Editorial Commentary

Tumor human papillomavirus: a potential test for cervical cancer prognosis

Tan Minh Le[1,2]^, Gun Oh Chong[3,4], Hyung Soo Han[1,2,3,5]

[1]Department of Biomedical Science, Graduate School, Kyungpook National University, Daegu, Korea; [2]BK21 Four Program, School of Medicine, Kyungpook National University, Daegu, Korea; [3]Clinical Omics Institute, Kyungpook National University, Daegu, Korea; [4]Department of Obstetrics and Gynecology, Kyungpook National University Chilgok Hospital, Daegu, Korea; [5]Department of Physiology, School of Medicine, Kyungpook National University, Daegu, Korea

Correspondence to: Prof. Hyung Soo Han, MD, PhD. Director of Department of Physiology, School of Medicine, Kyungpook National University, 680 Gukchaebosang-ro, Jung-gu, Daegu 41405, Korea. Email: hshan@knu.ac.kr.

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Persistent human papillomavirus (HPV) infection, particularly high-risk genotypes (hrHPV), is known as a critical cause of uterine cervical cancer (CC) (1). HPV testing has been revealed to have higher sensitivity than cytology in light of detecting cervical intraepithelial neoplasia at grade 2 or worse (approximately 25%) (2). In 2021, the latest World Health Organization (WHO) guideline recommended hrHPV testing for primary CC screening (3).

Recently, tumor HPV status has received considerable attention as a potential marker for stratification and prognosis CC. However, there is a conflict among current studies (*Table 1*). Pilch *et al.* found that the presence of tumor HPV DNA, particularly HPV16, was a significantly worse prognostic factor [relative risk (RR) 2.856, P<0.003; RR 3.444, P<0.0001, respectively] (4). In line with this study, another retrospective study showed that disease outcomes were worsened in hrHPV-related tumors (7). On the contrary, Hang *et al.* and Chong *et al.* identified that the HPV16 DNA-positive status was associated with better disease-free survival (DFS), and HPV (–) was associated with worse outcomes (10,11). Clearly, the controversy about the role of tumor hrHPV status in CC can lead to confusing interpretations in a clinic.

Therefore, there is a need for a large prospective study to assess the performance of a tumor HPV test in CC prognosis.

In the *Journal of Clinical Oncology*, Lei *et al.* revealed a fifteen-year follow-up study of 2,845 invasive CC patients after HPV detection (12). In their study, 392 of 2,845 (13.8%) cases were HPV-negative using a polymerase chain reaction (PCR)-based HPV DNA test. RNA sequencing (RNAseq) was then implemented on all negative HPV samples and identified additional 169 HPV-positive cases. There were 1,006 (81.3%) and 159 (18.7%) deaths from the hrHPV-positive and HPV-negative groups, respectively. The five-year cumulative relative survival ratio was 0.74 [95% confidence interval (CI): 0.72–0.75] and 0.45 (95% CI: 0.39–0.51) in the hrHPV-positive and -negative cases, respectively. After adjusting for patient characteristics, excess mortality in the hrHPV (+) was a significant decrease compared with the negative group [excess hazard ratio (EHR), 0.57; 95% CI: 0.48–0.69]. Also, a similar result was observed for HPV-positive *vs.* HPV-negative groups (EHR, 0.44; 95% CI: 0.36–0.55).

Considering the HPV subgroup and prognosis, the authors found a significant increase in excess mortality

^ ORCID: 0000-0002-9621-8877.

Table 1 The tumor HPV status in cervical cancer prognosis according to different studies

Study	Sample size	Mean FU time (year)	Finding
Pilch *et al.* (4) (2001, Germany)	223	4.4	HPV (+) and HPV16 (+) had worse prognosis (RR 2.856, P<0.003 and RR 3.444, P<0.0001)
Füle *et al.* (5) (2006, Hungary)	150	4.0	No significant difference in survival outcome of HPV (+) or hrHPV (+) *vs.* HPV (–)
Im *et al.* (6) (2003, USA)	144	5.0	HPV18 had worse prognosis *vs.* non HPV18 (P=0.03)
de Cremoux *et al.* (7) (2009, France)	515	7.9	Worse DFS in hrHPV *vs.* intermediate-risk HPV (P=0.03)
Lai *et al.* (8) (2007, China)	1,067	6.4	HPV18 (+) had a worse prognosis (OS: HR, 1.7, P=0.01 and DFS: HR 1.8, P=0.009)
Rodríguez-Carunchio *et al.* (9) (2015, Spain)	136	–	HPV (–) had worse DFS *vs.* HPV (+) (P=0.010)
Hang *et al.* (10) (2017, China)	306	4.5	HPV16 (+) had a better prognosis (HR, 0.36; P=0.005)
Chong *et al.* (11) (2018, Korea)	248	5.0	hrHPV (–) had a worse prognosis (HR, 3.97; P=0.0005); HPV16 (+) had a better prognosis (HR, 0.41; P=0.0019)

