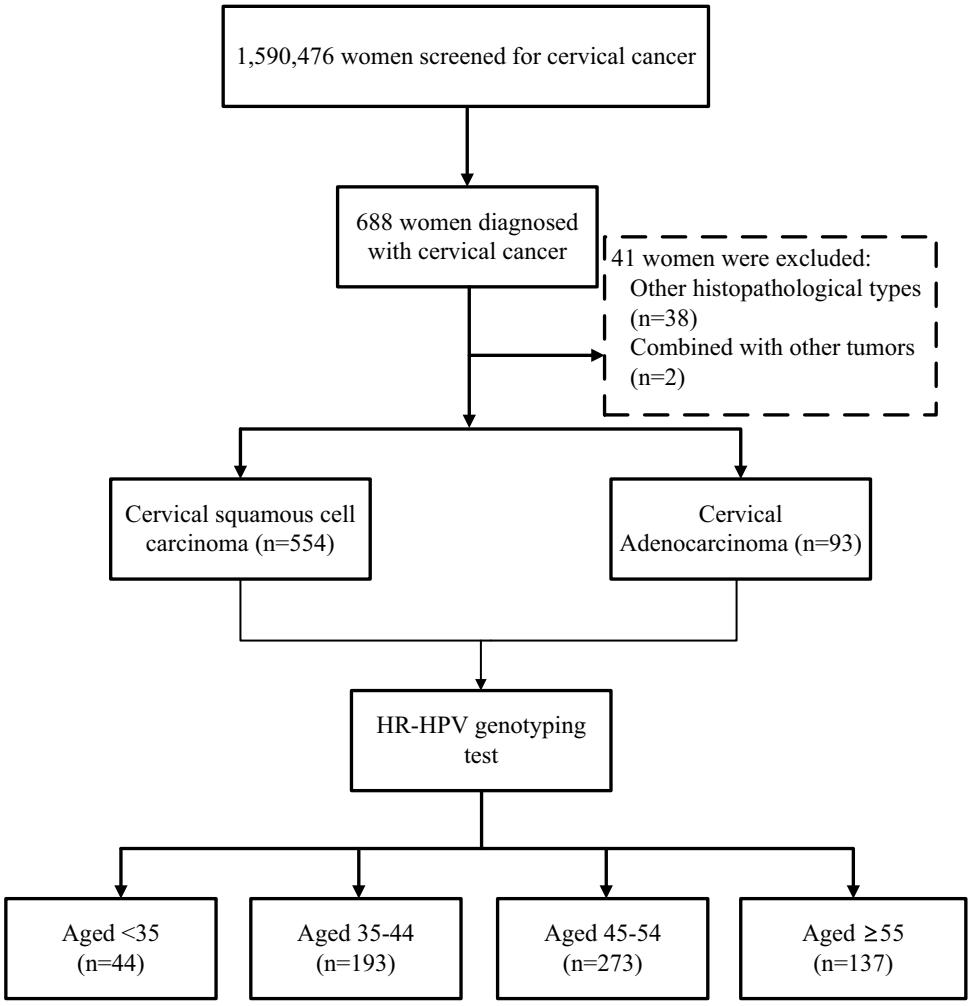

Figure 1 Flowchart of the study.
Abbreviation: HR-HPV, high-risk human papillomavirus.

(Figure 3C). In SCC patients, the HPV infection rate showed a head-tail bimodal trend in age, and the HPV infection rate was highest in patients aged <35 years (100.0%), followed by patients aged ≥55 years (93.5%) (Figure 3D).

The most prevalent HR-HPV genotypes were variable in different populations in ADC and SCC (Figure 3E–H). In the age<35 group, HPV-16 was the most prevalent genotype in both ADC and SCC (50.0% in ADC; 89.2% in SCC). In the 35–44 age group, HPV-16 was still the most prevalent in SCC (71.8%), but the prevalence of both HPV16 and HPV18 in ADC was 40.5%. In SCC aged between 45–54 years, the top 5 rates were HPV-16, −58, −52, −51, and −31, but they were HPV-18, −16, −51, −68, and −52 in ADC cases. The HPV-16 genotype still accounts for the greatest proportion of SCC patients aged ≥55 years old, followed by HPV-58, −52, −59, and −33, from highest to lowest. The most prevalent genotypes were HPV-18, −16, −45, −52, −56 and −39 in cases with ADC.

