Outcomes in HrHPV-positive women with low grade cervical smears and normal or low grade initial colposcopy results

Erica Winsley, Dushyant Maharaj, Peter Abels, Diane Kenwright, Fali Langdana

Abstract

**Aim** To determine outcomes in HrHPV-positive women with low grade cervical smears and normal or low grade initial colposcopy biopsy results in a cohort of women over a 2-year follow-up period.

**Background** The revised National Cervical Screening (NCS) programme guidelines in New Zealand were implemented in October 2009. The guidelines state that women 30 years and older should undergo reflex HPV testing. If this test confirms the presence of HrHPV, women are to be referred for a colposcopic assessment. The guidelines do not mention what the follow-up period should be of women with HrHPV and normal or low grade abnormalities at colposcopy/biopsy.

**Method** In this study we followed up women 30 years and older referred to Wellington Hospital from 1/10/2009 to 1/10/2011 with a LGSIL or ASC-US smear and positive HrHPV test. Those with a normal or low grade biopsy result were followed over a 2-year period to determine outcomes.

**Results** Our study found that 4% of women with initial normal biopsy results and 15.2% with initial low grade results had progressed to high grade (CIN 2/3/invasion) over a 2-year follow-up period. During the same time period, 68% of women with an initial normal biopsy and 61% with a low grade biopsy had a normal colposcopy after 2 years. Twenty-eight percent of women with normal and 24% of those with initial with low grade biopsy continued to have LG abnormalities at 2 years of follow-up.

**Conclusion** Women 30 years and older who are HrHPV-positive and have low grade abnormalities at colposcopic biopsy may be followed up with a 12-month cervical smear rather than repeat colposcopy as the risk of progression to a high grade abnormality is low.

Genital human papillomavirus (HPV) infection is the most commonly diagnosed sexually transmitted infection in New Zealand.\(^1\) Figures from the United States estimate that about 26.8% of women 14–59 years old are infected with the human papilloma virus,\(^2\) with about a 75% lifetime risk of acquiring an HPV infection.\(^3\)

HPV infection is now known to be a prerequisite for the development of cervical cancer,\(^4\) and virtually all cervical cancers are associated with persistent high-risk types of HPV (HrHPV) infection.\(^5\)

More than 120 types of HPV have been identified,\(^6,7\) of which about 40 types can infect the genital tract.\(^4\) Of these, approximately 13 to 19 types are considered high risk, meaning that persistent infection with these types is associated with an increased risk of cervical, anogenital, and other cancers.\(^8\)
HPV type 16, the most common HrHPV type, persists longer than other types and is especially carcinogenic. Persistent infection with HrHPV leads to the development of cervical intraepithelial neoplasia 3 (CIN 3) in about 40% of cases over 5 years.9

For a patient with cervical cytology abnormalities and a positive HrHPV DNA test result, ideal management must balance the need to identify and treat abnormalities that are likely to progress to invasive cancer, as opposed to the avoidance of unnecessary treatment related to transient HPV infection.10

The revised National Cervical Screening (NCS) programme guidelines in New Zealand was implemented in October 2009.11 Management of women with a first low grade smear (low grade squamous intraepithelial lesion – LGSIL, or atypical squamous cells of undetermined significance – ASC-US) has significantly changed with the introduction of these guidelines.

The recommendation for women less than 30 years old with a first low grade smear is to undergo a repeat smear in 12 months, whereas women 30 years and older with a first low grade smear undergo reflex HPV testing. If this test confirms the presence of HrHPV, women are referred for a colposcopic assessment as progression of disease from low grade to high grade may be higher in this group.

High grade disease is treated according to the NCS guidelines:11 in women with HrHPV and normal or low grade abnormalities at colposcopy/biopsy, the guidelines state that, “where findings on colposcopy/histology are negative or show low-grade changes only and the discordance persists following case review, HrHPV testing can be a useful adjunct to further management”.

The NCSP recommends a woman return to three-yearly screening only after two negative sets of HrHPV plus cytology tests 12 months apart.

We undertook this study to determine outcomes in HrHPV-positive women with low grade cervical smears and normal or low grade initial colposcopically directed biopsy results in a cohort of women over a 2-year follow-up period.

Material and Methods

From 1/10/2009 to 1/10/2011 we followed a cohort of 364 women 30 years and older who were referred to the colposcopy clinic at Wellington Hospital, New Zealand, with a LGSIL or ASC-US smear and positive HrHPV test who had diagnostic, colposcopically directed biopsies. Women who had high grade smears at referral (CIN2 or CIN 3) or a cervical malignancy were excluded from the study as were women with a prior history of CIN2/3 or adenocarcinoma in situ (AIS), or if they had undergone a prior excisional/ablative procedure.

Those women who did not undergo a biopsy at a subsequent visit or for whom results were not available at follow-up visits were excluded from the study, as were women who were deemed to have had unsatisfactory biopsy results at the subsequent visits.

