Utilisation of co-testing (human papillomavirus DNA testing and cervical cytology) after treatment of CIN: a survey of GPs' awareness and knowledge

Aime Munro
Jim Codde
James Semmens
Yee Leung
Katrina Spilsbury
Vincent Williams
Nerida Steel
Paul Cohen
Heidi Pavicic
Vicki Westoby
Peter O'Leary

Background

Patients have an increased risk of persistent/recurrent cervical disease if they received treatment for a high-grade squamous intraepithelial lesion (HSIL). Consequently, understanding whether co-testing (human papillomavirus [HPV] DNA testing and cervical cytology) is fully utilised by general practitioners (GPs) is paramount.

Methods

After consultation with key stakeholders, an anonymous, self-completion questionnaire was developed and disseminated to GPs who had provided cervical cytology.

Results

Responses were received from 745 GPs (30.9% response rate). A significant number (34.3%) of GPs were unaware of the use of co-testing (HPV DNA testing and cervical cytology) for the management of patients after HSIL treatment. Additionally, the majority of GPs reported they did not 'always' receive a clear follow-up plan for patients after treatment of an HSIL.

Discussion

GPs require further support and education to ensure successful adoption of co-testing (HPV DNA testing and cervical cytology), specifically, for patients treated for an HSIL.

Keywords

cervical intraepithelial neoplasia; human papillomavirus DNA tests; Papanicolaou test; general practice

Conventional cervical cytology is the standard screening test for identifying women who are at increased risk of cervical cancer by detecting premalignant cervical lesions.[1–3] Worldwide, countries that have adopted an organised approach to cervical screening have been successful in detecting and treating high-grade squamous intraepithelial lesions (HSIL) before possible progression to cervical cancer.[1–3] HSIL refers to moderate-to-severe changes in the cells of the cervix known as cervical intraepithelial neoplasia (CIN) 2 or CIN 3.[4] A study conducted recently reported the positive predictive value of biopsy confirmed precancerous cervical lesions to be as high as 71% for patients with an HSIL cervical cytology test result.[5] Consequently, a patient with an HSIL result should be referred as soon as practicable for colposcopic assessment and targeted biopsy.[4]

Acceptable treatment options for patients with an HSIL cytology test result that was confirmed with colposcopy and biopsy include ablative or excisional modalities.[4] However, if colposcopy is unsatisfactory or if the HSIL persists, a diagnostic excision is recommended.[4] The majority of patients will clear human papillomavirus (HPV) infection within 24 months post-treatment; however, previous studies have shown that patients with a history of treated CIN 2 and/or CIN 3 are at increased risk of recurrent high-grade disease and cervical cancer.[6] Persistent disease (≥6 months post-treatment) is often associated with endocervical gland involvement[7] and continuing HPV infection[8,9] (specifically high-risk HPV[16]). Our improved understanding that oncogenic HPV infection is instrumental in the development of cervical cancer has led to the development and utilisation of tests that can detect HPV DNA oncogenic types.[5,6,10–12]

HPV DNA testing may be implemented as an auxiliary tool, in combination with cervical cytology, to improve the management of patients at risk of further cervical disease.[4,12–14] This screening protocol takes advantage of the high sensitivity of HPV DNA tests and also the specificity of cervical cytology.[12] In 2005, best practice guidelines, known as the 'Test of Cure', were implemented in Australia. These guidelines recommend that patients should have a colposcopy and cervical cytology test 4–6 months after treatment for an HSIL.[4] If these two tests (using the two modalities) are negative, then the patient is able to return to the care of the GP and should be managed as follows:

- Cervical cytology accompanied by high-risk HPV DNA testing should commence 12 months after treatment and continue annually until the patient has tested negative for both tests on two consecutive occasions.[4]
- When the above four tests (using two modalities) are negative, the patient is encouraged to return to a regular screening regimen as appropriate for the general female population.[4]