Risk of Cervical Invasive Adenocarcinoma and Invasive Squamous Cell Carcinoma in Women Infected with Different HR-HPV Genotypes

Table 3 presents the risk factors for women with cervical invasive adenocarcinoma and invasive squamous cell carcinoma. The results showed that SCC patients had a higher risk of infection with HR-HPV than ADC patients (OR, 0.497; 95% CI, 0.279–0.884; $p < 0.017$). In different HR-HPV genotypes, compared with SCC, HPV-18 infection manifested the greatest differences in ADC (OR, 12.109; 95% CI, 7.470–19.631; $p < 0.001$). Other HR-HPV genotypes that were more often to occur in ADC were as follows: HPV-45 (OR, 4.150; 95% CI, 1.114–15.461; $P < 0.034$), HPV-51

Table 1 Characteristics of the Participants in This Study

	Invasive Adenocarcinoma (n=93)	Invasive Squamous Cell Carcinomas (n=554)	*P*-value
Age	46.25±8.27	47.84±8.76	0.103
Menopause			0.008
Pre-	71.0%(66/93)	56.3%(312/554)	
Post-	29.0%(27/93)	43.7%(242/554)	
BMI	22.84±3.22	23.09±3.08	0.471
FIGO2009			0.003
<IB1	8.6%(8/93)	21.8%(121/554)	
≥IB1	91.4%(85/93)	78.2%(433/554)	
Symptom			0.119
Yes	31.2%(29/93)	23.6%(131/554)	
No	68.8%(64/93)	76.4%(423/554)	
Lymphatic Metastasis			0.140
Yes	9.7%(9/93)	15.5%(86/554)	
No	90.3%(84/93)	84.5%(468/554)	
Vascular tumor thrombus			<0.001
Yes	3.2%(3/93)	28.2%(156/554)	
No	96.8%(90/93)	71.8%(398/554)	
Deep muscular layer invasion			0.803
Yes	40.9%(38/93)	42.2%(234/554)	
No	59.1%(55/93)	57.5%(320/554)	
Tumor diameter			0.022
<2cm	21.5%(20/93)	12.6% (70/554)	
≥2cm	78.5%(73/93)	87.4% (484/554)	
HR-HPV			0.005
Negative	18.3%(17/93)	8.8%(49/554)	
Positive	81.7%(76/93)	91.2%(505/554)	
SCC(ng/mL)			<0.001
<1.5	76.3%(71/93)	49.5%(274/554)	
≥1.5	23.7%(22/93)	50.5%(280/554)	
CA125(U/mL)			<0.001
<35	78.5%(73/93)	91.7%(508/554)	
≥35	21.5%(20/93)	8.3%(46/554)	
CA153(U/mL)			0.020
<31	95.7%(89/93)	98.9%(548/554)	
≥31	4.3%(4/93)	1.1%(6/554)	
CA199(U/mL)			<0.001
<37	79.6%(74/93)	94.7%(525/554)	
≥37	20.4%(19/93)	5.3%(29/554)	
CEA(ng/mL)			0.327
	88.2%(82/93)	91.3%(506/554)	
	11.8%(11/93)	8.7% (48/554)	

Abbreviations: BMI, body mass index, FIGO2009, 2009 versions of International Federation of Gynecology and Obstetrics clinical staging of cervical cancer; SCC, Squamous Cell Carcinoma Antigen; HR-HPV, high-risk human papillomavirus.

Table 2 Infection Characteristics of Different Genotypes of HR-HPV in Participants with Cervical Adenocarcinoma and Squamous Cell Carcinoma

HR-HPV	Invasive Adenocarcinoma (n=93)	Invasive Squamous Cell Carcinomas (n=554)	P-value
HR-HPV			0.005
Negative	18.3%(17/93)	8.8% (49/554)	
Positive	81.7%(76/93)	91.2%(505/554)	
HPV16			<0.001
Negative	68.8%(64/93)	30.0%(166/554)	
Positive	31.2%(29/93)	70.0%(388/554)	
HPV18			<0.001
Negative	54.8%(51/93)	93.0%(515/554)	
Positive	45.2%(42/93)	7.0%(39/554)	
HPV31			0.373
Negative	98.9%(92/93)	96.6%(535/554)	
Positive	1.1%(1/93)	3.4%(19/554)	
HPV33			0.065
Negative	100.0%(93/93)	95.3%(528/554)	
Positive	0.0%(0/93)	4.7%(26/554)	
HPV35			0.672
Negative	100.0%(93/93)	98.9%(548/554)	
Positive	0.0%(0/93)	1.1%(6/554)	
HPV39			0.672
Negative	100.0%(93/93)	98.9%(548/554)	
Positive	0.0%(0/93)	1.1%(6/554)	
HPV45			0.614
Negative	96.8%(90/93)	98.2%(544/554)	
Positive	3.2%(3/93)	1.8%(10/554)	
HPV51			0.013
Negative	93.5%(87/93)	98.4%(545/554)	
Positive	6.5%(6/93)	1.6%(9/554)	
HPV52			0.717
Negative	96.8%(90/93)	95.3%(528/554)	
Positive	3.2%(3/93)	4.7%(26/554)	
HPV56			0.885
Negative	96.8%(90/93)	97.7%(541/554)	
Positive	3.2%(3/93)	2.3(13/554)	
HPV58			0.034
Negative	100.0%(93/93)	94.2%(522/554)	
Positive	0.0%(0/93)	5.8%(32/554)	
HPV59			0.148
Negative	93.5%(87/93)	97.1%(538/554)	
Positive	6.5%(6/93)	2.9%(16/554)	
HPV66			0.723
Negative	97.8%(91/93)	98.9%(548/554)	
Positive	2.2%(2/93)	1.1%(6/554)	

(*Continued*)

Table 2 (Continued).

