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Human papillomavirus genotype and prognosis of cervical cancer: Favorable survival of patients with HPV16-positive tumors

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ABSTRACT

The prognostic impact of human papillomavirus (HPV) type on invasive cervical cancer (ICC) was analyzed for 137 women treated for ICC at a single institution between 1999 and 2007. The study subjects were divided into three groups according to HPV genotype: HPV16-positive (n = 59), HPV18-positive (n = 33), and HPV16/18-negative ICC (non-HPV16/18, n = 45). The median follow-up time was 102.5 months (range, 5–179). The 10-year overall survival (10y-OS) rates in women with FIGO stage I/II disease were similar among HPV genotypes: 94.7% for HPV16 (n = 39), 95.2% for HPV18 (n = 26), and 96.4% for non-HPV16/18 (n = 29). However, the 10y-OS rates in women with FIGO stage III/IV tumors were 73.7% for HPV16 (n = 20), 45.7% for HPV18 (n = 7), and 35.7% for other types (n = 16), with significantly higher survival in HPV16-positive compared with HPV16-negative ICC (10y-OS; 73.7% vs. 39.5%, P = 0.04). This difference in FIGO stage III/IV tumors remained significant after adjusting for age and histology (hazard ratio 0.30, 95% confidence interval 0.09–0.86, P = 0.02). These results suggest that detection of HPV16 DNA may be associated with a favorable prognosis in patients with FIGO stage III/IV ICC. Given that most women with FIGO stage III/IV tumors received concurrent chemoradiotherapy, this finding may imply that HPV16-positive tumors are more chemoradiosensitive.

1. Introduction

Infection with a high-risk human papillomavirus (HPV) is an established major risk factor for the development of cervical cancer [1]. HPV16 is the most common genotype detected in invasive cervical cancer (ICC) worldwide, followed by HPV18, while the 3rd and 4th most common HPV types vary geographically [2]. Eight HPV genotypes (16, 18, 31, 33, 35, 45, 52, and 58) have been shown to confer higher risks of progression to cervical cancer and its immediate premalignant lesions (cervical intraepithelial neoplasia [CIN] grade 3) compared with other high-risk and low-risk HPV types in Japan [3,4]. Based on these data, the clinical guidelines issued by the Japan Society of Obstetrics and Gynecology and the Japan Association of Obstetricians and Gynecologists recommend a CIN-management algorithm that incorporates HPV genotyping for risk stratification of progression to CIN3 [5].

However, the association between HPV genotype and the prognosis of ICC remains controversial. Many studies have reported that HPV18-positive tumors are associated with a poor prognosis [6–11], while others failed to identify this relationship [12–17]. Some groups suggested that HPV16-positive and HPV16/18- positive tumors were associated with better survival in Chinese and British populations, respectively [12,13], while favorable outcomes were reported for HPV58-positive tumors in one Taiwanese population [14], and for HPV31-positive tumors in another Taiwanese study [15]. In contrast, other studies found no associations between HPV genotype and cervical cancer prognosis in Russian and Korean populations [16,17]. These conflicting results may be at least partially due to geographical differences in HPV-type prevalences.

The present study focused on the impact of HPV types on the survival of Japanese patients with ICC. We previously analyzed short-term follow-up data from three institutions (median follow-up, 33 months) and found that HPV18-positive tumors were associated with poor survival [8]. In the current study, we analyzed long-term follow-up data for a different ICC cohort from a single hospital (median follow-up, 102 months). The results suggested that HPV16-positive tumors may be associated with favorable survival, compared with poorer survival of patients with HPV18-positive tumors.

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2. Methods

2.1. Study design

We previously analyzed HPV DNA data for 2282 Japanese women (1517 normal cytology, 318 CIN grade 1, 307 CIN2–3, and 140 ICC) who visited the University of Tsukuba Hospital or Ibaraki Seinan Medical Center Hospital for screening or treatment of cervical diseases between 1999 and 2007 [2]. The present study focused on the prognostic impact of HPV types on ICC, based on the follow-up data for patients with ICC. Three patients with ICC were treated or followed up at other hospitals, and we therefore analyzed the clinical data for 137 patients who were treated and followed up for ICC at the University of Tsukuba Hospital. Written informed consent was obtained from all patients. The institute ethical and research review board approved the study protocol.

