

The Prevalence of High Grade Cervical Intraepithelial Neoplasia (CIN) in a Primary Human Papillomavirus (HPV) Cervical Screening Programme Population with HPV Positive and Cytology Negative Smear Results

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How to cite this paper: Williams, S.G., Anwar, A., Wijesiri, S.G., Palaparthy, S. and Winter, E. (2020) The Prevalence of High Grade Cervical Intraepithelial Neoplasia (CIN) in a Primary Human Papillomavirus (HPV) Cervical Screening Programme Population with HPV Positive and Cytology Negative Smear Results. *Open Journal of Obstetrics and Gynecology*, **10**, 902-908. <https://doi.org/10.4236/ojog.2020.1070085>

Received: May 21, 2020

Accepted: July 17, 2020

Published: July 20, 2020

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Abstract

High-risk HPV is found in 99.7% of cervical cancers. The causative role of HPV in cervical cancer has led to the inclusion of HPV testing as part of cervical screening. A pilot of HPV testing as primary screening was commenced in 2013 at six pilot sites in England. North Cumbria Integrated Care (NCIC) NHS Foundation Trust took part in the pilot, in which women with an HPV-positive/cytology-negative result were recalled at 12 months. Women with HPV type 16/18 found at initial screening and persisting at 12 months in spite of negative cytology were referred to Colposcopy services at 12 months. Women with smear positive for hrHPV other than 16/18 types were recalled twice at 12 and 24 months before referral to colposcopy. Persistent hrHPV positive/cytology negative smear at 12 and 24 months initiated a colposcopy referral. **Objective:** To assess the prevalence of high grade CIN and invasive cancer in patients referred to colposcopy services at NCIC NHS Foundation Trust with hrHPV positive/cytology negative smears. **Method:** The study was conducted at NCIC NHS Foundation Trust between January 2015 and December 2017. Data was collected retrospectively from the colposcopy data base (INFOFLEX). All patients with HPV positive/cytology negative smears seen in colposcopy clinic during the study period were included. Patients with high grade CIN, cervical glandular intraepithelial neoplasia (CGIN) or invasive cancer were recorded.

Results: 763 women were included in the study. A total of 50 (6.6%) women had high grade CIN, CGIN or invasive cancer. 40 of these 50 women (80%) were treated by large loop excision of the transformation zone (LLETZ). **Conclusion:** HPV primary screening is more effective than cytology-based screening. A high grade HPV positive result with negative cytology, persisting for one year in type 16/18 and for two years in other high-risk HPV types, warrants referral for colposcopy, as 6.6% of women in this study had high grade or invasive pathology.

Keywords

Cervical Screening, Cervical Intraepithelial Neoplasia, Cervical Cancer, Human Papillomavirus, Colposcopy

1. Introduction

Cervical cancer is ranked as the fourth most common cause of cancer incidence and mortality in women worldwide [1]. A well organized and quality assured cervical screening programme can reduce cervical cancer incidence by over 80% [2].

In UK, the NHS National Cervical Screening Programme (NHSCP) was launched in 1988. Traditionally the cervical screening programme was cytology based, however the causative role of high risk human papillomavirus (hrHPV) has led to inclusion of hrHPV testing as a part of cervical screening.

Evidence suggests that using hrHPV DNA testing as the primary test in cervical screening is more sensitive for detecting cervical intraepithelial neoplasia (CIN) and provides greater protection against cervical cancer [3] [4] [5] [6] [7].

HPV triage of mild and borderline cytology and test of cure for treated cases was introduced into the NHS National Cervical Screening Programme in the UK in 2012 [8]. Introduction of HPV triage to liquid based cytology screening was concluded to be feasible, acceptable to women and cost effective in terms of quality and of life years saved [9].

In recent years, several countries have updated their screening guidelines and are switching from primary liquid based cytology with hrHPV triage to primary hrHPV testing with liquid based cytology triage. The UK National Screening Committee recommended a switch to hrHPV primary screening in January 2016. In support of the anticipated roll-out in 2019, a pilot of HPV primary screening with cytology triage was established in 2013 involving a group of six screening laboratories in the NHS Cervical Screening Programme in England. North Cumbria Integrated Care (NCIC) Foundation trust is linked to one of the pilot site laboratories.

The shift to an HPV primary testing algorithm means that samples taken from women attending cervical screening are first tested for hrHPV, and cytology is only carried out on those samples that are hrHPV positive. Women with hrHPV negative samples are returned to routine recall in 3 or 5 years depending on age.

Women testing positive for hrHPV with abnormal cytology are referred immediately for colposcopy.