HR-HPV	Invasive Adenocarcinoma (n=93)	Invasive Squamous Cell Carcinomas (n=554)	P-value
HPV68			0.448
Negative	100.0%(93/93)	98.4%(545/554)	
Positive	0.0%(0/93)	1.6%(9/554)	
16/18 types			0.033
Negative	20.4%(19/93)	12.3%(68/554)	
Positive	79.6%(74/93)	87.7%(486/554)	
Non-16/18 types			0.305
Negative	78.5%(73/93)	73.5%(407/554)	
Positive	21.5%(20/93)	26.5%(147/554)	
α 5/6 HR-HPV			0.031
Negative	89.2%(83/93)	94.9%(526/554)	
Positive	10.8%(10/93)	5.1%(28/554)	
α 7 HR-HPV			<0.001
Negative	49.5%(46/93)	85.6%(474/554)	
Positive	50.5%(47/93)	14.4%(80/554)	
α 9 HR-HPV			<0.001
Negative	66.7%(62/93)	17.9%(99/554)	
Positive	33.3%(31/93)	82.1%(455/554)	
HR-HPV			0.006
Single infection	68.8%(33/48)	84.5%(424/502)	
Multiple infection	31.3%(15/48)	15.5%(78/502)	

Abbreviations: α 5/6, alpha 5/6; α 7, alpha 7; α 9, alpha 9; HR-HPV, high-risk human papillomavirus.

(OR, 3.109; 95% CI, 1.077–9.892; p = 0.045), HPV-59 (OR, 1.607; 95% CI, 0.507–5.088; P= 0.420), HPV-56 (OR, 1.392; 95% CI, 0.379–5.118; p = 0.609), and HPV-68 (OR, 1.247; 95% CI, 0.256–6.068; P= 0.785). For HPV species, ADC patients were at higher risk of α 7 HR-HPV infection than SCC patients (OR, 8.574; 95% CI, 5.472–13.434; p < 0.001), while α 9 HR-HPV infection was more likely to occur in SCC patients than ADC patients (OR, 0.099; 95% CI, 0.063–0.156; P< 0.001). Regarding tumor markers, ADC patients presented a higher frequency of increases in CA125≥35, CA153≥31 and CA199≥37 than SCC patients (OR, 2.562; 95% CI, 1.578–4.158; P< 0.001), (OR, 3.358; 95% CI, 0.646–17.448; P =0.015), (OR, 3.653; 95% CI, 1.726–7.733; P< 0.001).

Discussion

Due to the extensive promotion and development of HPV primary screening in clinical practice,[16] the vast majority of cervical precancerous lesions have been detected earlier and earlier. In the past few decades, the incidence of cervical cancer in developed countries has decreased significantly, especially the decline in the incidence of SCC. While ADC is a relatively rare pathological type, its incidence has been increasing year by year in recent years.[6–8,17] The increase is especially obvious in young women. In addition, ADC presented a poorer prognosis than concurrent SCC; however, the screening of ADC is not as effective as that of SCC. HPV infection plays an important role in the occurrence and development of cervical cancer. Therefore, it is of great significance for the prevention and treatment of cervical adenocarcinoma to study the genotype and age distribution of HPV infection in large samples of ADC. In this retrospective study, we evaluated the clinicopathological characteristics and HPV infection characteristics of SCC and ADC with age stratification on a large scale in China.

HPV has long been the central cause of cervical cancer.[10,18] However, individual HPV genotypes differ greatly in their relative oncogenic potential, and HPV-16 and −18 are viewed as the most oncogenic genotypes, but the

