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HPV-based cervical cancer screening- facts, fiction, and misperceptions

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Abstract

Several randomized trials have demonstrated that HPV-based cervical cancer screening is more effective than cytology-based screening. A pooled analysis of long-term follow-up data from these trials has shown reduced cervical cancer mortality in women screened with HPV compared to cytology. As a consequence, many health systems are currently transitioning to HPV-based screening programs. However, there are several controversies that influence whether and how HPV-based cervical cancer screening is implemented in different settings. Here, we discuss the most important controversies surrounding cervical cancer screening using primary HPV testing in light of published data from clinical trials and large observational studies. Overall, there is strong and uniform evidence for the efficacy of HPV-based screening, and little evidence for the usefulness of adding cytology to primary screening. However, there is currently limited data on optimal triage strategies for HPV-positive women, a critical component of an HPV-based screening program. There will likely be multiple choices for integrated screening programs and implementation may differ depending on risk perception, healthcare funds, assay costs, and available infrastructure, among other factors, in different settings. A particular challenge is the integration of screening and vaccination programs, since increasingly vaccinated populations will have a continuous decrease of cervical cancer risk.

Understanding that HPV is a necessary factor of most cervical cancers has led to two important developments for cervical cancer prevention, HPV vaccination as a highly efficacious primary prevention strategy and HPV DNA testing as new approach for screening and/or management of screen positive women. Many cervical cancer prevention programs are currently undergoing an important transition phase, with vaccinated women reaching the age of screening and new molecular tests introduced.

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In this issue, Tota et al. (1) present an evidence review on the role of HPV testing in cervical cancer screening. This report, along with several previous evidence reviews on this topic (2–5) concludes that HPV screening allows earlier detection of cancer precursors and is more effective than cytology screening, permitting extension of screening intervals at equal or better safety while reducing harm from too frequent screening. Ultimately, these changes can lead to higher program efficiency.

However, the conclusions drawn from these reports differ in many healthcare settings and frequently are controversial. Here, we address some of the controversies, with a particular focus on how cervical cancer screening is organized in European healthcare settings. There is a wide range of acting on the evidence presented by Tota et al. (1) or others: For example, the Netherlands are moving to an organized HPV-based screening program with long intervals, offering self-sampling to women who do not participate in office-based screening (6). On the other hand, several European countries currently are not considering changing their cytology-based screening programs. And, as discussed by Kinney and Huh (7), in this issue of the journal, in places like the U.S., issues of safety are prioritized over screening harms and efficiency.

The reasons for the different reactions to the existing evidence vary. For example, a country with low cervical cancer rates and an established cytology-based screening program may not have an incentive to change existing practice. However, in increasingly vaccinated populations, at some point the benefits of switching to an HPV-based program may outweigh the efforts required to implement such a program (as outlined in the reports in this issue: (1;8;9)). Cytology-based screening will become less efficient in vaccinated women, since abnormal cytology results shift to minor abnormalities caused by less carcinogenic types with low cancer risk (10). Conversely, in primary screening based on HPV testing, HPV positive women can be managed based on genotyping, particularly HPV16/18 and cytology. Cytology triage in HPV+ women will maintain efficiency, since the PPV will still be sufficiently high in this risk group, even if vaccinated. However, biomarker enhanced cytology may be more accurate than conventionally stained cytology (11).

Some healthcare authorities require demonstrating effectiveness or feasibility locally before considering a switch to new screening strategies that have been proven effective elsewhere. However, systematic reviews have shown that the efficacy data for HPV screening are very consistent across randomized trials and observational studies from many countries, suggesting that new trials in different settings will most likely show the same results (12). Instead, it is important to focus on approaches to evaluate the population effectiveness of HPV-based screening programs. Implementation studies can evaluate the performance of an entire screening program, from primary screening to triage, treatment, and follow up and will consider benefits and harms on the population level. Even if a new primary screening strategy can be implemented successfully, the program can still fail if the downstream elements (adherence to screening policy; participation at longer intervals, effectiveness of and compliance with the recommended triage and management of screen-positive women) do not work (13).