2.2. HPV genotyping

HPV DNA genotyping was carried out by PCR-based assay, as described previously [18]. In brief, exfoliated cells from the ectocervix and endocervix were collected in a tube containing 1 ml of PBS and stored at −30 °C until DNA extraction. Total cellular DNA was extracted from cervical samples by a standard SDS-proteinase K procedure. HPV DNA was amplified by PCR using consensus-primers (L1C1/L1C2 + L1C2M) for the HPV L1 region. A reaction mixture without template DNA was included in every set of PCR runs as a negative control. Primers for a fragment of the β-actin gene were used as a control to rule out false-negative results in samples with no detectable HPV DNA. HPV types were identified by restriction fragment length polymorphism (RFLP), which has been shown to identify at least 26 types of genital HPVs [18].

2.3. Statistical analysis

With the sample size of 137 patients, the present study had > 80% statistical power to detect a relative reduction of 20% in the rate of death in women with HPV16-positive ICC as compared with those with HPV16-negative ICC, assuming a 10-year overall survival rate of 70% in the HPV16-negative group, with the use of a two-sided test at an alpha level of 0.05.

Associations between HPV genotypes and clinicopathologic data were evaluated using $\chi 2$ or Fisher's exact probability tests as appropriate. Continuous variables were analyzed by Student's *t*-tests. HPV genotype-specific prognoses among women with ICC were estimated using the Kaplan-Meier method and compared with log-rank tests. Because we aimed to calculate cervical cancer-specific survival, patients who died from other diseases were censored as of the date of death. Statistical adjustments were made using the Cox regression model. Age at diagnosis, FIGO stage, histology, and HPV genotype were included in the multivariate model. All analyses were carried out using the JMP® 10.0 statistics packages (SAS Institute Inc., Cary, NC, USA). Two-sided P values were calculated throughout and values < 0.05 were considered to be significant.

3. Results

The clinicopathological characteristics of the patients in this study are summarized in Table 1. Tumors were classified as FIGO stage I in 68 patients (49.6%), stage II in 26 patients (19.0%), stage III in 38 patients (27.7%), and stage IV in five patients (3.7%). Histologic analysis indicated 121 tumors (88.3%) as squamous cell carcinoma (SCC) and 16 (11.7%) as adenocarcinoma (AC), including two cases of adenosquamous carcinoma and one case of clear cell carcinoma. Most stage I/II patients (86%) underwent surgery (with or without adjuvant therapy), while most stage III/IV patients (97.6%) received radiotherapy alone or concurrent chemoradiation therapy (CCRT). The median follow-up period was 102.5 months (range, 5–179).

Based on HPV genotyping results, the study subjects were divided into three groups: HPV16-positive (n = 59, 43.1%), HPV18-positive (n = 33, 24.1%), and HPV16/18-negative (non-HPV16/18; n = 45, 32.8%). Patients positive for other types in addition to HPV16 or HPV18 were classified into the HPV16- or HPV18-positive group, respectively. No patients were positive for both HPV16 and HPV18. The non-HPV16/18 group included nine HPV-negative patients and 36 patients with the following genotypes: HPV31 (n = 2), HPV33 (n = 5), HPV39 (n = 2), HPV51 (n = 1), HPV52 (n = 12), HPV 53 (n = 2), HPV58 (n = 5), HPV68 (n = 1), and undetermined types (n = 6). The mean age of the HPV16/18-positive groups was significantly younger than that of the non-HPV16/18 group (47.2 vs. 53.1 years, P = 0.02), in keeping with our previous study [8]. There was no significant correlation between HPV genotype and FIGO stage. There was a higher proportion of AC in the HPV18-positive compared with the HPV18-negative group (17.7% vs. 9.4%), but the difference was not significant (P = 0.21).

Univariate analysis including tumors of all stages did not identify HPV16 positivity as a significant prognostic factor (Table 2). However, multivariate analysis adjusting for age at diagnosis, FIGO stage, and histology suggested that women with HPV16-positive ICC were likely to have a better prognosis. The difference was marginally significant (hazard ratio [HR] 0.44, 95% confidence interval [CI] 0.15–1.04, P = 0.06).