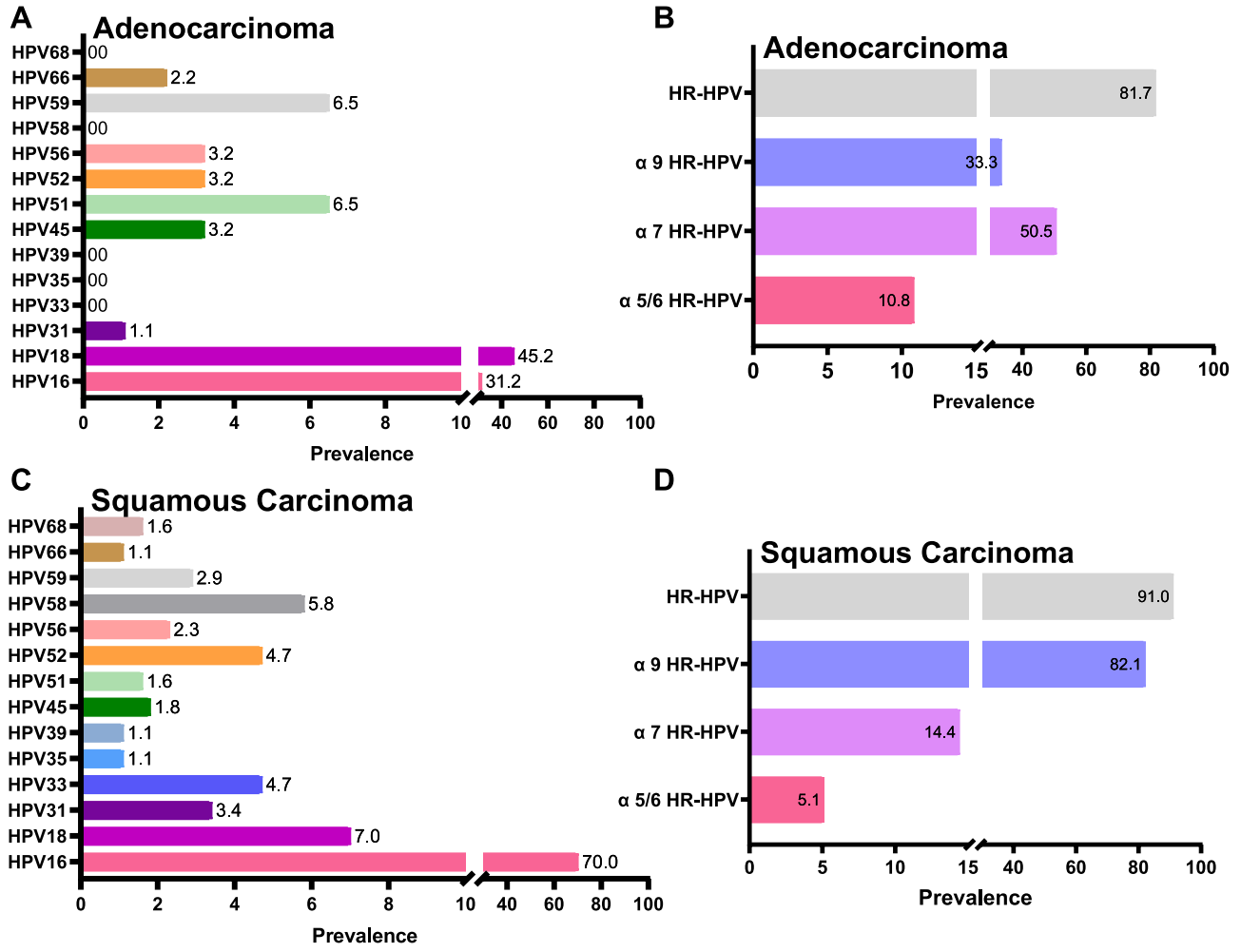

Figure 2 HPV infection rates in patients with ADC and SCC.
Notes: (**A**) HR-HPV genotype infection rates in patients with ADC. (**B**) HR-HPV species infection rates in patients with ADC; (**C**) HR-HPV genotype infection rates in patients with SCC; (**D**) HR-HPV species infection rates in patients with SCC.
Abbreviations: ADC, cervical adenocarcinoma; SCC, cervical squamous cell carcinoma; HPV, human papillomavirus.

prevalence differs greatly in different cervical pathological types.[19,20] In our study, compared with ADC, SCC showed a significantly higher HPV prevalence rate (91.0% vs 81.7%), which suggested that the current screening efficiency of ADC is not as effective as that of SCC. As HPV-based testing has been recommended as the primary screening method in cervical cancer, this may explain why the incidence of SCC has decreased while that of adenocarcinoma has increased in recent years. In clinical practice, more vigilance and effective screening methods are needed for ADC. Our results also confirmed that in the cases of SCC, HPV-16 is the predominant HPV genotype, followed by HPV-58, and HPV-18 was in third place, in line with the reports of other articles.[20,21] In cases with ADC, HPV-18 presented a much higher prevalence than that in SCC (45.2% vs 7.0%), and the ratio of HPV-18 to HPV-16 was 1.5. The results are higher than the conclusions of other studies.[22] These results suggested that special attention should be given to the close follow-up, diagnosis and treatment of patients infected with HPV-16 and −18 in clinical work to achieve early detection and early treatment and reduce the incidence. According to the IARC Monograph Working Group, the HR-HPV species A7 and A9 are carcinogenic and probably carcinogenic.[10] In this study, the most common HR-HPV species was A9, followed by A7, in patients with SCC. Women with ADC were mostly infected with species A7.