HPV screening efficacy trials have been criticized by some for not including cervical cancer endpoints. This has led to downgrading of evidence from these trials in formal evidence assessments. The reason for choosing precancer endpoints in most trials is the rarity of cervical cancers in existing screening programs that makes it difficult to power trials for cancer endpoints. The concern has been raised that simply showing an increased detection of CIN3 by HPV testing does not prove that HPV screening will lead to greater reductions of cancers, since the additional detection could be due to precancers that would not progress to cancer (overdiagnosis). Therefore, longitudinal data (cumulative incidence of CIN3+) showing lower rates of CIN3+ after a negative HPV test than after a negative Pap were requested before accepting new European guidelines for HPV-based screening (4). Pooled data from the European trials demonstrated lower cancer rates in women screened with HPV testing, demonstrating that the proxy indeed works (12;14).

In most countries with cervical cancer screening programs, the majority of cervical cancers occur in women who do not participate in regular screening. Thus, it is not expected that switching to HPV screening will lead to a substantial reduction in cervical cancer rates, unless participation in screening can be improved. Importantly, HPV testing, in contrast to cytology, permits the offer of self-sampling to initial non-participants, which can increase the screening coverage and reduce cervical cancer rates in populations that would otherwise not be screened (15). This approach will be used in the new HPV-based Dutch screening program. If self-sampling is offered as a strategy, a clinically validated PCR assay or one of similar sensitivity should be chosen in order to approach the same accuracy as on clinician collected samples (16).

It is often argued that extending cervical cancer screening intervals may increase risk of loss to follow up and may deprive women from other benefits offered by more frequent visits. While decrease in coverage at longer intervals would be a concern in an opportunistic screening triggered by spontaneous action, in a well-organized program women are sent invitations and reminders for screening visits and extended intervals should not impact participation. Another advantage of an organized system is the possibility to track non-responders and offer alternative screening options, most importantly self-sampling. This can lead to higher overall screening rates. Some countries with an opportunistic screening program, like Germany, now have a mandate to switch to an organized, HPV-based screening. Other potential benefits to women from an annual or biannual visit to the gynecologist are controversially discussed and only some of these possible benefits have been systematically evaluated. For example, no benefit was found for an annual pelvic examination, which resulted in a formal recommendation against an annual pelvic examination in asymptomatic women (17). It is also very important to consider the harms of too frequent screening, which are often neglected. Recently, it was estimated that the population effectiveness of cervical cancer screening in the US and the Netherlands is very similar, but that the US approach with more intensive screening has substantially more screening-related harms (18).

Recently published retrospective analyses of large laboratory data have suggested that HPV testing may miss a subset of cervical cancers and have therefore strongly called for doing HPV-cytology co-testing over HPV alone. Some limitations of study designs with

retrospective testing have been pointed out that can lead to biased estimates of sensitivity for HPV testing and cytology (19). Still, in many studies of HPV testing of cervical cancers, a subset of cervical cancers tests negative with common HPV DNA assays but positive for cytology (20). These findings are often presented as argument for co-testing (screening with cytology and for HPV test). There are several possible explanations for HPV-negativity in cervical cancer series: First, there is a very small group of cervical cancers that are not caused by HPV, but this is extremely rare. Second, there are very rare cancers caused by HPV types not included in the typical panel of 13 to 14 high-risk types (21). Third, it has been suggested that in the progression to cancer, parts of the HPV genome may be lost due to HPV integration, affecting the detectability with L1-based HPV assays. However, there is no systematic evaluation that supports this point. Fourth, in advanced cervical cancers, cervical samples often contain large amounts of necrotic material that does not yield adequate DNA for HPV detection. Importantly, the goal of cervical cancer screening is the detection of precancers that can be treated and prevent cancers from occurring. Prospective studies have shown only minimal benefit of adding cytology to HPV screening at the cost of conducting a second test in the whole population (22).