A key difference with HPV primary testing is that it creates a new group of women; those who are hrHPV positive but have negative cytology results. Under the liquid based cytology screening protocol, these samples would never have been tested for hrHPV, given the negative cytology. In the pilot, women with hrHPV positive/cytology negative results were recalled early for a repeat smear at 12 months. Women with persistent 16/18 type HPV positive/cytology negative smears were referred to colposcopy at 12 months' recall. Women with smear positive for hrHPV other than 16/18 types with negative cytology were recalled twice at 12 and 24 months and persistent hrHPV positive/cytology negative smear at 12 and 24 months initiated a colposcopy referral.

Using hrHPV primary screening in a sample of more than 183,000 women, the HPV primary screening sentinel sites pilot detected 50% more CIN2 or worse, 40% more CIN3 or worse, and 30% more cervical cancer in the prevalence round, compared with liquid-based cytology [10].

2. Objective

The objective was to assess the prevalence of high grade cervical intraepithelial neoplasia (CIN), high grade glandular intraepithelial neoplasia (CGIN) and invasive cancer in women referred to colposcopy services at North Cumbria Integrated Care (NCIC) NHS Foundation Trust with hrHPV positive/cytology negative smear results.

3. Methods

This was a retrospective cohort study. The study was conducted at NCIC NHS Foundation Trust which provides acute and community-based health care services to a large area in North-West England, covering a population of approximately 323,000.

The colposcopy services were provided by 6 colposcopists running 36 clinics in 4-week cycle across two different sites. The service accommodates 9 patients per clinic.

The smears (taken mainly in community services) were processed at the regional laboratory, which was one of the six sites taking part in the HPV primary screening pilot. All women referred and seen in colposcopy services at NCIC NHS Foundation Trust between 1st January 2015 and 31st December 2017 with hrHPV positive and cytology negative results were included in the study. Data was collected retrospectively from the electronic colposcopy database (INFOFLEX).

Colposcopic findings and biopsy results were collated, and women with high grade CIN, cervical glandular intraepithelial neoplasia (CGIN) or invasive cancer were recorded. The clinical notes for all women with high grade CIN, CGIN and cervical cancers were then evaluated in order to record the treatments offered to each patient.

The study was approved locally by the Trust Audit Department.

4. Results

During the study period, a total of 6895 women were seen in colposcopy services at NCIC NHS Foundation Trust across two sites.

Of these 6895 women, a total of 763 had been referred with hrHPV positive and cytology negative smear results, representing 11% of the total number of women attending colposcopy services over the study period.

Table 1 summarizes the initial findings at colposcopy in these women. 531 women (69.6%) had normal colposcopy. A total of 169 women (22.1%) had colposcopic findings suggestive of CIN, while 44 women (5.8%) had transformation zone type 3 resulting in unsatisfactory colposcopy.

Biopsy of the cervix was performed in 491 women (64.4%) at initial colposcopy assessment. Histology results of the cervical biopsies are shown in **Figure 1**.

Table 2 summarizes the prevalence of high grade CIN and CGIN on initial biopsy, expressed as a percentage of the total hrHPV positive/cytology negative group.

These women were further evaluated. The distribution by age was: 28 (56%) were aged 30 or less, 14 (28%) were 30 - 40, 5 (10%) were 40 - 50 and 3 (6%) were 50 - 65.

Initial biopsies were performed as punch biopsies in 48 women. Large loop excision of the transformation zone (LLETZ) was performed at initial assessment in two women, where high grade lesions were seen on colposcopy. Histology results confirmed CIN3 from both these LLETZ samples.

40 of 50 women with high grade histology on biopsy had LLETZ treatment either at initial assessment or at a subsequent visit. The histology results of the LLETZ samples are shown in **Table 3**. One LLETZ sample showed adenocarcinoma, where initial punch biopsy had shown high grade CGIN with possible invasion.

Table 1. Colposcopic Opinion.

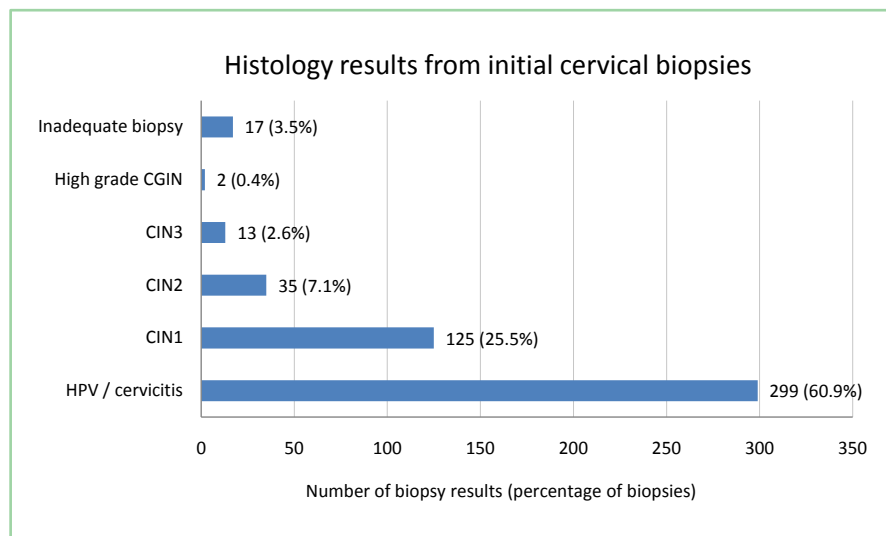
Colposcopic opinion in all women (N = 763)	
Findings	Number (%)
Normal	531 (69.6)
Low grade lesions	148 (19.4)
Unsatisfactory	44 (5.8)
High grade lesions	21 (2.8)
Other, benign	19 (2.5)
Colposcopic opinion where biopsy was not performed (N = 272)	
Normal	226 (83.1)
Unsatisfactory	29 (10.7)
Other, benign	11 (4.0)
Low grade lesions	6 (2.2)