After age stratification, both SCC and ADC showed an onset peak in the age group of 35–54 years, exceeding 70% of all included patients, which means that the incidence of cervical cancer has a younger trend. This phenomenon may be

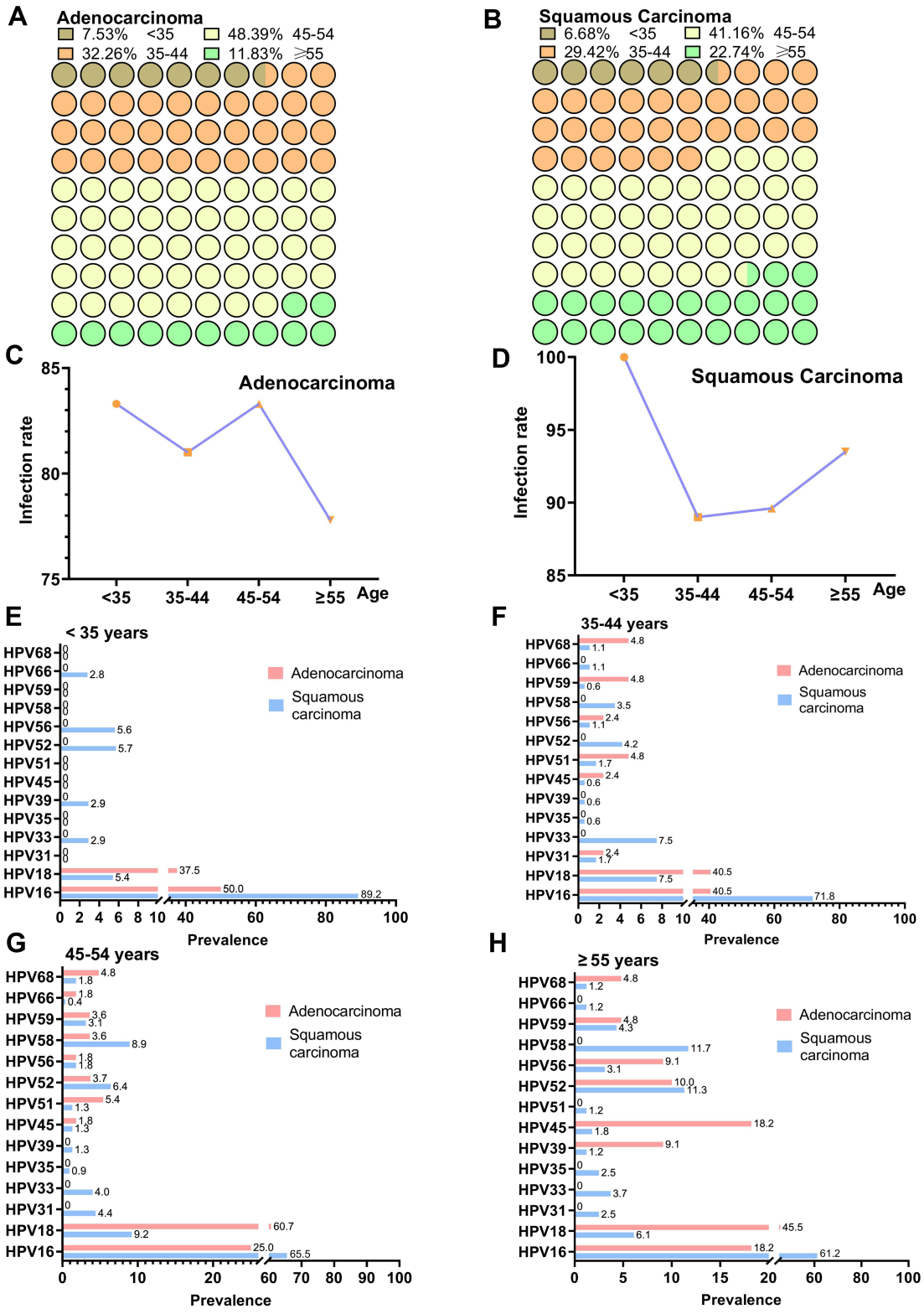

Figure 3 Age stratification analysis of HPV in patients with ADC and SCC.

Notes: (**A**) The distribution of ADC patients in different age groups. (**B**) The distribution of SCC patients in different age groups. (**C**) The age distribution characteristics of HR-HPV in ADC patients. (**D**) The age distribution characteristics of HR-HPV in SCC patients. (**E**) The prevalence of HPV genotypes in patients with ADC and SCC aged <35 years; (**F**) The prevalence of HPV genotypes in patients with ADC and SCC aged 35–45 years. (**G**) The prevalence of HPV genotypes in patients with ADC and SCC aged <45–54 years old. (**H**) The prevalence of HPV genotypes in patients with ADC and SCC aged ≥55 years old.

Abbreviations: ADC, cervical adenocarcinoma; SCC, cervical squamous cell carcinoma; HPV, human papillomavirus.

