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Triage options for HPV-positive women in cervical cancer screening

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Human papillomavirus (HPV) infection is a necessary cause of cervical cancer, the first step in a carcinogenic process that can take decades (1). Thus, a negative result from a sensitive HPV test provides sufficient reassurance that cervical cancer will not develop over a long period of time and allows extending screening intervals for at least 3–5 years. These findings have led to the incorporation of HPV testing into screening programs in several countries.

However, it is less clear how to manage women who test HPV-positive since most HPV infections will resolve after months to a few years. It is important to identify women with a prevalent precancer who need treatment while avoiding unnecessary referral of women who have only transient infections.

In this issue of the Lancet Oncology, Carozzi et al. present the first longitudinal data of p16 cytology as a triage test in HPV-positive women from the NTCC trial (2). Forty-two % of such women tested p16 positive and would be referred to colposcopy. The three-year sensitivity of p16 was 83.7% for CIN3 and cancer (CIN3+). The three-year risk of CIN3+ in p16-positive women was 9.7%, while the risk in p16-negative women was 1.7%. The authors concluded that p16 could be used as a triage tool for HPV-positive women and that p16-negative women could be safely re-tested after 2–3 years. It has to be noted that a new assay based on dual staining for p16 and Ki-67 has been introduced which obviates the need for morphological evaluation of p16-stained cells as performed by Carozzi et al. However, a cross-sectional study using the new assay suggested a similar performance for detecting cervical precancer compared to the older assay (3).

It is very instructive to compare p16 cytology to HPV16/18 genotyping, another approach proposed to triage HPV-positive women. HPV16 and HPV18 predict a much higher risk of precancer compared to other carcinogenic HPV types over a long period of time (4). HPV16/18 genotyping is objective, and is directly provided as part of some HPV assays. In contrast, p16 is a marker of HPV oncogene activity that works independent of carcinogenic type and indicates early stages of transformation (5). The p16 assay requires preparation of a cytologic slide and microscopic evaluation for p16 staining.

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Several parameters have to be considered when deciding which strategies to use for triage of HPV-positive women. Overall triage test positivity indicates the percentage of the HPV-positive population that will be referred to colposcopy. Absolute risk levels and difference of risk in testpositives and test-negatives show whether different management is warranted based on the test result. The longitudinal risk in test-negatives (equal to 1-negative predictive value) indicates how long test intervals can be safely extended (6).

The table shows several of these key measures for triage of HPV-positive women from the ATHENA trial evaluating various combinations of HPV16/18 genotyping and cytology (7) and from the Italian screening trial evaluating p16 (2;8).

The baseline prevalence, or pre-test risk, of CIN3+ in HPV-positive women was higher in the ATHENA trial compared to NTCC (7.2% vs. 3.7%). The relative increase in risk among triage test-positives was similar for the various strategies in the ATHENA trial and p16 cytology (about 2-fold increase in risk among test-positives compared to the pre-test risk). Of all strategies, p16 had the highest sensitivity at baseline (91%), and the percent referral was the second highest of all strategies (42%). Although comparisons across the two studies have to be made with caution, sensitivity of p16 was higher, but referral was lower than the combination of HPV16/18 positivity or ASC-US+, one of the currently recommended triage strategy for HPV-positive women (9).

Improving management of HPV-positive women can identify more disease at the initial screening round while safely releasing more women to extended re-testing intervals. The 3-year follow-up data from the Italian trial suggest that the risk in p16-negative women is low enough to extend re-testing up to 2–3 years. Longitudinal data from the ATHENA trial, available soon, will be important evidence for determining screening intervals in HPV16/18-based triage.

The data presented by Carozzi et al. suggest that p16 can be added to the menu of triage options for HPV-positive women. The p16 findings reported here need to be replicated in other populations with the new dual stain assay and evaluation of p16 and HPV genotyping in the same population will be important to formally compare these options.

It is likely that different triage strategies will be optimal for different healthcare settings, e.g. an organized invitation-based screening program is more likely to adopt extended screening intervals than settings with opportunistic screening that suffer from loss to follow-up. Due to the inherent complexity of evaluating management strategies of HPV-positive women, cost-effectiveness modeling will be very important to evaluate various triage options and provide guidance for implementation.

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Table

Triage options for HPV-positive women in cervical cancer screening

Triage strategy	Referral %	Baseline			3-year follow-up		
		Sensitivity for CIN3+ %	Risk of CIN3+ in testpositives %	Risk of CIN3+ in testnegatives %	Sensitivity for CIN3+ %	Risk of CIN3+ in testpositives %	Risk of CIN3+ in testnegatives %
ATHENA trial			Castle Lancet Oncology 2011 (7)			Data not reported yet	
Immediate colposcopy	100		7.2				
ASC-US+	27	53	14.1	NR			
HPV16/18	28	60	15.5	NR			
HPV16/18 or LSIL+	38	72	13.9	NR			
HPV16/18 or ASC-US+	45	78	12.6	NR			
NTCC trial			Carozzi Lancet Oncology 2008 (8)			Carozzi Lancet Oncology 2012 (2)	
Immediate (and 3-year follow-up) colposcopy	100		3.7			5.7	
P16	42	91	7.7	NR	82	9.7	1.7

NR: Not reported