Cervical Screening: Not Yet Time to Abandon Pap Tests for HPV Testing

Theunis van Zyl, BSc, MD Candidate 2018[1]

[1]Schulich School of Medicine & Dentistry, Western University

Background

Cervical cancer is a common but extremely preventable cancer, with a survival rate of 93% if detected early.[1] The Papanicolaou test, or "Pap" test, has been the mainstay in cervical cancer screening since inception of cervical cancer screening in the 1960s. Pap tests aim to detect the presence of atypical or pre-cancerous cells, utilizing cytology, in the hopes of preventing progression to cervical cancer. Current Canadian Task Force on Preventative Health Care (CTFPHC) guidelines recommend screening sexually active women between the ages of 25 and 69 every 3 years.[2]

Given that human papilloma virus (HPV) is responsible for 99% of cervical cancers, some clinicians have instead suggested that screening should be done for HPV infection.[3] With the recent introduction of HPV DNA tests, there has been a movement to replace routine Pap tests with regular HPV DNA tests. The idea is to identify HPV carriers before the infection progresses to cervical cancer. Supporting this movement are a few major studies on the benefits of HPV testing. In this paper, the arguments for and against abandoning Pap tests in favour of HPV testing in Canada will be explored.

Benefits of HPV Testing

Recently there have been a number of randomized controlled trials (RCTs) comparing HPV DNA testing to Pap tests and cytology in the detection of cancerous and pre-cancerous cervical lesions. Many studies have shown that HPV testing is more sensitive than Pap tests in detecting abnormalities or cancers.[4-7] HPV testing, in addition to having a higher negative predictive value, has a sensitivity of 76.1%, almost double the sensitivity of Pap tests and cytology, which is 47.8%.[8] Three large RCTs, which examined over 150,000 patients, found that HPV testing had a 60% higher detection rate for grade CIN3 (cervical intraepithelial neoplasia) pre-cancerous cervical lesions than Pap tests.[6-8] The results also showed that HPV testing had a 50-68% higher detection rate for CIN2 lesions.[6,7] When examining only younger women, aged 25-34, one study found that HPV testing had a 127% higher detection rate of CIN2 and CIN3 lesions compared to Pap tests.[6]

In addition, decreased rates of cervical cancer have been shown for up to 6.5 years in patients screened with HPV testing versus Pap tests alone, suggesting earlier detection of pre-cancerous lesions with HPV testing.[4,6] One of these studies, drawing on 4 RCTs done in Europe, found that HPV testing provided 60-70% more prevention of cervical cancer than regular Pap test and cytology screening.[4] This evidence strongly suggests that HPV testing detects pre-cancerous cervical lesions earlier, resulting in fewer cases of progression to cervical cancer.

When examining evidence on Pap tests, there are many limitations that may favour HPV testing. As described, Pap tests have a sensitivity of 47.8%, which confers a higher false negative rate.[8] One study found that Pap tests may miss up to 50% of CIN3 cervical lesions.[8] Pap tests also appear to have a high rate of loss to follow up at 33%, twice the rate compared to that of HPV testing.[9] However, in the study describing discrepancies in loss to follow up, positive Pap tests were only referred after a 6 month follow up , while patients with positive HPV testing were immediately referred to colposcopy.[9] This difference in time between referrals may account for the increased loss of follow-up in Pap tests.

Limitations of HPV Testing

While there are many benefits of HPV testing, such as earlier detection of cervical lesions and possible increased detection rates, this test itself does not come without limitations.

One of the major limitations of all HPV DNA studies described above was the total lack of or very short follow up periods of 3-4 years in most trials, with only one following patients for up to 6.5 years.[4,6-8] Evidence shows that mild, pre-cancerous cervical lesions have a mean progression time to high-grade dysplasia or cancer of over 7 years.[10] Given the slow growth and progression of cervical pre-cancers, more longitudinal studies are required to determine the benefit of this screening method.