Table 3 Risk of Cervical Invasive Adenocarcinoma and Invasive Squamous Cell Carcinoma in Women Infected with Different HR-HPV Genotypes

HR-HPV Types	OR Invasive Squamous Cell Carcinomas [n=554, OR(95% CI)]	OR Invasive Adenocarcinoma [n=93, OR(95% CI)][a]	*P*-value
HR-HPV(+)	Reference (OR=1.000)	0.497(0.279–0.884)	0.017
HPV16(+)	Reference (OR=1.000)	0.198(0.128–0.308)	<0.001
HPV18(+)	Reference (OR=1.000)	12.109(7.470–19.631)	<0.001
HPV31(+)	Reference (OR=1.000)	0.279(0.036–2.136)	0.219
HPV33(+)	Reference (OR=1.000)	0.000(0.000–1.000)	0.998
HPV35(+)	Reference (OR=1.000)	0.000(0.000–1.000)	0.999
HPV39(+)	Reference (OR=1.000)	0.845(0.100–7.169)	0.878
HPV45(+)	Reference (OR=1.000)	4.150(1.114–15.461)	0.034
HPV51(+)	Reference (OR=1.000)	3.109(1.077–9.892)	0.045
HPV52(+)	Reference (OR=1.000)	0.440(0.132–1.466)	0.181
HPV56(+)	Reference (OR=1.000)	1.392(0.379–5.118)	0.609
HPV58(+)	Reference (OR=1.000)	0.240(0.057–0.817)	0.043
HPV59(+)	Reference (OR=1.000)	1.607(0.507–5.088)	0.420
HPV66(+)	Reference (OR=1.000)	0.898(0.104–7.739)	0.922
HPV68(+)	Reference (OR=1.000)	1.247(0.256–6.068)	0.785
α 5/6 HR-HPV	Reference (OR=1.000)	1.892(0.851–4.207)	0.118
α 7 HR-HPV	Reference (OR=1.000)	8.574(5.472–13.434)	<0.001
α 9 HR-HPV	Reference (OR=1.000)	0.099(0.063–0.156)	<0.001
Post-menopause	Reference (OR=1.000)		
FIGO2009≥IB1	Reference (OR=1.000)	3.731(2.015–6.907)	<0.001
Vascular tumor thrombus	Reference (OR=1.000)	0.252(0.139–0.456)	<0.001
Tumor diameter≥2cm	Reference (OR=1.000)	0.407(0.220–0.754)	0.004
SCC≥1.5	Reference (OR=1.000)	0.277(0.181–0.422)	<0.001
CA125≥35	Reference (OR=1.000)	2.562(1.578–4.158)	<0.001
CA153≥31	Reference (OR=1.000)	3.358(0.646–17.448)	0.150
CA199≥37	Reference (OR=1.000)	3.653(1.726–7.733)	0.001

Notes: [a]Risk (OR) of invasive adenocarcinoma when the variable is positive, as compared with invasive squamous cell carcinoma of the cervix.
Abbreviation: OR, odds ratio.

explained by the earlier age of sexual life in Chinese women; however, the HPV vaccine has not been fully popularized and promoted in China. It is a debatable question whether the screening age of cervical lesions should be advanced. For HPV, there were two peaks of HR-HPV prevalence in the ADC women who were <35 years and 45–54 years, respectively, and the prevalence showed a downward trend with age after 55 years. In SCC women, a head-tail bimodal trend of HPV infection in age was presented in age<35 years and ≥55 years. However, the onset age peaks were women

aged between 45–54 years (41.16%). Although SCC patients had the highest HPV-16 infection rate regardless of age group, HPV-16 infection was highest among SCC patients <35 years old. Indeed, although HR-HPV infections are more frequent in younger women than in elderly women, the risk of persistent infections increases with age,[23,24] which leads to a higher risk of cervical lesions. Thus, more attention needs to be paid to elderly women with HPV-16 infection in clinical practice. In addition, in this study, there was a phenomenon in which the HR-HPV infection rate varied with the age of patients with ADC. HPV-18 is recognized as the most common HPV genotype among ADC, but there are age differences in its prevalence. Our results show that the infection rate of HPV-18 exceeds that of HPV-16 only in people aged 45–54 and ≥55 years in ADC patients. In the age range of 45–54 years, HPV-18 infection is overwhelming, which may be due to the peak incidence of ADC being 45–54 years old in this study.

We also evaluated the risk of cervical invasive adenocarcinoma and invasive squamous cell carcinoma in women infected with different HR-HPV genotypes. HPV-18 infection was found to have the highest correlation with the incidence of ADC (OR, 12.109; 95% CI, 7.470–19.631; P< 0.001), which is consistent with other studies.[15] HPV-45 and HPV-51 were also found to be associated with the occurrence of ADC rather than SCC. In addition, our study also suggested that species A9 infection was overwhelming in women with ADC. HPV-45 and HPV-51 were also found to be associated with the occurrence of ADC rather than SCC. Therefore, HPV-18, −45, and −51 infections and HPV species A9 could be used to triage patients who are at high risk for ADC. HPV-16 infection greatly increased the risk of having histological SCC. According to our results, species A9 infection showed an estimated OR of 0.099 (95% CI, 0.063–0.156) for histological ADC compared with SCC, which indicates a high risk of A9 species infection in SCC patients.