Treatment modalities differed between early- and late-stage tumors, and we therefore also analyzed survival data for FIGO stage I/II and III/IV tumors separately. The 10-year overall survival (10y-OS) rates were similar among the three groups in women with FIGO stage I/II disease: 94.7% for HPV16, 95.2% for HPV18, and 96.4% for non-HPV16/18 (Fig. 1A). There was also no difference in survival among FIGO stage I/II patients who received adjuvant radiation therapy for high-risk of recurrence (data not shown). However, the 10y-OS rates were 73.7% for HPV16 (n = 20), 45.7% for HPV18 (n = 7), and 35.7% for non-HPV16/18 (n = 16) in women with FIGO stage III/IV tumors (Fig. 1B), with a significant difference between HPV16-positive and HPV16-negative ICC (10y-OS; 73.7% vs. 39.5%, P = 0.04) (Fig. 1C). This difference remained significant even after adjusting for age at diagnosis and histology (HR 0.30, 95%CI 0.09–0.86, P = 0.02), demonstrating that the risk of death was reduced by 70% in patients with HPV16-positive tumors. When the analysis was confined to patients with SCC, the survival of patients with FIGO stage III/IV HPV16-positive cervical SCC was significantly better than that of patients with HPV16-negative tumors (10y-OS; 73.7% vs. 40.7%, P = 0.04). However, we could not perform a sub-analysis for AC because of the small sample size.

We also analyzed survival data by papillomavirus genus species. HPV31, 33, 35, 52 and 58 are phylogenetically related to HPV16, and therefore these types are classified into α9 species [19]. Similarly, HPV18, 39, 45, 59 and 68 are classified into α7 species. The 10y-OS rates were 70.0% for α9 species (n = 30) and 48.6% for α7 species (n = 9) in women with FIGO stage III/IV tumors, but the difference was not statistically significant (P = 0.44).

4. Discussion

Our results suggested that HPV16 positivity may be a favorable prognostic factor in patients with FIGO stage III/IV ICC. These findings were consistent with previous studies reporting poor survival associated with HPV18-positive tumors, in that patients with HPV18-positive tumors had a poorer prognosis than patients with HPV16-positive tumors [6–11]. Unlike these earlier studies, however, tumors positive for other HPV types (HPV31, HPV33, HPV52, HPV58 etc.) had similar prognoses to HPV18-positive tumors, thus suggesting that HPV16-positivity was associated with overall favorable survival. A recent study also reported a favorable prognosis in Chinese patients with HPV16-positive tumors

Table 1
Characteristics of the study subjects according to HPV genotype.

	All	HPV genotype		
	(n = 137)	HPV16 (n = 59)	HPV18 (n = 33)	Non-HPV16/18 (n = 45)
Age				
Mean ± SD (year)	49.2 ± 14.8	49.0 ± 14.1	44.1 ± 14.9	53.1 ± 14.8
< 50	80	35	23	22
≧ 50	57	24	10	23
FIGO stage				
I	68	27	22	19
II	26	12	4	10
III	38	18	7	13
IV	5	2	0	3
Histology				
SCC	121	53	27	41
Non-SCC	16	6	6	4
Treatment by FIGO stage				
Stage I/II	94	39	26	29
Surgery ± adjuvant therapy	83	34	24	25
CCRT	7	3	1	3
Radiotherapy alone	4	2	1	1
Stage III/IV	43	20	7	16
CCRT	35	16	6	13
Radiotherapy alone	6	3	1	2
Chemotherapy alone	2	1	0	1

Abbreviations: HPV, human papillomavirus; SD, standard deviation; FIGO, The International Federation of Gynecology and Obstetrics; SCC, squamous cell carcinoma, CCRT, concurrent chemoradiation therapy.

Table 2
Univariate and multivariate analyses of prognostic factors for overall survival in patients with invasive cervical cancer.

	n	Univariate analysis		Multivariate analysis	
		10y-OS	P value	Hazard Ratio (95%CI)	P value
Age					
< 50	80	0.84	0.85	2.52 (1.01–6.46)	0.048
≧ 50	57	0.82		1	
FIGO stage					
III/IV	43	0.57	< 0.0001	18.9 (6.50–68.7)	< 0.0001
I/II	94	0.95		1	
Histology					
Non-SCC	16	0.86	0.68	0.95 (0.15–3.51)	0.95
SCC	121	0.83		1	
HPV16 DNA					
Positive	59	0.88	0.30	0.42 (0.15 − 1.04)	0.06
Negative	78	0.80		1	

Abbreviations: HPV, human papillomavirus; FIGO, The International Federation of Gynecology and Obstetrics; SCC, squamous cell carcinoma; 10y-OS, 10 year-overall survival; 95%CI, 95% confidence interval.

[12]. Apparently conflicting results regarding the survival of patients with HPV16/18-negative tumors may be due to misclassification of HPV genotypes in earlier studies, or geographical differences in HPV-type prevalences.

The current study showed stage-specific results, with the favorable survival effect of HPV16 positivity restricted to FIGO stage III/IV tumors. However, several studies have reported significant associations between HPV18 detection and poor prognosis in early-stage ICC [6,7,11], suggesting rapid spread of HPV18-positive tumors during the early stage. Given that few patients with FIGO stage I/II tumors died from the disease in the present study, our sample size may have been too small to detect any slight differences in survival among early-stage tumors with different HPV genotypes.