Table 1. Characteristics of survey respondents

	Survey respondents	
Characteristics	**n = 745**	**Percentage (%)**
Sex		
Female	431	57.9
Male	311	41.8
Not reported	3	0.4
Age (years)		
<35	64	8.6
35–44	188	25.2
45–54	239	32.1
≥55	252	33.8
Not reported	2	0.3
Years practicing as a GP		
<2	41	5.5
2–5	70	9.4
6–10	81	10.9
11–19	172	23.1
≥20	379	50.9
Not reported	2	0.3
Direct patient contact hours per week		
<10	32	4.6
11–20	133	17.9
21–40	397	53.3
41–60	164	22.0
>60	14	1.9
Not reported	5	0.7
Index of relative social disadvantage		
Most disadvantaged	48	6.4
More disadvantaged	94	12.6
Middle	94	12.6
Less disadvantaged	162	21.7
Least disadvantaged	265	35.2
Not reported	85	11.4
Accessibility/Remoteness Index of Australia		
Major city	361	48.5
Inner regional	186	25.0
Outer regional	62	8.3
Remote/Very remote	51	6.9
Not reported	85	11.4

To date, no studies have addressed compliance with the Test of Cure. Recently, Dr Heley, a senior liaison physician with the Victorian Cytology Service raised a concern that health practitioners in Australia were failing to perform HPV tests on eligible women.[15] Understanding whether this pathway has been fully utilised by GPs is important given the risk of persistent/recurrent cervical disease for patients treated for an HSIL.[6,15] Consequently, the aims of this study were to investigate GPs' awareness of and compliance with performing co-testing (high-risk HPV DNA and cervical cytology) on eligible patients (as per Australian guidelines) and the perception of support from specialist obstetrician/gynecologists (ob/gyns) in providing clear care plans that promote this management pathway for patients after treatment of an HSIL.

Methods

Participants

The Cervical Cytology Registry (CCR) of Western Australia identified all GPs who had provided a cervical cytology test in the period 1 July 2012 to 30 June 2013. Data cleansing (contacting the GP practice and reviewing the Medicare Australia list of provider contact details) was undertaken for all individual GPs to ensure the Registry had up-to-date demographic details.

Measures

The survey design included a combination of questions with categorical and Likert scale response options and, where applicable, space for participants to provide additional comments. Information was collected about the GP respondents (age, number of direct patient contact hours, number of years practicing as a GP) and questions were focused on current practices regarding management of patients who had been treated for an HSIL.

Procedure

Following approval by the Curtin University Ethics Committee (Reference number HR 86/2012), the survey was mailed to GPs, together with a covering letter and reply paid envelope. To encourage GP participation in this study, and to ensure confidentiality, the survey respondents were de-identified.

Statistical analysis

Anonymous postal survey responses were manually entered into a specific Survey Monkey collation spreadsheet and then exported into STATA/IC 13.0 (STATA Corporation, College Station, USA) for statistical analysis. GPs' age (at the time of the survey) was classified into <35, 35–44, 45–54, ≥55 years age groups. Practice postcode was used to assign the practice location into quintiles of Index of Relative Social Disadvantage (ABS 2011) and into one of three Accessibility/Remoteness Index of Australia (ARIA) levels. Logistic regression analysis was used to investigate GP factors associated with the odds of having Test of Cure knowledge and involved purposeful selection of covariates at the 5% significance level.

Results

According to the CCR of Western Australia, 2545 GPs had performed a cervical cytology test in the 12-month period from 1 July 2012 to 30 June 2013. Of these 2545 GPs, to whom surveys were posted, responses were received from 745 (29.3%) GPs. After removing the 136 (5.4%) surveys that were returned as 'undeliverable' or 'blank', this corresponded to an adjusted response rate of 30.9%. As GPs have different provider numbers for each practice, the number of GPs offering cervical screening services may have been overestimated. GP demographic details are summarised in *Table 1*. The majority (79.7%) of responding GPs reported being aware of the current National Health and Medical Research Council (NHMRC) guidelines and almost 60% (59.6%) reported that they always complied with the recommendations. Almost one-third (29.5%) of participating GPs reported that they 'always' received a clear follow-up plan from gynaecologists/colposcopists for patients following treatment of an HSIL. Overall, just over one-third (34.3%) of GPs were unable to identify all of the steps in the NHMRC's Test of Cure management pathway (*Table 2*).