Although great progress has been made in the screening and management of HPV-related women and cervical lesions, serum biomarkers are still needed to further improve the monitoring, diagnosis and prognosis of cervical cancer.[25] Squamous cell carcinoma antigen (SCCa) is the most widely used and reliable tumor marker of SCC.[26] The CA125 protein is an important antigen of ovarian cancer and is mainly used for the early prognosis of ovarian cancer and cervical cancer.[27,28] In our study, the tumor marker SCC was closely related to the incidence of the increase in SCC. However, CA125≥35 was more easily abnormal in ADC patients. CA153≥31 and CA199≥37 also presented a high frequency of abnormality for ADC patients. Other risk factors were also analyzed. In our study, the presence of FIGO 2009≥IB1 was found to occur more often in ADC patients, which meant that ADC patients more often had an advanced stage. Vascular tumor thrombus and tumor diameter ≥2 cm were more often present in SCC patients.

Despite the large sample size and the rigorous classification, our study suffers from several limitations. First, this is a hospital-based retrospective study requiring a short sample collection time, which makes it difficult to avoid selection bias. In addition, since only central hospitals were selected for cooperation, case recruitment in urban areas may be higher than that in rural areas. This is a retrospective study, and more mechanistic and prospective studies are needed to further explore the relationship between HPV and SCC and ADC.

Conclusions

In conclusion, both SCC and ADC showed an onset peak in the age group of 35–54 years. HPV-16 was much more prevalent than HPV-18 in SCC, regardless of age. The prevalence of HPV-18 exceeds HPV-16 only in ADC patients aged ≥45 years. Future work should focus on the evaluation of HPV genotypes in large-scale follow-up and different populations.

Data Sharing Statement

The data used and/or analyzed in the present study are available from the corresponding author Liying Zhong (zhongliying@fjmu.edu.cn) on reasonable request.

Ethics Approval and Consent to Participate

We confirm that our study complies with the Declaration of Helsinki. The study protocol was approved by the ethics committee of Fujian Maternal and Child Health Hospital (approval number: 2020YJ239). Informed consent in our study was waived because of retrospective and anonymous analysis.

Acknowledgments

We thank all participants of this study and the staff of the laboratory and medical record section from Fujian Maternal and Child Health Hospital for their help with technical assistance and information service.

Funding

This work was supported by the Fujian Provincial Maternity and Child Hospital Natural Science Foundation (grant no. YCXM19-07).