In addition, the evidence on the effectiveness of HPV testing for cervical cancer screening is not unanimous. Two large European RCTs found no difference in overall detection rates of high-grade cervical dysplasia when comparing cytology plus HPV testing to cytology alone.[11,12] However, one of these studies found that HPV and cytology resulted in more CIN3 cases being detected earlier, with cases being identified in the first round of screening, as opposed to the second.[11] This suggests that while HPV testing may lead to earlier detection of cervical lesions, it does not appear to lead to increased detection overall. Moreover, none of the mentioned studies

have shown any mortality or survival benefit for HPV screening compared to Pap testing.

Despite evidence suggesting earlier detection, many of the aforementioned trials reveal other limitations of using HPV testing as a screening test for cervical cancer. For the healthcare system, an individual HPV test costs 50% more than a standard Pap test, at $30 per HPV test versus $20 for a Pap test.[9]

It is also important to consider that Pap tests and cytology screen for pre-cancerous changes while HPV testing screens for the causative agent, which does not necessarily lead to cervical changes. As a result, HPV testing results in more false positive screens than Pap tests, leading to a significant increase in colposcopy referrals and follow up tests.[6-8,13,14] In one large RCT mentioned earlier, HPV testing nearly doubled the number of required colposcopies, with a 95% increase in colposcopies performed.[8] This has the potential to drastically increase the cost of cervical cancer screening. An Ontario study found that HPV testing cost an additional $3000 for each additional CIN 2 or 3 lesion it identified.[9] Research modeling total downstream costs per quality adjusted life year (QALY) estimated that biennial HPV plus Pap tests cost $70,000/QALY, in contrast to $30,000/QALY for biennial Pap tests alone.[15] Furthermore, studies have shown that many of the pre-cancerous lesions that HPV testing detects would naturally be cleared by the immune system in younger women without detrimental effects.[6,13] Schlecht and colleagues found that 93% of mild cervical lesions regress within 2 years.[10] One of the studies stated that HPV testing leads to overdiagnosis of self-regressing CIN2 lesions.[6]

In summary, it appears that higher rates of detection for HPV testing may be due to higher detection of early lesions in younger women that often spontaneously regress. This is important to consider for a screening test that is performed on such a large percentage of the population. High rates of false positive tests and increased colposcopies cause unnecessary stress and anxiety for patients, as well as cost to the healthcare system. This is especially important given that many of these lesions would clear on their own and, as mentioned earlier, that HPV testing has not shown any mortality or overall cost reduction benefit for the increased follow-up and up-front costs.

Conclusion

Given all of these factors, there is not yet enough evidence to support switching from Pap tests to HPV testing as the primary modality for cervical cancer screening in Canada. Multiple trials have shown HPV testing to be effective at screening for cervical cancer and its precursor lesions. Evidence strongly suggests that HPV testing is effective at detecting CIN2 and CIN3 cervical lesions earlier than Pap tests before they progress to cancer. However, there is inconsistency in the evidence as to whether or not HPV testing leads to overall increased rates of detection.

Additionally, there is not yet any evidence of mortality or net cost benefit from cervical cancer screening with HPV testing compared to Pap tests and cytology. HPV testing has been shown to increase false positive screening tests, resulting in a large increase in follow up tests – in particular, colposcopies. Strong evidence exists supporting the effectiveness of HPV testing in cervical screening, but more evidence is needed on the net cost and mortality benefits of switching to this this test, which has a higher up-front cost.

Given patient anxiety from a high rate of false positive results, increased up-front costs with no proven long-term benefit, conflicting evidence on overall detection rates for cervical lesions using HPV testing, and the duty to conserve medical resources in a publicly funded healthcare system, it is not yet time to abandon Pap tests in favour of HPV testing as the primary screening method for cervical cancer.