There were identifiable factors associated with GPs' awareness of the Test of Cure management pathway (*Table 3*). Younger female GPs were more likely to be aware of the screening pathway when compared with male GPs aged over 55 years. Statistical differences in the awareness of the Test of Cure by the accessibility (metro, rural, remote) and socioeconomic status of the practice location were also analysed (*Table 3*).

Of the 34.3% of GPs who did not know the Test of Cure guidelines, the following comments were included with their surveys:

'I am unsure of HPV DNA testing'
'I know nothing about this test'
'I did not know this existed'
'I am not confident with this test or its follow-up at all'
'Unsure of guidelines on this; would this be offered by a specialist?'
'I don't offer it – I am uncertain where it fits in the management algorithm'.

Table 2. Percentage of participants who answered selected items correctly

Question	Percentage correct (%)
Q1 Factors considered most important when offering an HPV DNA test:	
• If the patient has received treatment for an HSIL	85.3
• The patient enquires about the test	40.5
• Test of Cure management pathway	44.1
Q2 Immediate guideline recommendation for patients who have received treatment for a HSIL? (colposcopy and Pap smear at 4–6 months post-treatment)	64.2
Q3 If the colposcopy and first Pap smear are both negative what is the next step for your patients? (Pap smear and HPV DNA test at 12 months post-treatment)	73.9
Q4 Once patients have had two consecutive annual tests (2 x Pap smears and 2 x HPV DNA tests) that are negative, what would be your recommendation for a patient? (return to routine (2-yearly) screening)	69.3
Correct answers are in parentheses where applicable	

Discussion

Our study specifically investigated the management of patients after treatment for CIN 2 and/or CIN 3, and identified that the majority of GPs did not 'always' receive a clear follow-up plan from the specialist ob/gyn to whom the patient had been referred. A proportion of GPs were unaware of these post-treatment best practice guidelines, which is inefficient. The use of co-testing (HPV DNA testing and cervical cytology) in general practice is a useful tool to identify patients with a history of HSIL, who are at the greatest risk of disease persistence/recurrence.[12,16]

The major knowledge gaps identified in this study include knowing when it was appropriate to perform HPV DNA tests and how to manage patients if they had two consecutive annual negative test results (2 x Pap smears and 2 x HPV DNA tests). We found that female GPs were more likely to be aware of the Test of Cure management pathway than male GPs. This difference may be a reflection of women's preference to see a female healthcare provider to discuss sensitive topics, and the GP's personal motivation to know the Test of Cure management pathway.

Our study's results and qualitative feedback suggest that there is a clear need for further education and promotion of using high-risk HPV DNA tests as a management pathway for GPs. The GP's armamentarium should include knowledge of how and when HPV DNA testing should be performed. GPs should have confidence in the use of this testing modality because, even if a cervical cytology test result is normal, the increased sensitivity of the HPV DNA test will detect high-risk HPV DNA types, indicating the presence of persistent cervical disease. Patients who successfully complete the Test of Cure should then be encouraged to return to routine cervical screening with a high degree of confidence.[5,10,12,16,17]

This is beneficial, as the patient will not be required to return for annual screening.[15] Improved communication between the specialist ob/gyn and GP, through provision of clear follow-up instructions, will ensure GPs are equipped to provide patients with care that is effective and delivers a high level of surveillance.[15]

One of the limitations of this study was the low GP response rate (30.9%). However, it is well recognised that collecting information via surveys is difficult, specifically from physicians in the primary healthcare setting, and is challenging as time commitments may preclude GPs' participation in survey initiatives.[18–20] Nonetheless, the number of GP responses in our study has assisted in the provision of the first preliminary insight into GPs' receipt of patient follow-up plans and their awareness of utilising co-testing (HPV DNA testing and cervical cytology) for patients who have been treated for an HSIL.

Given the benefits and importance of the Test of Cure management pathway, there is a role for professional development activities, such as workshops, conferences and online educational models, to provide GPs with contemporary knowledge of clinical practices in the area of cervical cancer prevention. Further efforts should be aimed at specifically enhancing GPs' skills in managing patients with cervical abnormalities detected through screening, and providing information about high-risk HPV DNA testing. This information could assist GPs in transitioning these high-risk patients back to the recommended screening interval. There is also an opportunity for specialist obs/gyns who perform colposcopy and surgical procedures to assist GPs in the management of these patients by providing a clear follow-up plan for patients who have undergone treatment for an HSIL when they are discharged from specialist care.

