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Minimizing verification bias in cervical cancer screening of HIV-infected women

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Synopsis

Approximately one-third of cervical intraepithelial neoplasia 2 and above can be missed by only biopsying quadrants of the cervix with visible lesions by digital cervicography.

Keywords

Biopsy; Cervical cancer; HIV; Screening; Verification bias; Zambia

HIV infection is associated with a higher incidence rate of cervical lesions and increased risk of cervical cancer [1]. New cervical cancer screening tests are available or in development, and many biomarkers hold promise for screening. It is important to evaluate the clinical performance characteristics of new screening tests in HIV-infected women, to inform possible introduction in this population. Histopathology is commonly used as the gold standard diagnosis in cervical cancer screening studies; however, verification bias can occur if none or only a subset of screen negatives receives histopathology. Verification bias results in an overestimation of sensitivity and underestimation of specificity of the screening test.

After receiving ethical approval from appropriate institutional bodies, 268 HIV-infected women accessing cervical cancer screening in Zambia were enrolled in the study [2]. Each woman provided written informed consent and was screened using cytology and visual

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Conflict of interest
The authors have no conflicts of interest.

inspection with acetic acid coupled with digital cervicography (DC) [3]. Women with a lesion identified by DC received a biopsy from an area within the lesion most likely representing the most advanced degree of neoplasia, as well as a random biopsy from a quadrant without a lesion (if such a quadrant was present). Women with no visible lesions by DC received a random biopsy. Cervical disease was more advanced in biopsies from quadrants with visible lesions (Table 1), but approximately one-third of cervical intraepithelial neoplasia 2 and above (CIN2+) were from quadrants without lesions (17/55; 31%), demonstrating that not all lesions are visible by DC. The results were stratified based on if one versus multiple cervical sites were sampled (Table 1). There was more disease in quadrants with visible lesions, but a substantial proportion of disease was identified in quadrants without visible lesions.

By obtaining a punch biopsy from cervical quadrants with and without visible lesions we estimated the amount of disease typically missed when biopsies are restricted to visible lesions. Approximately one-third of all CIN2+ were from quadrants without visible lesions, analogous to results by Pretorius et al. [4] who reported that 37% of all CIN2+ lesions in HIV-negative women were from colposcopically normal-appearing areas on the cervix. We recommend that screening studies include systematic sampling for histopathology regardless of the screening result, to minimize verification bias in cervical cancer screening trials.

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Table 1

Histopathology diagnosis from cervical quadrants with or without visible lesions.[a]

Histopathology diagnosis	Random biopsy from cervical quadrants *without* visible lesions			Targeted biopsy from cervical quadrants *with* visible lesions		
	Total [b]	Women with no cervical quadrants with visible lesions	Women with one or more cervical quadrants with visible lesion	Total [b]	Women with all cervical quadrants occupied by visible lesions	Women with one or more cervical quadrants without visible lesion
Benign	113 (52.8)	77 (58.3)	36 (43.9)	41 (30.2)	11 (20.4)	30 (36.6)
CIN1	84 (39.3)	47 (35.6)	37 (45.1)	57 (41.9)	23 (42.6)	34 (41.5)
CIN2	10 (4.7)	4 (3.0)	6 (7.3)	17 (12.5)	9 (16.7)	8 (9.8)
CIN3	4 (1.9)	2 (1.5)	2 (2.4)	19 (14.0)	10 (18.5)	9 (11.0)
Cancer	3 (1.4)	2 (1.5)	1 (1.2)	2 (1.5)	1 (1.9)	1 (1.2)

Abbreviation: CIN, cervical intraepithelial neoplasia.

[a] Values are given as number (percentage).

[b] Distribution of biopsy results from cervical quadrants *with* visible lesions is significantly more advanced than biopsy results from quadrants *without* visible lesions ($P<0.001$ by χ^2 test).