Disclosure

The authors declare that they have no competing interests in this work.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68(6):394–424. doi:10.3322/caac.21492
2. Mishra GA, Pimple SA, Shastri SS. An overview of prevention and early detection of cervical cancers. *Indian J Med Paediatr Oncol*. 2011;32(3):125–132. doi:10.4103/0971-5851.92808
3. Arbyn M, Weiderpass E, Bruni L, et al. Estimates of incidence and mortality of cervical cancer in 2018: a worldwide analysis. *Lancet Glob Health*. 2020;8(2):e191–e203. doi:10.1016/S2214-109X(19)30482-6
4. Spriggs AI, Boddington MM. Progression and regression of cervical lesions. Review of smears from women followed without initial biopsy or treatment. *J Clin Pathol*. 1980;33(6):517–522. doi:10.1136/jcp.33.6.517
5. Kosary CL. FIGO stage, histology, histologic grade, age and race as prognostic factors in determining survival for cancers of the female gynecological system: an analysis of 1973–87 SEER cases of cancers of the endometrium, cervix, ovary, vulva, and vagina. *Semin Surg Oncol*. 1994;10(1):31–46. doi:10.1002/ssu.2980100107
6. Mathew A, George PS. Trends in incidence and mortality rates of squamous cell carcinoma and adenocarcinoma of cervix--worldwide. *Asian Pac J Cancer Prev*. 2009;10(4):645–650.
7. Vizcaino AP, Moreno V, Bosch FX, et al. International trends in incidence of cervical cancer: II. Squamous-cell carcinoma. *Int J Cancer*. 2000;86(3):429–435. doi:10.1002/(SICI)1097-0215(20000501)86:3<429::AID-IJC20>3.0.CO;2-D
8. Wang SS, Sherman ME, Hildesheim A, Lacey JV Jr, Devesa S. Cervical adenocarcinoma and squamous cell carcinoma incidence trends among white women and black women in the United States for 1976–2000. *Cancer*. 2004;100(5):1035–1044. doi:10.1002/cncr.20064
9. Davy ML, Dodd TJ, Luke CG, Roder DM. Cervical cancer: effect of glandular cell type on prognosis, treatment, and survival. *Obstet Gynecol*. 2003;101(1):38–45. doi:10.1016/s0029-7844(02)02275-5
10. Bouvard V, Baan R, Straif K, et al. A review of human carcinogens--part B: biological agents. *Lancet Oncol*. 2009;10(4):321–322. doi:10.1016/S1470-2045(09)70096-8
11. Bosch FX, Lorincz A, Muñoz N, Meijer CJ, Shah KV. The causal relation between human papillomavirus and cervical cancer. *J Clin Pathol*. 2002;55(4):244–265. doi:10.1136/jcp.55.4.244
12. Altekruse SF, Lacey JV Jr, Brinton LA, et al. Comparison of human papillomavirus genotypes, sexual, and reproductive risk factors of cervical adenocarcinoma and squamous cell carcinoma: northeastern United States. *Am J Obstet Gynecol*. 2003;188(3):657–663. doi:10.1067/mob.2003.132
13. Smith JS, Lindsay L, Hoots B, et al. Human papillomavirus type distribution in invasive cervical cancer and high-grade cervical lesions: a meta-analysis update. *Int J Cancer*. 2007;121(3):621–632. doi:10.1002/ijc.22527
14. Sun P, Song Y, Ruan G, et al. Clinical validation of the PCR-reverse dot blot human papillomavirus genotyping test in cervical lesions from Chinese women in the Fujian province: a hospital-based population study. *J Gynecol Oncol*. 2017;28(5):e50. doi:10.3802/jgo.2017.28.e50
15. Li N, Franceschi S, Howell-Jones R, Snijders PJ, Clifford GM. Human papillomavirus type distribution in 30,848 invasive cervical cancers worldwide: variation by geographical region, histological type and year of publication. *Int J Cancer*. 2011;128(4):927–935. doi:10.1002/ijc.25396
16. Perkins RB, Guido RS, Castle PE, et al. Erratum: 2019 ASCCP risk-based management consensus guidelines for abnormal cervical cancer screening tests and cancer precursors. *J Low Genit Tract Dis*. 2021;25(4):330–331. doi:10.1097/LGT.0000000000000628
17. Kumar N, Gupta R, Gupta S. Glandular cell abnormalities in cervical cytology: what has changed in this decade and what has not? *Eur J Obstet Gynecol Reprod Biol*. 2019;240:68–73. doi:10.1016/j.ejogrb.2019.06.006
18. Muñoz N, Bosch FX, de Sanjosé S, et al. Epidemiologic classification of human papillomavirus types associated with cervical cancer. *N Engl J Med*. 2003;348(6):518–527. doi:10.1056/NEJMoa021641
19. Lo KW, Wong YF, Chan MK, et al. Prevalence of human papillomavirus in cervical cancer: a multicenter study in China. *Int J Cancer*. 2002;100(3):327–331. doi:10.1002/ijc.10506
20. de Sanjose S, Quint WG, Alemany L, et al. Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study. *Lancet Oncol*. 2010;11(11):1048–1056. doi:10.1016/S1470-2045(10)70230-8
21. Bhatla N, Lal N, Bao YP, Ng T, Qiao YL. A meta-analysis of human papillomavirus type-distribution in women from South Asia: implications for vaccination. *Vaccine*. 2008;26(23):2811–2817. doi:10.1016/j.vaccine.2008.03.047
22. Chen W, Molijn A, Enqi W, et al. The variable clinicopathological categories and role of human papillomavirus in cervical adenocarcinoma: a hospital based nation-wide multi-center retrospective study across China. *Int J Cancer*. 2016;139(12):2687–2697. doi:10.1002/ijc.30401
23. Schiffman M, Rodríguez AC. Heterogeneity in CIN3 diagnosis. *Lancet Oncol*. 2008;9(5):404–406. doi:10.1016/S1470-2045(08)70110-4
24. McCredie MR, Sharples KJ, Paul C, et al. Natural history of cervical neoplasia and risk of invasive cancer in women with cervical intraepithelial neoplasia 3: a retrospective cohort study. *Lancet Oncol*. 2008;9(5):425–434. doi:10.1016/S1470-2045(08)70103-7

25. Charakorn C, Thadanipon K, Chaijindaratana S, Rattanasiri S, Numthavaj P, Thakkinstian A. The association between serum squamous cell carcinoma antigen and recurrence and survival of patients with cervical squamous cell carcinoma: a systematic review and meta-analysis. *Gynecol Oncol*. 2018;150(1):190–200. doi:10.1016/j.ygyno.2018.03.056
26. Zhou Z, Li W, Zhang F, Hu K, Consolaro MEL. The value of squamous cell carcinoma antigen (SCCa) to determine the lymph nodal metastasis in cervical cancer: a meta-analysis and literature review. *PLoS One*. 2017;12(12):e0186165. doi:10.1371/journal.pone.0186165
27. Boichenko AP, Govorukhina N, Klip HG, et al. A panel of regulated proteins in serum from patients with cervical intraepithelial neoplasia and cervical cancer. *J Proteome Res*. 2014;13(11):4995–5007. doi:10.1021/pr500601w
28. Sasaki A, Akita K, Ito F, Mori T, Kitawaki J, Nakada H. Difference in mesothelin-binding ability of serum CA125 between patients with endometriosis and epithelial ovarian cancer. *Int J Cancer*. 2015;136(8):1985–1990. doi:10.1002/ijc.29185