Editorial

J Gynecol Oncol Vol. 25, No. 4:265-266
http://dx.doi.org/10.3802/jgo.2014.25.4.265
pISSN 2005-0380 · eISSN 2005-0399

Journal of Gynecologic Oncology
jgo

Human papillomavirus: wearisome or awesome issue?

Nam Hoon Cho
Department of Pathology, Yonsei University College of Medicine, Seoul, Korea

See accompanying article by Guo and colleagues on page 287.

With the rapid spread of high-throughput technologies, human papillomavirus (HPV) screening triage is becoming increasingly important as an alternative algorithm to replace the cervicovaginal Pap smear. Because HPV infection does not always involve extensive destruction of the host microenvironment, despite being a crucial causative factor in cervical cancer, triage algorithm any legal ground to stand on is mandatory.

There are two main reasons for HPV screening: infection with certain HPV types is predictive of cervical cancer progression, and determining the status of HPV infection will help to control the spread of the virus.

Despite the immense volume of available HPV data and the development of modern high-throughput technologies, there are two major obstacles to HPV studies: a lack of longitudinal studies and a lack of a gold standard for generating comparative HPV data.

An unavoidable loophole in the study of HPV exists in the accuracy of the atypical squamous cells of undetermined significance (ASC-US) and cervical intraepithelial neoplasia (CIN) grading systems as well as in the time that it takes to evaluate the virus status. However, the most common, albeit overlooked, pitfall is the lack of a faithful gold standard for diagnosis, whether the diagnosis is based on biopsy or sequencing. A longitudinal study design based on traditional triage could produce new insights.

Guo et al. [1]'s study design associated with CIN 3 is thought to be fair and less biased. mRNA targeting of E6/E7 takes greater advantage of valuable messages compared with DNA targeting of L1. E6/E7 expression acts as a dominant oncogene, with immortalization and transformation activities, whereas L1 merely represents a lifelong infectious sign, even if the infection was remote. Nonetheless, further issues regarding the use of HPV mRNA and HPV DNA for diagnosis include the following:

(1) mRNA+/DNA−: arbitrary; not decisive enough to be used regularly

(2) mRNA−/DNA+: same clinical triage as the traditional algorithm

(3) mRNA−/DNA−: in case of APTIMA/Hybrid Capture 2 (HC2), it can exclude the possibility of the other HPV genotypes; clinical surveillance to determine whether the infection is active or general may be warranted

(4) mRNA+/DNA+: more specific for CIN 3+, but less specific for CIN 2 or lower; good predictor of CIN 3 progression (odds ratio of HPV 16 mRNA was 5.14; odds ratio of high-risk HPV [HR-HPV] mRNA was 3.37 over a 3-month period) [2].

In terms of the CIN concept, the CIN background switches to the squamous intraepithelial lesion (SIL) concept with the emergence of HPV as a crucial causative factor. CIN 1 is traditionally the period from which worse grading (i.e., CIN 2 or 3) develops. Like CIN, SIL involves cytopathic changes that are restricted to the epithelial environment but are insufficient for neoplasia. An HPV-associated cytopathic effect alone is not sufficient to indicate neoplasia, because low-grade SIL (LSIL) is often reversible, although the virus is infectious. With the physical integration of the viral E6/7 genes into the host genome and the subsequent uncontrolled kinetic activation of the cell cycle, atypia in the parabasal and intermediate layers of the epithelium increase and high-grade SIL (HSIL) may develop, which is mostly irreversible, encompassing CIN 2 and 3.

Cytology, based on cells scraped from the most superficial layers of the cervical epithelium, benefits from the HPV life cycle, because the rapidly replicating, virion-harboring koilocytes colonize the upper layers of the epithelium. It is even more fortunate that CIN 3 reaches to the top layer. CIN 2/3 in the HSIL category shares identity, and very often coexists, with

Correspondence to Nam Hoon Cho
Department of Pathology, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 120-752, Korea. E-mail: CHO1988@yuhs.ac

Copyright © 2014. Asian Society of Gynecologic Oncology, Korean Society of Gynecologic Oncology

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/3.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

viral replication, as does LSIL.

LSIL cytology does not necessarily manifest as CIN 2/3 in a biopsy outcome, which is not surprising. CIN 2 is the most perplexing diagnosis, because this heterogeneous entity comprises viral replication and neoplastic transformation in the same lesion. Once transformation activity commences in the parabasal layer, by definition, the lesion is called a HSIL. Because viral replication remains active in the surface layers, however, as in LSIL, the final result of cytology tends to be, not surprisingly, LSIL. For standardization and reproducibility among pathologists, it might be reasonable to abandon the use of CIN 2 and merge CIN 2 with CIN 3. What is important is that LSIL (CIN 1) is discriminated from HSIL (CIN 3).