HPV, human papillomavirus; FU, follow-up; RR, relative risk; hr, high risk; DFS, disease-free survival; OS, overall survival; HR, hazard ratio.

and five-year CC-specific mortality of HPV18-positive *vs.* HPV16-positive CC (EHR, 1.55; 95% CI: 1.23–1.94; five-year incidence rate ratio, 1.65; 95% CI: 1.31–2.08, respectively). However, excess mortality in hrHPV-positive cases did not show a significant difference with hrHPV (–) among patients who only underwent surgery or received surgery followed by radiochemotherapy (EHR, 0.29; 95% CI: 0.13–0.66).

The finding from this large prospective study dramatically contributes to the current knowledge about tumor HPV status-related CC prognosis. The authors proved that tumor hrHPV is a potential marker with significant prognostic value. This study's results are similar to a recent meta-analysis study that revealed tumor hrHPV (+) as a good prognosis factor [OS: pooled hazard ratio (HR) 0.628; 95 % CI: 0.429–0.922, P=0.017 and DFS: pooled HR 0.355; 95% CI: 0.226–0.559, P<0.001] (13). Although the underlying mechanism of the association between HPV (–) and poorer prognosis has not been established, patients with HPV-negative tumors should be cautious and closely monitored.

Another essential point of the study is the investigators elucidated the role of RNASeq in HPV detection assay. According to this, half of the HPV-negative cases with the PCR-based method were positive with the RNASeq-based assay. Furthermore, the PCR–/RNASeq+ group had a 44% reduction in excess mortality compared with PCR–/RNASeq– one (EHR, 0.56; 95% CI: 0.39–0.79).

Even though HPV was confirmed as the main etiology of CC, it is inevitable that some CCs were reported with hrHPV (–) by 7–15% (14,15). The explanations for hrHPV-negative tumors can be as follow: First, CCs are independent of hrHPV (true negative). Second, lose the expression of HPV. Third, small HPV fragments or rare HPV genotypes or mutations that do not detect by traditional PCR. Fourth, the HPV test method issues, including sampling and targeted region of HPV DNA test (most commercial HPV DNA tests only select L1 for the targeted region). Fifth, misclassified cancers, e.g., endometrial cancer or metastasis from other tumors (15-17). The true HPV-negative result would not conflict with the benefit of a HPV-based screening program (15). However, false-negative results will lead to worse prognosis and stratification, so when receiving a HPV-negative CC result, the physicians should consider two questions, including "misdiagnosis?" and "re-tested?". This approach will avoid or reduce mistreatment. Moreover, a positive result after re-testing can determine whether the false negative result is due to infection with other HPV subtypes or the failure of the first test to detect hrHPV.

Recently, it is becoming extremely difficult to ignore the role of next-generation sequencing (NGS), particularly the RNASeq-based method in the HPV detection assay. The RNAseq-based HPV test could detect a wide range of HPV genotypes to overcome the limitation of rare HPV types. Moreover, an mRNA-based hrHPV test can identify

precancerous cervical lesions higher than that of cytology (P<0.001) (17). Finally, RNASeq can provide insight into the mechanisms of carcinogenicity. It is known that HPV E6/E7 plays a critical role in CC. E6 and E7 can lead to cancer progression by degrading two suppressor proteins, including p53 and retinoblastoma (18). Using RNASeq analysis, Ruiz *et al.* proved that there was a lower expression of E6 and the alternative transcript E6*I in HPV16 (+) *vs.* other HPV genotypes (+), which was associated with better survival outcomes in HPV16 (+) after chemotherapy (19). This result provided further studies with a hint for investigating the underlying biologic mechanism of the abovementioned findings. With all these premises, RNASeq can be a valuable tool for CC patients. However, the practical application of sequencing should be considered. For a long time, high cost has been the most significant barrier for applying NGS to clinical practice. Fortunately, the "game" has changed in recent years, and it is expected that NGS can be rapidly adopted in HPV screening.

In conclusion, the tumor HPV test should be routinely implemented to improve stratification and prognosis for CC patients. Additionally, the RNASeq-based HPV detection assay can be a potential complementary tool for better cancer management in the clinic.

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