In summary, there is overwhelming evidence demonstrating that a HPV-based screening program at longer intervals can be more efficient with potentially fewer screening-related harms compared to cytology screening. When considering switching to HPV-based screening, several important factors need to be considered: (1) What HPV screening assay should be used? The performance of FDA-approved HPV DNA assays is very similar, but assays may differ with respect to partial genotyping. International criteria have been defined regarding minimal requirement to accept new HPV DNA assays and list of tests fulfilling these guidelines were published recently (23). (2) What screening interval should be used for HPV-negatives? In organized screening programs, 5-year intervals are very safe and can be extended even longer in women with repeated negative screens who have the lowest risk of cancer. (3) What triage test should be used? There is a growing number of options of assays for triage of HPV-positive women, including cytology, partial genotyping, p16/Ki-67, methylation, and others (24;25). Currently, large head-to-head comparisons of these options are lacking. Clearly, there is no one-size-fits all for designing an HPV-based screening program. The risk perception and tolerance in a society, the amount of healthcare funds, the existing infrastructure and pricing of specific assays may be important factors for choosing the individual components of an integrated HPV screening program. The greatest benefit of an integrated HPV-vaccination and screening approach can be reached in an organized setting with vaccination and screening registries that allow tailoring screening according to the vaccination status of the individual woman or to the vaccination coverage of the cohort.

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Reference List

1. Tota J, Bentley J, Blake J, Coutlee F, Duggan M, Ferenczy A, et al. Introduction of molecular HPV testing as the primary technology in cervical cancer screening: Acting on evidence to change the current paradigm. *Preventive Medicine*. 2016 (in this issue).
2. Health Council of the Netherlands. Population screening for cervical cancer. The Hague: Health Council of the Netherlands; 2011. (No. 2011/07E)
3. Lew JB, Simms K, Smith M, Kang YK, Xu X, Caruana M, et al. National Cervical Screening Program Renewal: Effectiveness modelling and economic evaluation in the Australian setting. Medical Services Advisory Committee Australia. 2013 MSAC Application No. 1276(1276).
4. von Karsa L, Arbyn M, De Vuyst H, Dillner J, Dillner L, Franceschi S, et al. European guidelines for quality assurance in cervical cancer screening. Summary of the supplements on HPV screening and vaccination. *Papillomavirus Res*. 2015; 1:22–31.
5. World Health Organization. Comprehensive cervical cancer control: a guide to essential practice. http://apps.who.int/iris/bitstream/10665/144785/1/9789241548953_engpdf?ua=1 2014
6. Rozemeijer K, de Kok IM, Naber SK, van Kemenade FJ, Penning C, van RJ, et al. Offering Self-Sampling to Non-Attendees of Organized Primary HPV Screening: When Do Harms Outweigh the Benefits? *Cancer Epidemiol Biomarkers Prev*. 2015 May; 24(5):773–782. [PubMed: 25432954]
7. Kinney W, Huh W. Protection Against Cervical Cancer versus Decreasing Harms from Screening - What Would U.S. Patients and Clinicians Prefer, and Do Their Preferences Matter? *Preventive Medicine*. 2016 (in this issue).
8. Rossi PG, Carozzi F, Federici A, Ronco G, Zappa M, Franceschi S, et al. Cervical cancer screening in women vaccinated against human papillomavirus infection: Recommendations from a consensus conference. *Preventive Medicine*. 2016 (in this issue).
9. Tota J, Bentley J, Blake J, Coutlee F, Duggan M, Ferenczy A, et al. Approaches for triaging women who test positive for human papillomavirus in cervical cancer screening. *Preventive Medicine*. 2016 (in this issue).
10. Franco EL, de SS, Broker TR, Stanley MA, Chevarie-Davis M, Isidean SD, et al. Human papillomavirus and cancer prevention: gaps in knowledge and prospects for research, policy, and advocacy. *Vaccine*. 2012 Nov 20; 30(Suppl 5):F175–F182. [PubMed: 23199961]
11. Wentzensen N, Fetterman B, Castle PE, Schiffman M, Wood SN, Stiemerling E, et al. p16/Ki-67 Dual Stain Cytology for Detection of Cervical Precancer in HPV-Positive Women. *J Natl Cancer Inst*. 2015 Dec.107(12):djv257. [PubMed: 26376685]
12. Arbyn M, Ronco G, Anttila A, Meijer CJ, Poljak M, Ogilvie G, et al. Evidence regarding human papillomavirus testing in secondary prevention of cervical cancer. *Vaccine*. 2012 Nov 20; 30(Suppl 5):F88–F99. [PubMed: 23199969]
13. Passamonti B, Gustinucci D, Giorgi RP, Cesarini E, Bulletti S, Carlini A, et al. Cervical human papilloma virus (HPV) DNA primary screening test: Results of a population-based screening programme in central Italy. *J Med Screen*. 2016 Sep 10.
14. Ronco G, Dillner J, Elfstrom KM, Tunesi S, Snijders PJ, Arbyn M, et al. Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials. *Lancet*. 2014 Feb 8; 383(9916):524–532. [PubMed: 24192252]
15. Verdoodt F, Jentschke M, Hillemanns P, Racey CS, Snijders PJ, Arbyn M. Reaching women who do not participate in the regular cervical cancer screening programme by offering self-sampling kits: a systematic review and meta-analysis of randomised trials. *Eur J Cancer*. 2015; 51(16):2375–2385. [PubMed: 26296294]
16. Arbyn M, Verdoodt F, Snijders PJ, Verhoef VM, Suonio E, Dillner L, et al. Accuracy of human papillomavirus testing on self-collected versus clinician-collected samples: a meta-analysis. *Lancet Oncol*. 2014 Feb; 15(2):172–183. [PubMed: 24433684]
17. Qaseem A, Humphrey LL, Harris R, Starkey M, Denberg TD. Screening pelvic examination in adult women: a clinical practice guideline from the American College of Physicians. *Ann Intern Med*. 2014 Jul 1; 161(1):67–72. [PubMed: 24979451]
18. Habbema D, Weinmann S, Arbyn M, Kamineni A, Williams AE, de Kok IM, et al. Harms of Cervical Cancer Screening in the United States and the Netherlands. *Int J Cancer*. 2016 Nov 16.

