

DOI: 10.1093/jnci/djq357
Advance Access publication on September 14, 2010.

© The Author 2010. Published by Oxford University Press. All rights reserved.
For Permissions, please e-mail: journals.permissions@oxfordjournals.org.

Persistent HPV Infection and Cervical Cancer Risk: Is the Scientific Rationale for Changing the Screening Paradigm Enough?

Eduardo L. Franco

Correspondence to: Eduardo L. Franco, DrPH, Departments of Oncology and Epidemiology, McGill University, 546 Pine Avenue West, Montreal, QC, Canada H2W1S6 (e-mail: eduardo.franco@mcgill.ca).

Few cancer prevention discoveries have been as unequivocal as the finding that human papillomavirus (HPV) infection is a necessary cause of cervical cancer (1). The fact that HPV nucleic acid is found in nearly every exfoliated cervical cell specimen from women with high-grade cervical intraepithelial neoplasia (CIN) or cervical can-

cer is the justification for designing molecular-based assays to be used in screening. Yet, the paradigm for secondary prevention of this disease has thus far been difficult to challenge. Pap cytology testing has been the technological mainstay of cervical cancer screening programs for more than 50 years. North American and

Western European countries have relied on the Pap test for their organized or opportunistic cervical screening programs, which have been largely successful in reducing cervical cancer morbidity and mortality. In most of the developing world, however, replicating the experience of resource-rich countries has left much to be desired. Effective cervical screening programs require large and equitable coverage, that high-quality cytology standards be maintained, and that diagnostic and treatment resources for managing cases of disease identified on screening be provided. Blind pursuit of high and frequent screening coverage without fulfilling the latter two requirements has been the reason why Pap cytology screening programs have not been as successful in developing countries. Pap cytology has a high false-negative rate for lesion detection even in settings that meet quality assurance standards (2), which forms the basis for public health guidelines recommending that the test be done frequently enough to compensate for its low sensitivity. Annual Pap tests have been the norm in many countries. Only after two or three negative results women are told by their physicians that they can return less often for subsequent Pap tests. Therefore, sustaining secondary prevention programs that rely on a core technology that is insensitive even in optimal deployment conditions becomes an expensive and highly demanding public health activity; only resource-rich nations have been able to reap the full benefits from Pap cytology screening.

DNA testing for high-risk HPV genotypes (types for short) fulfills all essential criteria for a candidate cervical cancer screening tool. It is substantially more sensitive compared with Pap cytology for detecting high-grade CIN (3,4), which provides a better margin of safety in extending screening intervals (5). It can be automated, and interpretation of the test results is based on instrument readout, thus eliminating the vagaries of subjective interpretation of cell type distributions in smears by cytotechnicians who have different levels of training, experience, and alertness. Concerns about overdetection bias were largely assuaged by findings from trials that showed a reduction in CIN grade 2 and CIN grade 3 (CIN3) on subsequent screening rounds (6–8). Most importantly, a recent cluster randomized trial has shown that HPV testing reduces cervical cancer mortality to a greater extent than Pap cytology (9), a litmus test for any candidate screening technology.

In the face of so much evidence, the obvious question is then “Why isn’t HPV testing used in cervical cancer screening as the core technology?” In the United States, HPV testing has been approved at most as an adjunct test, an ostensibly timid moniker that emphasizes the notion that cytology is the core technology and that the HPV molecular test has at best an ancillary value. Elsewhere, HPV testing has not yet been approved as a stand-alone cervical cancer screening test. Cost considerations, fear of shifting from a public-domain technology (Pap test) to a commercially based one, provider and patient education issues, and the need for retraining the laboratory workforce are undoubtedly chief concerns that cannot be solved by research alone. Among clinicians and policymakers, there is still substantial uncertainty about the clinical significance of a positive HPV DNA test result. The latter is a scientific tractable question that the study by Kjær et al. (10) in this issue of the Journal has gone to great lengths in answering.

This Danish study (10) was a well-conducted prospective epidemiological investigation that combined state-of-the-art molecular testing for HPV with record linkage to centralized national pathology databases to ascertain the 12-year cervical lesion histories of nearly 8000 women with normal Pap cytology at enrollment. The investigation was unique in that it permitted examining the value of HPV type-specific persistence in predicting subsequent risk of high-grade CIN, and more importantly, of CIN3, the more credible and reproducible precancerous lesion (10). It was already known that high-risk HPV types vary with respect to their oncogenic potential, with HPV16 infection being unequivocally the strongest risk predictor and HPV18 infection following close behind in the risk spectrum in part because of its delayed effect in inducing lesions (11). What was not known was the relative importance of the remaining 13 high-risk HPV types. Do they represent an indistinguishable third tier in terms of risk of present and future risk or are there variations among types? Is persistent infection with types other than HPV16 or HPV18 equally predictive of CIN3? Kjær et al. (10) were able to address these important questions. They found that although infection with some types, such as HPV53, HPV56, HPV59, and HPV68, were prone to persist for 2 years, they did not lead to lesions during the entire follow-up period. Other types, such as HPV31 and HPV33, yielded comparable risks that were practically indistinguishable from that of HPV18 and formed a second tier of clinical relevance. Their finding that an HPV16 infection was not only more likely to persist but also led to the greatest risk of CIN3 among all HPV types comes as no surprise. What is impressive is the observation of a nearly 50% absolute risk of CIN3 at the end of follow-up for women with persistent HPV16 infections. Also noteworthy was the observation that an incident HPV16 infection implied the same CIN3 risk as that borne by women with persistent positivity in the Hybrid Capture 2 assay (Qiagen, Inc, Valencia, CA), a clinically validated test that does not distinguish among types. Largely on the basis of these findings, the authors advance the argument that women with an HPV16 infection (nota bene: genotyped after a positive Hybrid Capture 2 result) would benefit from immediate colposcopy (10). Conversely, HPV-negative women had very low risk of CIN3 throughout the entire follow-up and were thus likely to benefit from a policy of extended screening intervals.