Based on history, all women were HIV negative and not on immunosuppressive medication. Women with a normal result (including a diagnosis of cervicitis or other non-neoplastic findings) or low grade abnormality (CIN 1, CIN 1/HPV) on biopsy were followed at a subsequent appointment and the second biopsy or treatment biopsy result was recorded. None of the 364 women were lost to follow up. Fifty eight women (23%) included in the study underwent a repeat biopsy. This included 25 women from the normal group and 33 women from the low grade group.

Women were assigned to two groups – those with a normal result and those with CIN 1/HPV on biopsy. Data on persistence of CIN 1/HPV, progression to CIN 2, CIN 3 or malignancy or regression to normal at 6 months, 12 months and 24 months were recorded and analysed to ascertain the percentage
of women with a positive HrHPV test and a subsequent normal or low grade abnormality on initial biopsy who had persistence, progression or regression of CIN or HPV effect on subsequent biopsies. The percentage figure for each group of women at each of the 3 time periods was calculated by using the number of women who at that time had had a follow up visit as the denominator. The time elapsed between the initial visit and the second visit was also recorded, and the median time for follow up for the three groups of women (normal, CIN 1 and CIN 1/HPV) was calculated.

Smear analysis employed liquid-based cytology, and the Abbott RealTime High Risk (HR) HPV assay and the COBAS 4800 platform (Roche) were used to identify 14 types of HrHPV.

**Results**

Over the study period, 364 women 30 years and older were seen at the colposcopy clinic at Wellington Hospital, with a LGSIL smear and positive HrHPV test. Based on results from colposcopically directed biopsies 105 (29%) of these women had a normal biopsy, 146 (40%) had low grade biopsies (HPV, CIN 1 or CIN 1/HPV) and 113 (31%) were found to have high grade lesions on biopsy.

Fifty-eight women (23%) included in the study underwent a repeat colposcopy and subsequent biopsy. This included 25 women from the normal group and 33 women from the low grade group. The remaining 306 women who did not undergo a subsequent biopsy were discharged to community health practitioners for a repeat smear in 12 months.

The main results of the study are shown in Tables 1, 2 and 3 and in Figure 1 below. Women in the normal and low grade groups showed equivalent clearance over follow-up at 6 months, 12 months and 24 months (Tables 1 and 2)

**Table 1. Percentage of women in each group (initial normal, CIN1) who had a normal result at 6, 12 and 24 months**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Initial normal (n=25)</th>
<th>Initial low grade (n=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% normal at 6 months</td>
<td>75 (12/16)</td>
<td>53.3 (8/15)</td>
</tr>
<tr>
<td>% normal at 12 months</td>
<td>73.9 (17/23)</td>
<td>55.2 (16/29)</td>
</tr>
<tr>
<td>% normal at 24 months</td>
<td>68 (17/25)</td>
<td>60.6 (20/33)</td>
</tr>
</tbody>
</table>

**Table 2. Percentage of women in each group who had a low grade [cervical smears] result at 6, 12 and 24 months**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Normal (n=25)</th>
<th>Low grade (n=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% low grade at 6 months</td>
<td>18.8 (3/16)</td>
<td>20 (3/15)</td>
</tr>
<tr>
<td>% low grade at 12 months</td>
<td>21.7 (5/23)</td>
<td>31 (9/29)</td>
</tr>
<tr>
<td>% low grade at 24 months</td>
<td>28 (7/25)</td>
<td>24.2 (8/33)</td>
</tr>
</tbody>
</table>

Women in the low grade group showed greater progression to high grade disease at 6 months, 12 months and 24 months (Table 3).
Table 3. Percentage of women in each group who had a high grade [cervical smears] result at 6, 12 and 24 months

<table>
<thead>
<tr>
<th>Variables</th>
<th>Normal (n=25)</th>
<th>Low grade (n=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% high grade at 6 months</td>
<td>6.3 (1/16)</td>
<td>26.7 (4/15)</td>
</tr>
<tr>
<td>% high grade at 12 months</td>
<td>4.4 (1/23)</td>
<td>13.8 (4/29)</td>
</tr>
<tr>
<td>% high grade at 24 months</td>
<td>4 (1/25)</td>
<td>15.2 (5/33)</td>
</tr>
</tbody>
</table>

Figure 1. Percentage of women (y-axis) in each group (x-axis) who had a high grade result at 6 months, 12 months and 24 months (z-axis)

During the study period, 23% of women (n=58) referred to the colposcopy clinic with a HrHPV-positive result and LGSIL smear who had a normal or low grade initial biopsy had a follow-up colposcopy and repeat biopsy. These women were followed up at varying lengths of time, with the shortest follow up period of around 2 months (63 days), and the longest around 19 months (598 days), as a recommended follow up time was not specified in the NCS guidelines.