19. Giorgi RP, Ronco G, Dillner J, Elfstrom KM, Snijders PJ, Arbyn M, et al. Why follow-back studies should be interpreted cautiously: The case of an HPV-negative cervical lesion. *Cancer Cytopathol.* 2016 Jan; 124(1):66–67. [PubMed: 26356132]
20. Wentzensen N, Schiffman M, Dunn T, Zuna RE, Gold MA, Allen RA, et al. Multiple human papillomavirus genotype infections in cervical cancer progression in the study to understand cervical cancer early endpoints and determinants. *Int J Cancer.* 2009 Nov 1; 125(9):2151–2158. [PubMed: 19585494]
21. Arbyn M, Tommasino M, Depuydt C, Dillner J. Are 20 human papillomavirus types causing cervical cancer? *J Pathol.* 2014 Dec; 234(4):431–435. [PubMed: 25124771]
22. Gage JC, Schiffman M, Katki HA, Castle PE, Fetterman B, Wentzensen N, et al. Reassurance against future risk of precancer and cancer conferred by a negative human papillomavirus test. *J Natl Cancer Inst.* 2014 Aug.106(8)
23. Meijer CJ, Berkhof J, Castle PE, Hesselink AT, Franco EL, Ronco G, et al. Guidelines for human papillomavirus DNA test requirements for primary cervical cancer screening in women 30 years and older. *Int J Cancer.* 2009 Feb 1; 124(3):516–520. [PubMed: 18973271]
24. Wentzensen N, Schiffman M. Filling a gap in cervical cancer screening programmes. *Lancet Oncol.* 2014; 15(3):249–251. [PubMed: 24529698]
25. Wentzensen N, Schiffman M, Palmer T, Arbyn M. Triage of HPV positive women in cervical cancer screening. *J Clin Virol.* 2016 Mar; 76(Suppl 1):S49–S55. [PubMed: 26643050]

Highlights

- Controversies about HPV testing influence its implementation in screening
- There is clear evidence that HPV testing is more effective than cytology
- There is limited data on optimal triage strategies for HPV-positive women
- Implementation of HPV screening programs will vary in different settings