The resistance of policymakers to a change in cervical cancer screening paradigm from the relatively insensitive and poorly reproducible Pap cytology to the more sensitive and reproducible HPV DNA test is based on uncertainty about the outcome of HPV infections without coexisting cervical abnormalities. The emerging knowledge from molecular epidemiological investigations (11,12), certainly bolstered by the Danish study (10), has led some thought leaders to propose risk stratification algorithms to assist clinicians in estimating present and future risk of cervical lesions for their patients, thus enabling more rational management strategies to tailor treatment while minimizing harm (13). Will policymakers and clinical guidelines adopt a simple change in screening paradigm by placing the emphasis on HPV DNA testing irrespective of genotype [perhaps with Pap triage of those who are HPV positive (14)], or will genotyping be incorporated at the outset to permit a more refined risk stratification? The Danish study raises the stakes in this debate, providing strong scientific arguments for the latter option.

However, as the history of cervical cancer prevention has shown, it will take more than science to change the screening paradigm.

References

1. Walboomers JM, Jacobs MV, Manos MM, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol.* 1999;189(1):12–19.
2. Cuzick J, Clavel C, Petry KU, et al. Overview of the European and North American studies on HPV testing in primary cervical cancer screening. *Int J Cancer.* 2006;119(5):1095–1101.
3. Koliopoulos G, Arbyn M, Martin-Hirsch P, Kyrgiou M, Prendiville W, Paraskevaidis E. Diagnostic accuracy of human papillomavirus testing in primary cervical screening: a systematic review and meta-analysis of non-randomized studies. *Gynecol Oncol.* 2007;104(1):232–246.
4. Mayrand MH, Duarte-Franco E, Rodrigues I, et al. Human papillomavirus DNA versus Papanicolaou screening tests for cervical cancer. *N Engl J Med.* 2007;357(16):1579–1588.
5. Dillner J, Rebolj M, Birembaut P, et al. Long term predictive values of cytology and human papillomavirus testing in cervical cancer screening: joint European cohort study. *BMJ.* 2008;337:a1754doi: 10.1136/bmj.a1754.
6. Bulkmand NW, Berkhof J, Rozendaal L, et al. Human papillomavirus DNA testing for the detection of cervical intraepithelial neoplasia grade 3 and cancer: 5-year follow-up of a randomised controlled implementation trial. *Lancet.* 2007;370(9601):1764–1772.
7. Naucler P, Ryd W, Törnberg S, et al. Human papillomavirus and Papanicolaou tests to screen for cervical cancer. *N Engl J Med.* 2007; 357(16):1589–1597.
8. Ronco G, Giorgi-Rossi P, Carozzi F, et al. Efficacy of human papillomavirus testing for the detection of invasive cervical cancers and cervical intraepithelial neoplasia: a randomised controlled trial [published online ahead of print January 18, 2010]. *Lancet Oncol.* 2010;11(3): 249–257.
9. Sankaranarayanan R, Nene BM, Shastri SS, et al. HPV screening for cervical cancer in rural India. *N Engl J Med.* 2009;360(14):1385–1394.
10. Kjer SK, Frederiksen K, Munk C, Iftner T. Long-term absolute risk of cervical intraepithelial neoplasia grade 3 or worse following human papillomavirus infection: role of persistence. *J Natl Cancer Inst.* 2010;102(19): 1478–1488.
11. Khan MJ, Castle PE, Lorincz AT, et al. The elevated 10-year risk of cervical precancer and cancer in women with human papillomavirus (HPV) type 16 or 18 and the possible utility of type-specific HPV testing in clinical practice. *J Natl Cancer Inst.* 2005;97(14):1072–1079.
12. Schiffman M, Rodriguez AC, Chen Z, et al. A population-based prospective study of carcinogenic human papillomavirus variant lineages, viral persistence, and cervical neoplasia. *Cancer Res.* 2010;70(8):3159–3169.
13. Katki HA, Wacholder S, Solomon D, Castle PE, Schiffman M. Risk estimation for the next generation of prevention programmes for cervical cancer. *Lancet Oncol.* 2009;10(11):1022–1023.
14. Anttila A, Kotaniemi-Talonen L, Leinonen M, et al. Rate of cervical cancer, severe intraepithelial neoplasia, and adenocarcinoma in situ in primary HPV DNA screening with cytology triage: randomised study within organised screening programme. *BMJ.* 2010;340:c1804doi:10.1136/bmj.c1804.

Notes

The author has served as occasional advisory board member or consultant to companies involved with HPV vaccines (GlaxoSmithKline and Merck), HPV diagnostics (Gen-Probe, Roche, and Qiagen), or cervical cancer cytology screening (Cytoc and Ikonisys).

Affiliation of author: Departments of Oncology and Epidemiology, McGill University, Montreal, QC, Canada.