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Approaches for triaging women who test positive for human papillomavirus in cervical cancer screening

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ABSTRACT

Substantial evidence exists to support the introduction of molecular testing for human papillomavirus (HPV) as the primary technology in cervical cancer screening. While HPV testing is much more sensitive than cytology for detection of high-grade precancerous lesions, it is less specific. To improve efficiency, it is therefore recommended that a specific test (like cytology) be used in triaging HPV positive women to colposcopy. A number of studies have been conducted that support the use of cytology alone or in conjunction with HPV genotyping for triage. The decision to incorporate genotyping also depends on the commercial HPV test that is selected since not all tests provide results for certain individual high-risk types. Regardless of whether policy officials decide to adopt a triage approach that incorporates genotyping, the use of liquid based cytology (LBC) may also improve screening performance by reducing diagnostic delays. With LBC, the same cell suspension from a single collection may be used for HPV testing and a smear can be immediately prepared if HPV status is positive. This was a critical lesson from a community based demonstration project in Montreal (VASCAR study), where conventional cytology exists and specimen co-collection was not permitted for ethical reasons, requiring HPV positive women to return for an additional screening visit prior to colposcopy.

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1. Introduction

Human papillomavirus (HPV) testing is more sensitive and offers many other advantages over both conventional and liquid based cytology (LBC) in primary screening for cervical cancer (Tota et al., 2017-in this issue). As a result, many countries are considering or have already decided to implement HPV primary screening. However, an important concern related to adoption of this approach is the increased number of unnecessary colposcopy referrals that may result, unless a specific triage test/approach is applied. In this commentary, we summarize results from a number of studies focusing on triage of HPV positive women using either cytology (Pap) alone, or incorporating

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genotyping (e.g., HPV16/18) with cytology (Fig. 1a and b, respectively). We also comment on other methods, such as p16/Ki-67 duel staining, host and viral methylation, which are currently being evaluated.

2. HPV/Pap triage approach

The strategy of HPV/Pap triage (Cuzick et al., 2008) takes advantage of the desirable properties of both tests, i.e., the high sensitivity of HPV testing and the high specificity of cytology. The concerns associated with maintaining cytology as the primary screening test in the post-vaccine era (due to its subjective nature and low sensitivity) (Nanda et al., 2000) do not apply in this triage scenario; however, it is possible that smears evaluated by cytotechnologists known to have originated from HPV-positive women (unlike the current situation where cytotechnologists are generally unaware of the specimen HPV status) may be scrutinized more closely given the higher likelihood that a cervical abnormality is present. Originally, it was suggested that this 'artificially enriched' HPV positive population, with higher lesion prevalence and fewer cases of inflammation or reactive atypia (i.e., greater signal-to-noise ratio) would lead to improved diagnostic accuracy (Cuzick et al., 2008; Franco et al., 2009). However, in a recent Canadian study designed specifically to evaluate this question, investigators found that samples reread by cytotechnologists after revealing the patients' positive HPV status led to slightly worse diagnostic performance (somewhat greater number of false-positive results and lower specificity), perhaps due to heightened expectation of possible abnormalities (Richardson et al., 2015). In this study, sensitivity remained consistent (Richardson et al., 2015), whereas in another recent Italian study addressing the same question, investigators reported improved sensitivity when cytology was informed of HPV status (Bergeron et al., 2015a). Considering the subjective nature of cytology, these conflicting results should not come as a surprise. The HPV/Pap triage strategy is now being evaluated in the population based British Columbia HPV FOCAL trial (Ogilvie et al., 2016; Ogilvie et al., 2012), and was also recently evaluated in a community based demonstration project (VASCAR study) in Montreal (Louvanto et al., 2014). Results from both of these studies will provide critical information in guiding the development of screening recommendations focusing on this approach.