There is a glut of inventory among the many methods to identify HPV, which has a small circular DNA genome. Two major HPV test markets are those for RNA probes that hybridize with the viral DNA genome, as in the HC2 test, and DNA probes that hybridize with viral DNA amplicons on a chip platform. Unlike traditional DNA detection, targeting the E6/E7 mRNA aims at the crucial part of the genome.

According to a meta-analysis comparing the accuracies of the Food and Drug Administration (FDA)-approved HC2 test (Qiagen) and the APTIMA test (Gen-Probe), the signal strength cutoff value is an emission light unit over 1.0, which expresses semiquantitatively the viral load compared with a control sample containing 1 pg HPV DNA/mL.

An additional issue is coinfection involving multiple genotypes, which represent around 10% of HPV-infected cohorts. Excluding low-risk HPV (LR-HPV) and including any indeterminate risk type, conditions for a cumulative exhaustive principle could not be identified. As multiple lesions in combined infections or as synergistic aggravation or bystanders, combined infections currently remain poorly understood. For determining the mechanism and clinical implications of multiple infections, genotyping, rather than cocktail-based assays, is quite essential. To develop new triage techniques for cervical neoplasms and lesions associated with infection by multiple HPV types, well-designed longitudinal cohort studies with well-established gold-standard diagnoses, either after cloning into plasmids or by direct sequencing or biopsy, are also mandatory.

LR-HPV types could be discarded from both the APTIMA and the HC2 tests, because they compromise the efficiencies of the tests, and their presence is insufficient to evoke HSIL. The biochemical properties of LR-HPV include weaker transformation activities, telomerase activities, and lack of a PDZ domain.

So far, the following reasons to discriminate HR-HPV from LR-HPV are widely acknowledged.

(1) The probability of viral integration into the host genome exceeds 50% for HPV 16 and 18, whereas integration seldom or never happens for LR-HPV [3].

(2) Immortalizing activity is more likely to be caused by HR-HPV, due to high levels of CDK2 expression and low levels of p21/p27 expression, than by LR-HPV, due to decreased p21 abrogation [4].

(3) Telomerase activity is higher in HR-HPV E6 [5].

(4) HR-HPV E6 contains a PDZ domain (X-S/T-V/L/I)-containing protein, forming a p53-independent target, whereas LR-HPV E6 does not contain a PDZ domain [6].

According to the restricted FDA-approval items, future HPV data may be restricted to limited types of HR-HPV, ignoring genotypes, which raises questions about the direction of HPV research and whether such research will be a wearisome issue or an awesome issue open to new horizons beyond the classical approach to HPV in the future.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Guo Y, You K, Geng L, Qiao J. The clinical performance of APTIMA human papillomavirus and Hybrid Capture 2 assays in the triage of lesser abnormal cervical cytologies. J Gynecol Oncol 2014;25:287-92.
2. Discacciati MG, da Silva ID, Villa LL, Reis L, Hayashi P, Costa MC, et al. Prognostic value of DNA and mRNA e6/e7 of human papillomavirus in the evolution of cervical intraepithelial neoplasia grade 2. Biomark Insights 2014;9:15-22.
3. Matovina M, Sabol I, Grubisic G, Gasperov NM, Grce M. Identification of human papillomavirus type 16 integration sites in high-grade precancerous cervical lesions. Gynecol Oncol 2009;113:120-7.
4. Jones DL, Alani RM, Munger K. The human papillomavirus E7 oncoprotein can uncouple cellular differentiation and proliferation in human keratinocytes by abrogating p21Cip1-mediated inhibition of cdk2. Genes Dev 1997;11:2101-11.
5. Horikawa I, Barrett JC. Transcriptional regulation of the telomerase hTERT gene as a target for cellular and viral oncogenic mechanisms. Carcinogenesis 2003;24:1167-76.
6. Nguyen ML, Nguyen MM, Lee D, Griep AE, Lambert PF. The PDZ ligand domain of the human papillomavirus type 16 E6 protein is required for E6's induction of epithelial hyperplasia in vivo. J Virol 2003;77:6957-64.

 http://dx.doi.org/10.3802/jgo.2014.25.4.265