Table 2. Prevalence of high grade CIN/CGIN on initial biopsy.

Prevalence of high grade CIN/CGIN on initial biopsy (number of cases)	
CIN 2	4.6% (35)
CIN 3	1.7% (13)
CGIN	0.26% (2)

Table 3. Management of women with high grade CIN/CGIN on initial biopsy.

Management of women with high grade CIN/CGIN on initial biopsy (N = 50)	
Treatment	Number (%)
LLETZ	40 (80.0)
Active surveillance	7 (14.0)
Care transferred to another provider	2 (4.0)
Patient did not attend for follow-up	1 (2.0)
Histology results from LLETZ samples (N = 40)	
Result	Number (%)
No residual CIN	1 (2.5)
CIN 1	9 (22.5)
CIN 2	15 (37.5)
CIN 3	10 (25.0)
Ungraded CIN	3 (7.5)
High grade CGIN	1 (2.5)
Adenocarcinoma	1 (2.5)

**Figure 1.** Histology results from initial cervical biopsies.

7 women with CIN2 on initial biopsy opted for active surveillance rather than LLETZ. Our departmental policy on active surveillance of CIN2 involves follow up in colposcopy clinic every six months for two years, or until CIN resolves on biopsy with two consecutive HPV negative smears 6 months apart. In this study, histology results at the first 6-month follow up review showed resolution of CIN in 5 women, with persistent CIN 1 in two women.

5. Discussion

Our results are consistent with the findings of previous randomised trials that have shown increased sensitivity for primary screening with hrHPV as compared to liquid based cytology screening [3]-[8].

We detected 49 cases of high grade precancerous lesions and one case of cancer in our study, at the cost of seeing 763 extra cases.

The introduction of an HPV primary screening algorithm has resulted in a group of women that previously did not exist—those who are positive for hrHPV but have a negative cytology result. Positivity for hrHPV would not have been picked up in these women under the liquid-based cytology screening protocol, as with a normal cytology result HPV would not have been tested for, and these women would have been discharged to routine recall in 3 - 5 years depending on age. The additional cases of high grade CIN, CGIN and cervical cancer found in our cohort of women after repeat testing of those with hrHPV positive and cytology negative results at earlier recalls supports the relative safety of the implemented triage strategy, since these women would have been deferred to routine recall under the previous protocol.

However, there are implications in terms of the increase in colposcopy referrals and the impact this will have on colposcopy services. During the study period our colposcopy service saw an additional 763 cases, which is the equivalent of 85 additional clinics over the three-year period. It is essential that colposcopy services are aware of this increase in demand and take this into account when organising services for the move to HPV primary screening.

One challenge faced by colposcopists in this group of women is the management of those women with unsatisfactory colposcopy with no ectocervical lesions. Transformation zone type 3 is more likely to be seen in post-menopausal women and further research is needed to determine the incidence of high grade pre-cancerous lesions and cancers in this subgroup of women.

Limitations of the study included its retrospective nature, as well as the fact that there was no control group, meaning that we cannot directly compare the prevalence of high grade CIN, CGIN and cervical cancer in the study population to a group of women undergoing liquid based cytology screening. However it is reasonable to conclude that the cases of high grade CIN, CGIN and cervical cancer in the study population were diagnosed sooner than they would have been under a liquid based cytology protocol, given that under a liquid based cytology protocol all the women in the study group would have received negative smear results and had follow-up smears on a routine basis after 3 - 5 years depending on age.

6. Conclusion

Our results are in keeping with randomized controlled trial evidence suggesting that HPV primary screening is more effective than cytology-based screening. 6.6% of women in our sample had high grade CIN/CGIN on initial biopsy, with one woman subsequently found to have adenocarcinoma on histology from LLETZ.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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