The HPV FOCAL study is the first North American RCT to compare HPV testing (Hybrid Capture [HC] 2 assay with reflex Pap triage using LBC) versus Pap testing (with reflex HPV testing in triage of atypical squamous cells of undetermined significance [ASC-US] cases) in cervical cancer screening; with a screening interval of four years in the intervention HPV testing arm (two years in the safety check arm) and two years in the control arm (Ogilvie et al., 2010). As of January 2011, 18,648 females aged 25–65 years had been randomized to receive either HPV testing with the HC2 test ($n = 12{,}494$; including both intervention/safety check arms) or LBC with ThinPrep® ($n = 6{,}154$) as the primary screening test (Ogilvie et al., 2012). Interim results from round one of this screening trial suggest the HPV/Pap triage approach leads to greater overall detection rates of high-grade precancer/cancer (cervical intraepithelial neoplasia [CIN] 2+ and CIN3+; 16.1 and 8.0 per 1000 tested in the HPV arm compared with 11.0 and 5.0 per 1000 tested in the control arm, respectively) but also a greater number of colposcopy referrals (57.2 versus 33.2 per 1000 tests in the HPV and control arm, respectively) (Ogilvie et al., 2016; Ogilvie et al., 2012). Recognizing that increased colposcopy referrals and their associated diagnostic and treatment procedures (considered a surrogate for harms from screening) is important, Coldman and colleagues recently estimated the impact of implementing HPV primary screening (with Pap triage) on referral for colposcopy in the British Columbia screening program (Coldman et al., 2015). They utilized HPV FOCAL trial age-specific/screening-specific results (weighted by screening program distribution) and found that although HPV testing may initially increase rates of referral (compared with adoption of LBC primary screening), cumulative rates over four years would be similar, except among younger females aged 25–29 (for this group it would remain higher) and that adoption of either approach (primary HPV or LBC screening) would increase colposcopy referrals in the province, driven by more aggressive management of abnormalities in the trial protocol compared to current practice (Coldman et al., 2015).

The VASCAR study is the first community based demonstration project in North America to evaluate primary HPV DNA testing (using HC2) with conventional cytology (≥ASC-US) for triage to colposcopy (Louvanto et al., 2014). Beyond the collection of important information surrounding the performance of this approach compared with traditional screening practices, this project provides us with insight into the potential obstacles that must be overcome to ensure successful introduction of primary screening at the provincial/national level. 28,939 women were considered for inclusion in the study and after exclusion criteria were applied, screening results from 26,193 women aged 30–65 years were compared with the historic control era, i.e., cytology screening in the 3 years before VASCAR. Increases were observed in the detection of high-grade precancerous/cancerous lesions (CIN2+; 6.58 versus 2.37 per 1000 women), as well as in the detection rate of these high-grade lesions among women referred for colposcopy (340.00 versus 163.02 per 1000 colposcopies) and lower median time from a positive Pap triage result to colposcopy (3.14 months in VASCAR versus 10.98 months in the historic period), with a slight rise in rate of colposcopy referrals in this primary HPV screened population (19.36 versus 14.54 per 1000 women) (Louvanto et al., 2014). Investigators attributed the improvement in time to colposcopy to the reduced workload of Pap smears being read by cytotechnologists (93% reduction), and the heightened sense of urgency felt by providers to refer a patient with an abnormal Pap test and presence of high-risk (HR) HPV type(s) for colposcopy.

VASCAR provided also an important lesson in routine implementation of HPV testing. LBC is not currently publicly funded in Quebec, which prompted the need for conventional Pap tests to be used in triaging HPV-positive women. However, initial ethical approval of the study required that once a Pap smear is prepared it must be read and a result must be provided. LBC use would have obviated this legal concern because the cell suspension that serves for both HPV testing and Pap triage does not imply an accession number for the patient. The suspension can be safely stored and a smear prepared for reading only after the HPV test is completed and the result is positive. Therefore, this obstacle forced a second visit for a woman who was HPV positive. Expectedly, given the delays in having notifications sent out and scheduling new appointments for Pap tests, less than half of HR-HPV positive patients (first round screening) had been triaged with Pap cytology at the time of the VASCAR report (Louvanto et al., 2014).

This experience should serve as an important lesson for the introduction of primary HPV testing in settings that currently administer conventional Pap cytology screening. By switching to liquid based cytologic samples, efficiency could be improved because the screening process (i.e., all medical acts pre-colposcopy) could be reduced to a single visit. The other important lesson to be learned from this demonstration project is that in the initial rollout of HPV primary screening, there may be a learning curve for some healthcare workers who violate the new protocol. For example, in the VASCAR study, 3414 protocol violations were reported (11.7%), most of which occurred in the first year. A Pap smear being conducted at the initial screening visit (rather than the recommended HPV test) was the most common protocol violation (9.3%).

Additional European studies comparing a large number of screening strategies also support the approach of primary HPV testing with cytology triage (Naucler et al., 2009; Rijkaart et al., 2012). In an analysis of data from the intervention arm of the Swedescreen trial ($n = 6257$), investigators compared 11 different screening strategies (HPV DNA testing alone, cytology alone, and HPV DNA testing with cytology, including testing for different combinations of HR-HPV subtypes) and found that the strategy of HPV DNA testing with cytology triage (incorporating repeat HPV DNA testing of HPV+/Pap- women within