Finally, future research investigating longitudinal health outcomes associated with women who have undergone and completed the Test of Cure is required. Studies performing economic modelling to determine potential cost savings by the reduction in annual cytology tests and colposcopic examinations are required. Australia was the first country to introduce the Test of Cure pathway in 2006 and is well placed to provide such evidence.[15]

Table 3. Factors associated with GPs' awareness of the Test of Cure screening pathway

	Rate ratio	95% CI	P-value
Gender			
Female	2.3	1.6–3.2	0.000
Male (reference group)	1.0	–	–
Age (years)			
<35	1.4	0.7–2.5	0.315
35–44 (reference group)	–	–	–
45–54	0.8	0.5–1.2	0.327
≥55	0.5	0.3–0.8	0.002
Aware of NHMRC guidelines (Test of Cure)			
Yes (reference group)	–	–	–
No	0.5	0.3–0.8	0.003
Index of relative social disadvantage			
Most disadvantaged	0.6	0.2–1.4	0.215
More disadvantaged	1.2	0.6–2.2	0.644
Middle	1.9	1.2–3.2	0.012
Less disadvantaged	0.9	0.5–1.4	0.520
Least disadvantaged (reference group)	–	–	–
Accessibility/Remoteness Index of Australia			
Major city (reference group)	–	–	–
Inner regional	1.2	0.7–1.5	0.491
Outer regional	0.7	0.3–1.4	0.291
Remote/Very remote	0.9	0.4–2.0	0.838

Logistic regression was performed, estimating the odds of GPS being aware of the Test of Cure screening pathway.
CI, confidence interval

Implications for general practice:

- GPs should have confidence in HPV testing, as it is a sensitive test that can detect the presence of high-risk HPV oncogenic types.
- When HPV testing is utilised in the management of patients post HSIL treatment it is eligible for a Medicare rebate.
- Co-testing can assist GPs in transitioning high-risk patients back to the recommended screening interval with a high degree of confidence.

Acknowledgements

We thank the Western Australia Cervical Cancer Prevention Program for their contribution to coordinating and disseminating the survey to identified GPs throughout Western Australia. We must also extend a thank you to the GPs who participated in this initiative – your expertise, time and contribution is much appreciated.

Authors

Aime Munro BExSc, MSc, PhD Candidate, Senior Program Officer (Research), WA Cervical Cancer Prevention Program, Perth, WA. aime.munro@health.wa.gov.au

Jim Codde PhD, BSc, GDip Ed, Adjunct Professor, Curtin University, Centre for Population Health Research, Bentley, WA

James Semmens BSc, MSc, GDip ED, PhD, GAICD, Director, Centre for Population Health Research, Curtin University, Bentley, WA

Yee Leung MBBS FRANZCOG CGO, Professor, School of Women's and Infants' Health, University of Western Australia, Crawley, WA

Katrina Spilsbury BSc PhD GradDipPH MBiostats, Senior Research Fellow, Centre for Population Health Research, Curtin University, Bentley, WA

Vincent Williams PhD, MSc, BAppSci, FAIMS CF(IAC), FFSc (RCPA), Principal Clinical Professional Fellow, School of Biomedical Sciences, Curtin University, Bentley, WA

Nerida Steel, Program Manager, WA Cervical Cancer Prevention Program, Perth, WA

Paul Cohen BM BCh, MA (Oxon) Dip Obs FRANZCOG MD, Clinical Senior Lecturer, School of Women's and Infants' Health, University of Western Australia, Crawley, WA

Heidi Pavicic RN, NP, BN, MN, Clinical Nurse Consultant, WA Cervical Cancer Prevention Program, Perth, WA

Vicki Westoby MBBS (Hons), FRACGP, FARGP, DCH, DRANZCOG, GradDipRural, General Practice Liaison, Executive Services, King Edward Memorial Hospital, Subiaco, WA

Peter O'Leary BSc, PhD, MAACB, ARCPA, FFSc (RCPA), Research Professor, Faculty of Health Science, Curtin University, Bentley, WA

Competing interests: None.

