THE USE OF HUMAN PAPILLOMAVIRUS DNA METHYLATION IN CERVICAL INTRAEPITHELIAL NEOPLASIA: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Introduction/Background Methylation of viral DNA has been proposed as a novel biomarker for triage of HPV positive women at screening. This systematic review and meta-analysis aims to assess how methylation levels change with disease severity and to determine its diagnostic test accuracy in detecting high-grade cervical intra-epithelial neoplasia (CIN) in HPV positive women.

Methodology We performed searches in MEDLINE, EMBASE and CENTRAL from inception to September 2018. Studies were eligible if they explored HPV methylation levels in HPV positive women. Data were extracted in duplicate and requested from authors where necessary. Random-effects models and a bivariate mixed-effects binary regression model were applied to determine pooled effect estimates.

Results 43 studies with 8775 high-risk HPV positive women were eligible. The pooled estimates for positive methylation rate in HPV16 L1 gene were higher for ≥CIN2/HSIL (72.7% (47.8–92.2)) vs ≤CIN1/LSIL (44.4% (16.0–74.1)). The pooled difference in mean methylation level was significantly higher in ≥CIN2/HSIL vs ≤CIN1/LSIL for the HPV16 L1 gene (11.3% (6.5–16.1)). The pooled odds ratio of HPV16 methylation in the L1 gene was 6.57 (3.49–12.39) for ≥CIN2/HSIL vs. ≤CIN1/LSIL. HPV16 L1/L2 genes performed best in predicting CIN2 or worse (pooled sensitivity 77% (63–87), specificity 64% (55–71), area under the curve (AUC) 0.73 (0.69–0.76)) (figure 1). HPV16 L1/L2 methylation improved triage of HPV16 positive women (figure 2).

Conclusion Higher HPV methylation is associated with increased disease severity, whilst HPV16 L1/L2 genes demonstrate high diagnostic accuracy to detect high-grade CIN in HPV16 positive women. The direct clinical use of this marker in triage is limited by the need of a multi-genotype assay. Next-generation multiplex sequencing assays containing all HPV types are under development and have the potential to allow rapid, automated and low-cost methylation testing.
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Pre: pre-test probability; Post: post-test probability