References

1. Edge S, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti AI, editors. American Joint Committee on Cancer. AJCC cancer staging manual. 7th ed. New York: Springer; 2010. 648 p.
2. Canadian Task Force on Preventive Health Care. Recommendations on screening for cervical cancer. Can Med Assoc J 2013; 185(1):35-45.
3. Walboomers JM, Jacobs MV, Manos MM, Bosch FX, Kummer JA, Shah KV, Snijders PJ, Peto J, Meijer CJ, Munoz N. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol 1999; 189(1):12-9.
4. Ronco G, Dillner J, Elfström KM, Tunesi S, Snijders PJ, Arbyn M, Kitchener H, Segnan N, Gilham C, Giorgi-Rossi P, Berkhof J. Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials. Lancet 2014; 383(9916):524-32.
5. Whitlock EP, Vesco KK, Eder M, Lin JS, Senger CA, Burda BU. Liquid-based cytology and human papillomavirus testing to screen for cervical cancer: a systematic review for the US Preventive Services Task Force. Ann Intern Med 2011; 155(10):687-97.
6. Ronco G, Giorgi-Rossi P, Carozzi F, Confortini M, Dalla Palma P, Del Mistro A, Ghiringhello B, Girlando S, Gillio-Tos A, De Marco L, Naldoni C. Efficacy of human papillomavirus testing for the detection of invasive cervical cancers and cervical intraepithelial neoplasia: a randomised controlled trial. Lancet Oncol; 11(3):249-57.
7. Ogilvie GS, Krajden M, Van Niekerk DJ, Martin RE, Ehlen TG, Ceballos K, Smith LW, Kan L, Cook DA, Peacock S, Stuart GC. Primary cervical cancer screening with HPV testing compared with liquid-based cytology: results of round 1 of a randomised controlled trial–the HPV FOCAL Study. Brit J Cancer 2012; 107(12):1917-24.
8. Wright TC, Stoler MH, Behrens CM, Sharma A, Zhang G, Wright TL. Primary cervical cancer screening with human papillomavirus: end of study results from the ATHENA study using HPV as the first-line screening test. Gynecol Oncol 2015; 136(2):189-97.
9. Lytwyn A, Sellors JW, Mahony JB, Daya D, Chapman W, Ellis N, Roth P, Lorincz AT, Gafni A. Comparison of human papillomavirus DNA testing and repeat Papanicolaou test in women with low-grade cervical cytologic abnormalities: a randomized trial. Can Med Assoc J 2000; 163(6):701-7.
10. Schlecht NF, Platt RW, Duarte-Franco E, Costa MC, Sobrinho JP, Prado JC, Ferenczy A, Rohan TE, Villa LL, Franco EL. Human papillomavirus infection and time to progression and regression of cervical intraepithelial neoplasia. J Natl Cancer Inst 2003; 95(17):1336-43.
11. Rijkaart DC, Berkhof J, Rozendaal L, van Kemenade FJ, Bulkmans NW, Heideman DA, Kenter GG, Cuzick J, Snijders PJ, Meijer CJ. Human papillomavirus testing for the detection of high-grade cervical intraepithelial neoplasia and cancer: final results of the POBASCAM randomised controlled trial. Lancet Oncol 2012; 13(1):78-88.
12. Kitchener HC, Almonte M, Thomson C, Wheeler P, Sargent A, Stoykova B, Gilham C, Baysson H, Roberts C, Dowie R, Desai M. HPV testing in combination with liquid-based cytology in primary cervical screening (ARTISTIC): a randomised controlled trial. Lancet Oncol 2009; 10(7):672-82.
13. Castle PE, Katki HA. Benefits and risks of HPV testing in cervical cancer screening. Lancet Oncol 2010; 11(3):214-5.
14. Feldman S. Human papillomavirus testing for primary cervical cancer screening: is it time to abandon papanicolaou testing?. JAMA Intern Med 2014; 174(10):1539-40.
15. Mandelblatt JS, Lawrence WF, Womack SM, Jacobson D, Yi B, Hwang YT, Gold K, Barter J, Shah K. Benefits and costs of using HPV testing to screen for cervical cancer. JAMA 2002; 287(18):2372-81.