Provenance and peer review: Not commissioned, externally peer reviewed.

References

1. Australian Institute of Health and Welfare. Cervical Screening in Australia 2011–2012. Cancer series no. 82. Cat. No. CAN 79. Canberra: AIHW, 2014.
2. Arbyn M, Raifu AO, Weiderpass E, Bray F, Anttila A. Trends of cervical cancer mortality in the member states of the European Union. Eur J Cancer 2009;45:2640–48.
3. Peto J, Gilham C, Fletcher O, Matthews FE. The cervical cancer epidemic that screening has prevented in the UK. Lancet 2004;364:249–56.
4. National Health and Medical Research Council. Screening to prevent cervical cancer: Guidelines for the management of women with screen detected abnormalities. Canberra: NHMRC, 2005.
5. Katki HA, Schiffman M, Castle PE, et al. Five-year risks of CIN 3+ and cervical cancer among women with HPV-positive and HPV-negative high-grade Pap results. J Low Genit Tract Dis 2013;17:S50–55.
6. Rebolj M, Helmerhorst T, Habbema D, et al. Risk of cervical cancer after completed post-treatment follow-up of cervical intraepithelial neoplasia: population based cohort study. BMJ 2012;345:e6855.
7. Demopoulos RI, Horowitz LF, Vamvakas EC. Endocervical gland involvement by cervical intraepithelial neoplasia grade III. Predictive value for residual and/or recurrent disease. Cancer 1991;681932–36.
8. Gok M, Coupe V, Berkhof J, Verheijen RH, Helmerhorst TJ, Hogewoning CJ. HPV 16 and increased risk of recurrence after treatment for CIN. Gynecol Oncol 2007;104:273–75.
9. Nam K, Chung S, Kim J, Jeon S, Bae D. Factors associated with HPV persistence after conization in patients with negative margins. Gynecol Oncol 2009;20:91–95.
10. Paraskevaidis E, Koliopoulos G, Alamanos Y, Malamou-Mitsi V, Lolis ED, Kitchener HC. Human papillomavirus testing and the outcome of treatment for cervical intraepithelial neoplasia. Obstet Gynecol 2001;98:833–36.
11. Strander B, Andersson-Ellström A, Milsom I, Sparén P. Long term risk of invasive cancer after treatment for cervical intraepithelial neoplasia grade 3: population based cohort study. BMJ 2007;335:1077.
12. Thomsen L, Frederiksen K, Munk C, et al. High-risk and low-risk human papillomavirus and the absolute risk of cervical intraepithelial neoplasia or cancer. Obstet Gynecol 2014;123:57–64.
13. Moss S, Kelly R, Legood R, et al. Evaluation of sentinel sites for HPV triage and test of cure. Sheffield: NHS Cancer Screening Programmes, 2011.
14. Saslow D, Solomon D, Lawson HW, et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. J Low Genit Tract Dis 2012;16:175–204.
15. Heley S. HPV testing in the National Cervical Screening Program. When is it recommended? Aust Fam Physician 2013;42:463–66.
16. Ronco G, Dillner J, Elfström KM, et al. Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials. Lancet 2014;383:524–32.
17. Nobbenhuis MA, Meijer CJ, Van Den Brule AJ, et al. Addition of high-risk HPV testing improves the current guidelines on follow-up after treatment for cervical intraepithelial neoplasia. Brit J Cancer 2001;84:796–801.
18. Bonevski B, Magin P, Horton G, Foster M, Girgis A. Response rates in GP surveys. Trialing two recruitment strategies. Aust Fam Phys 2011;40:427–30.
19. Cummings SM, Savitz LA, Konrad TR. Reported response rates to mailed physician questionnaires. Health Serv Res 2001;35:1347–55.
20. Grava-Gubins I, Scott S. Effects of various methodologic strategies: survey response rates among Canadian physicians and physicians-in-training. Can Fam Physician 2008;54:1424–30.

correspondence **afp@racgp.org.au**