Most patients with FIGO stage III/IV disease received radiotherapy, and our findings thus suggested that HPV16-positive tumors may display greater radiosensitivity. Moreover, most of these cases received CCRT, also implying that HPV16 was associated with greater chemoradiosensitivity. Using an in vitro radiosensitivity assay for cervical tumors and cell lines, a recent study suggested that intrinsic radiosensitivity of cervical tumors may not vary by HPV genotype [20]. Another recent study reported that HPV genotype may affect risks of distant metastases after radiotherapy, but not risks of local recurrences in the radiation field [21]. Therefore, HPV genotype may be associated with chemosensitivity or chemoradiosensitivity of cervical tumors. Early studies employed radiation therapy alone for FIGO III/IV tumors [7–9,14], while recent studies have mainly used CCRT [12,13] since five randomized trials comparing CCRT with radiation alone showed that CCRT was associated with a significant reduction in recurrence and death [22]. Conflicting results regarding the associations between HPV type and survival may reflect this difference in radiotherapy, and recent studies reporting better survival in HPV16-positive or HPV16/18-positive tumors used CCRT for FIGO stage III/IV tumors [12,13].

The favorable survival effect of HPV16 positivity may be limited to SCC, and two studies to date have reported no impact of HPV type on survival in patients with AC [23,24]. In our earlier study, patients with HPV16-positive AC showed similar survival to those with HPV18-positive SCC and AC [8]. Unfortunately, we could not evaluate the association between HPV type and AC survival in the present study because most FIGO stage III/IV tumors showed SCC histology.

In the present study, other prognostic factors such as tumor size, lymph node status, and histological grade were not included in the multivariate analyses, and HPV genotype may therefore not be an independent prognostic factor in ICC. However, the results suggest that HPV genotype may still serve as a prognostic biomarker, if not necessarily an independent one, representing many prognostic factors or predicting radiation effects.

Several studies suggested that tumors positive for HPV α9 species (including HPV16) are associated with a better prognosis [20,21,25]. Our results were consistent with these studies, but the association did not reach statistical significance because tumors positive for HPV16-related types (HPV31, 33, 52 and 58) had similar prognoses to HPV18-positive tumors. To address whether species grouping is more useful for predicting prognosis of cervical cancer patients, large-scaled studies will be warranted.

