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How might HPV testing be integrated into cervical screening?

Hormuzd A. Katki, PhD[1,#] and **Nicolas Wentzensen, MD, PhD**[1]

[1]Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, DHHS, Bethesda, MD, USA

In this issue of *The Lancet Oncology*, data from the POBASCAM trial[1] demonstrates the power of HPV testing for cervical cancer screening. At baseline, HPV testing found 79 additional cervical precancers (CIN3), and 30 additional cancers, per 100,000 women compared to screening with cytology only. During the next five years, the improved detection of CIN3 at baseline led to the detection of 24 fewer precancers, and prevented 10 cancers, per 100,000 women per year. Moreover, assuming that all women in the intervention group testing HPV-negative with a normal Pap test returned on average in five years, we estimate a very low cancer risk of 2.2 per 100,000 women per year, demonstrating that five-year screening intervals are safe.

POBASCAM reinforces findings from meta-analyses[2], cohorts[3], clinical trials[4–6], and routine clinical practice[7] providing overwhelming evidence of the benefits of incorporating HPV testing into screening programs. However, clinical trials do not evaluate primary 'HPV testing' in isolation, but in the context of a full protocol that determines management of all HPV-positive and HPV-negative women. Detailed understanding of the protocol is important to evaluate the feasibility of introducing HPV testing in different settings and to formulate guidelines for implementation.

The POBASCAM finding that is most immediately translatable to screening programs worldwide is the five-year screening interval for women aged 30 and older who test HPV-negative with normal cytology. The low estimated cancer risk for these women in POBASCAM is similar to the estimate from a large clinical practice in the USA of 3.2 per 100,000 women per year.[7] These extremely low risks are consistent with our knowledge that HPV infection is the necessary cause of nearly all cervical cancer and that cancer usually requires decades to develop.[8] We expect that almost every woman testing HPV-negative, regardless of country or screening protocols, has an extremely low risk of cancer over three or five years.

In contrast, it is less clear how to manage HPV-positive women. Most HPV infections will clear naturally and only a minority of CIN2/3 will progress to cancer. Thus, an effective protocol that determines which HPV-positive women should be referred to colposcopy is crucial to limit unnecessary colposcopies and excisional procedures.[9] The most aggressive protocol refers all HPV-positive women to colposcopy, as was done in the New Technologies for Cervical Cancer screening (NTCC)[5] trial for women 35 years and older. POBASCAM employed a more conservative protocol, referring women to colposcopy only if they had >BMD cytology (equivalent to HSIL) at 6 months or >BMD or persistent HPV infection at 18 months. An aggressive protocol has the advantage of potentially preventing

[#]For correspondence: Division of Cancer Epidemiology and Genetics, National Cancer Institute, 6120 Executive Blvd. Room 8014, MSC 7244, Bethesda, MD 20892-7234, Phone: 301-594-7818, Fax: 301-402-0081, katkih@mail.nih.gov.

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more cancer, while a conservative protocol has the benefit of diagnosing fewer intermediate endpoints that may require unnecessary interventions.

In POBASCAM, 10 cancers were prevented, with only 32 additional CIN2/3 diagnosed (Table). HPV-positive/Pap-negative women had eight of the ten excess cancers, but also 26 of the 32 additional CIN2/3 diagnosed, confirming that HPV-testing identifies Pap-negative women at risk of cancer who are challenging to manage. Compared to NTCC, conservative management of HPV-positive women in POBASCAM resulted in a lower increase in CIN2 detection, and higher CIN3:CIN2 ratio, probably because of regression of transient CIN2 lesions not destined to progress to cancer. In spite of employing a more aggressive protocol, NTCC prevented fewer cancers than POBASCAM (9 cancers, but in over twice the number of women as POBASCAM), because NTCC had a lower baseline cancer rate in the cytology arm than POBASCAM (19 vs. 30 per 100,000). When disease is rarer, fewer cases can be prevented, and preventing them might require a very aggressive protocol to catch rare fast-progressing cancers, resulting in more overtreatment.[10]

In summary, the POBASCAM trial demonstrates that five-year screening intervals for HPV-negative women are safe, and that conservative management of HPV-positive women can control excess CIN2/3 diagnoses while still allowing powerful prevention of cervical cancer. However, it is unclear how the POBASCAM protocol would perform in other populations that have different baseline cancer rates, compliance, and management infrastructure. Basing clinical management on a woman's individual risk of cervical cancer might account for population-specific factors that can have substantial impact on the performance of screening protocols.[11]

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Table

Comparison of number of cancers prevented versus excess diagnosis of CIN2/3 requiring excisional therapy for each baseline HPV and Pap test result in POBASCAM. “Pap+” means any Pap abnormality.

Baseline HPV test result	Baseline Pap test result	Incident cancers in Pap arm	Incident cancers in HPV arm	Cancers prevented by HPV testing	Cumulative CIN2/3 in Pap arm	Cumulative CIN2/3 in HPV arm	Excess CIN2/3 in HPV arm
	Inadequate	0	0	0	0	2	2
HPV−	Pap−	4	2	2	74	86	12
HPV−	Pap+	0	0	0	22	16	−6
HPV+	Pap−	8	0	8	90	116	26
HPV+	Pap+	2	2	0	193	191	−2
Total		14	4	10	379	411	32