There was also a difference between median follow up times of the different groups, with women from the normal group being followed up after an average of 168 days or just under 6 months, and women from the low grade groups followed up at an average of 203 days or just over 6 months. This result seems unexpected, however it was not looked into further as there were no guidelines in place with which to compare results.

Discussion

Our study attempted to assess the persistence, regression and progression of normal and low grade abnormalities as determined by biopsy results in the presence of HrHPV at referral in an attempt to determine what the appropriate follow-up of these patients should be.
After 2 years, 4% of women with an initial normal biopsy result but HrHPV at referral had progressed to a high grade abnormality (CIN 2 or CIN 3). This result was similar to those published by Kelly et al., where the cumulative rate of CIN 2 and higher was found to be 4.4% after 3 years in HrHPV-positive women with a normal colposcopy.

There were no women in the CIN 1 only group who had progressed to a high grade abnormality; however 25% (n=20) of women with an initial CIN 1/HPV result had progressed to a high grade abnormality. When the CIN 1 group and the CIN 1/HPV group, i.e. low grade were combined, this number decreased to 15.2%. This figure is higher than that of the 10% of women with an initial CIN 1 biopsy who progressed to CIN 3 in Ostör’s study.13

Results from the ASCUS-LSIL Triage Study (ALTS) also indicate that the risk of developing CIN 3 within 2 years of a biopsy result < CIN 2 is around 12% in women who subsequently test positive for HrHPV.

The results of our study may be higher due to the limited sample size as well as HrHPV testing not being available in 1993 when Ostör published his work. Those women who test positive for HrHPV may be at higher risk for progression to high grade abnormalities, even with an initial result less than CIN 2. Another explanation may be that the endpoint for progression to high grade abnormalities in Ostör’s study was CIN 3, whereas we considered high grade abnormalities to be CIN 2 or CIN 3 which may well have increased the number of women in this group.

The principle of equal management for equal risk may be invoked, but that requires a discussion of the risks of CIN2+ in other groups at 1 year following evaluation which is not the intention of this study.

It is important to note that no women from any of the three groups went on to develop invasive malignant disease within the two year period. In that time, 68% of the women with initially normal biopsies remained normal, 92.3% of women with initial CIN 1 biopsies, and 35% of women with initial CIN 1/HPV biopsies regressed to normal. When the low grade (CIN 1 and CIN 1/HPV) groups were combined, 60.6% regressed to normal over the 2-year period. This result was similar to those found by Kelly et al12 and Ostör.13

Finally, it was found that 28% of women with initial normal biopsies at colposcopy progressed to CIN 1 or CIN 1/HPV over the 2-year period; women with an initial CIN 1 biopsy remained low grade over the same period.

In contrast, 40% of women with an initial CIN 1/HPV biopsy remained CIN 1/HPV or purely CIN 1 after 2 years. When the two latter groups (CIN 1/HPV and purely CIN 1) were combined, 24.2% of women remained the same after 2 years. This result differs from Ostör’s study in which women with the same initial biopsy result had 30% persistence of CIN 1.13

Our study was limited to a 2-year period, starting in October 2009, as it was around this time that the reflex HPV test was introduced into the NCS programme as a way of triaging woman over the age of 30 with a LGSIL or ASC-US cervical smear and no abnormal smears in the previous 5 years.11

Firstly, this limited the number of women who could be recruited for the study, and a further limiting factor became evident when it was realised that the majority of
women with an initial normal or low grade biopsy were not recalled for a subsequent colposcopy appointment and were discharged to their smear-takers. This was probably due to NCS guidelines not explicitly stating what the appropriate follow up should be for this group of women.

Secondly, it meant that we could only follow up women for a maximum of 2 years. Further research may be warranted to follow this group of women over a longer period of time to determine if there is a difference in outcomes.

Although it is difficult to draw a firm conclusion based on results from our study due to a limited sample size, it seems that of the HrHPV-positive women with an initial low grade biopsy result of CIN 1 or CIN 1/HPV, more regressed to normal over the two year period, while over the same time around 5% progressed to a high grade lesion and therefore less women than expected remained CIN 1 or CIN 1/HPV over the same time.

Over the study period, the majority of women with an initial normal result remained normal, although 28% progressed to a low grade lesion and a small number developed high grade abnormalities; this is consistent with other studies. 12,13

**Conclusion**

Women 30 years and older who are HrHPV-positive and have either normal or low grade abnormalities at colposcopic biopsy may be followed up with a 12-month cervical smear, as per current NCS guidelines, rather than a repeat colposcopy, as the rate of subsequent high grade CIN was sufficiently low to justify return to routine colposcopy recall.

The American Society of Colposcopy and Cervical Pathology in their guidelines state that women with a normal cytology and HrHPV-positive test could undergo either a repeat co-test in 12 months or immediate HPV genotype testing for HPV 16 or 16/18. If either the cotest or the HPV genotype specific test is positive, women should then be referred for colposcopy. 16

**Competing interests:** Nil.

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**References:**