The mechanisms whereby HPV genotypes affect the survival of

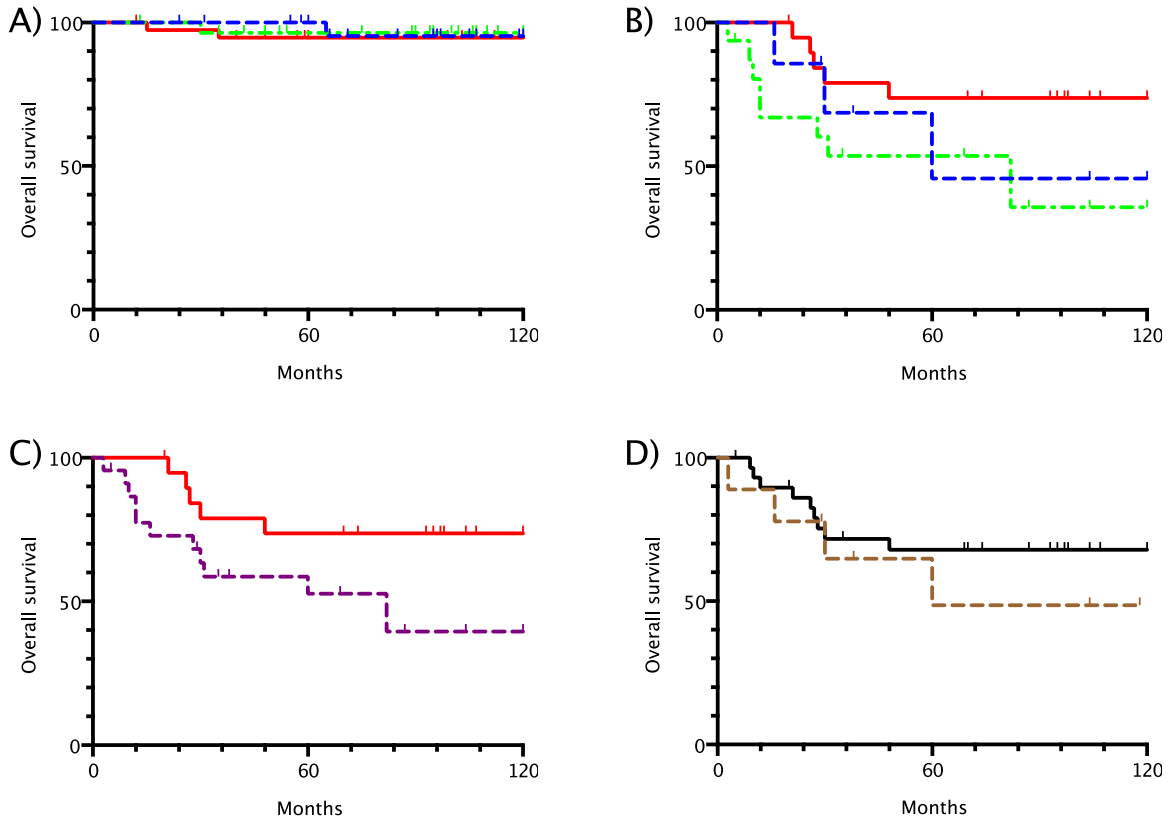

Fig. 1. Kaplan-Meier estimates of survival among patients with invasive cervical cancer according to HPV genotype. A) The 10-year overall survival rates in women with FIGO stage I/II disease were similar among all three groups; 94.7% for HPV16-positive tumors (red solid line —), 95.2% for HPV18-positive tumors (blue dotted line – – – – –), and 96.4% for HPV16/18-negative tumors (green dashed line — – —). B) The 10-year overall survival rates in women with FIGO stage III/IV diseases were 73.7% for HPV16-positive tumors (red solid line —), 45.7% for HPV18-positive tumors (blue dotted line – – – – –) and 35.7% for HPV16/18-negative tumors (green dashed line — – —). C) In women with FIGO stage III/IV diseases, the 10-year overall survival rate was significantly higher in patients with HPV16-positive (red solid line —) compared with HPV16-negative tumors (purple dotted line – – – – –) (73.7% vs. 39.5%, P = 0.04, log-rank test). D) The 10-year overall survival rate in women with FIGO stage III/IV diseases was higher in patients with α9 species-positive (black solid line __) compared with α7 species-positive tumors (brown dotted line _ _ _ _ _) (70.0% vs. 48.6%), but the difference did not reach statistical significance (P = 0.44). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

cervical cancer patients remain unknown. HPV16 and HPV18 are commonly associated with SCC and AC, respectively [2]. In addition, intra-type variant sequences related to HPV16-positive AC and HPV18-positive SCC have also been reported [26,27]. It is therefore likely that differences in HPV genome sequences may determine the biological characterization, as well as the histology, of cervical cancer cells. Recent studies have suggested that hot spots of HPV integration may be type-specific, and may determine the histology and biological characterization of ICC [28,29].

The main limitation of the present study was its small number of subjects. As noted above, we were unable to evaluate the impact of HPV16 on survival in patients with early-stage tumors or ACs because of this limitation. In addition, the present study was based on retrospective data analysis and not originally planned to evaluate the prognostic impact of HPV genotypes on ICC. The present study may not be able to draw definitive conclusions because of these limitations. To confirm our findings, a larger-scaled prospective study is now in progress in Japan.

In conclusion, the results of this study suggest that HPV16 positivity may be a favorable prognostic factor in patients with FIGO stage III/IV ICC, implying that HPV16 positivity may be associated with greater chemoradiosensitivity. A better understanding of the mechanisms underlying the association between HPV genotype and survival may lead to the development of new treatment approaches for patients with cervical cancer.

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Conflicts of interest

Koji Matsumoto received lecture and advisory fees from HOLOGIC Japan, Inc. and MSD K.K. and advisory fees from HOLOGIC Japan, Inc. Toyomi Satoh received lecture and advisory fees from Chugai Pharmaceutical Co., Ltd.; Daiichi Sankyo Co., Ltd.; Kyowa Hakko Kirin Co., Ltd.; Shionogi & Co., Ltd.; Eisai Co., Ltd.; AstraZeneca K.K.; Kaken Pharmaceutical Co., Ltd.; GE Healthcare Japan Corporation; Tsumura & Co.; Nippon Kayaku Co., Ltd.; Mochida Pharmaceutical Co., Ltd.; and Philips Japan, Ltd. Hiroyuki Yoshikawa received lecture and advisory fees from GlaxoSmith*KL*ine K.K.; MSD K.K.; Taiho Pharmaceutical Co., Ltd.; and Ono Pharmaceutical Co., Ltd.

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