Experience from a pilot site: a review of long-term outcomes of women referred to colposcopy with cytology-negative, HPV-positive cervical smears

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INTRODUCTION

Approximately 3,100 new cases of cervical cancer are diagnosed every year in the United Kingdom (UK), it is the most common cause of cancer in females below the age of 35 years.[1, 2] The National Cervical Cancer Screening Programme (NHSCSP) was introduced in 1988;[3] since then, age-standardised mortality rates have decreased by 66%.[4] Incidence rates have not followed the same trend, decreasing by only 38%.[2, 3] The screening programme invites all women aged between 25 and 64 years to participate in screening; those aged between 25 and 49 years, inclusive, are invited every 3 years, those who are between 50 and 64 years, inclusive, every 5 years.[5]

Cervical screening and HPV triage

In the UK, premalignant cervical changes were traditionally identified following a cervical smear test and microscopic cytological examination of the exfoliated cells. In the 1970s, Harald zur Hausen proposed the theory that Human Papilloma Virus (HPV) was involved in the pathogenesis of cervical cancer. Subsequently, the HPV genes responsible for promoting cell proliferation in oncotic tissue were identified via the viral DNA present.[6] His research led to the discovery of high-risk HPV (HR HPV) genotypes 16 and 18, which, combined, are understood to be responsible for approximately 70% of cervical carcinomas worldwide.[7-9]

Major changes have taken place in the cervical screening programme since 2011. The first of these was the introduction HPV triage where an HPV test is performed on smears with 'abnormal cells'. Figure 1 shows the current management of cervical smears in the UK screening programme.

At the University Hospitals of Morecambe Bay (UHMB) we are one of six exceptions to the national process in that we have been a sentinel site for primary HPV screening for cervical smears since 2012. Primary HPV screening involves a cervical smear being taken from the woman in the traditional way, but the sample is first tested for the presence of HR HPV; Figure 2 details the new management pathway of cervical smears as implemented at UHMB.

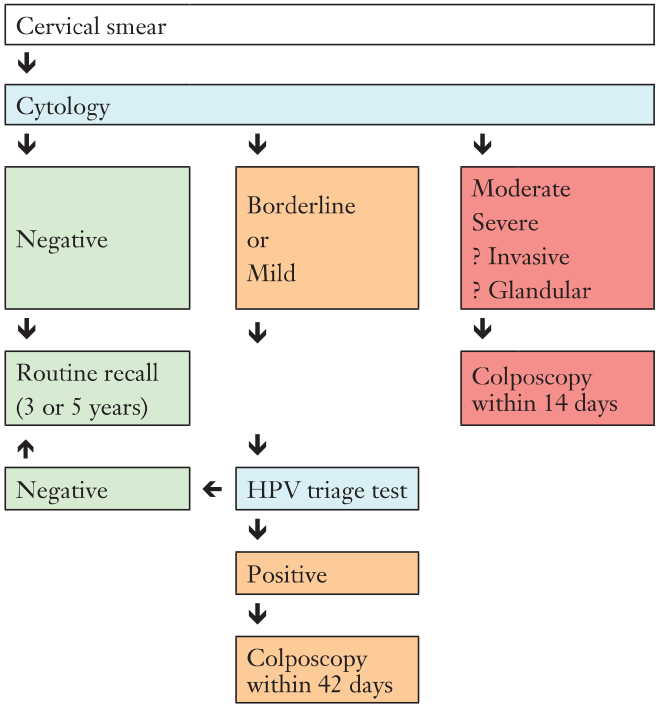

Figure 1: Current UK pathway for cervical smear tests where traditional cytology remains the first investigation.

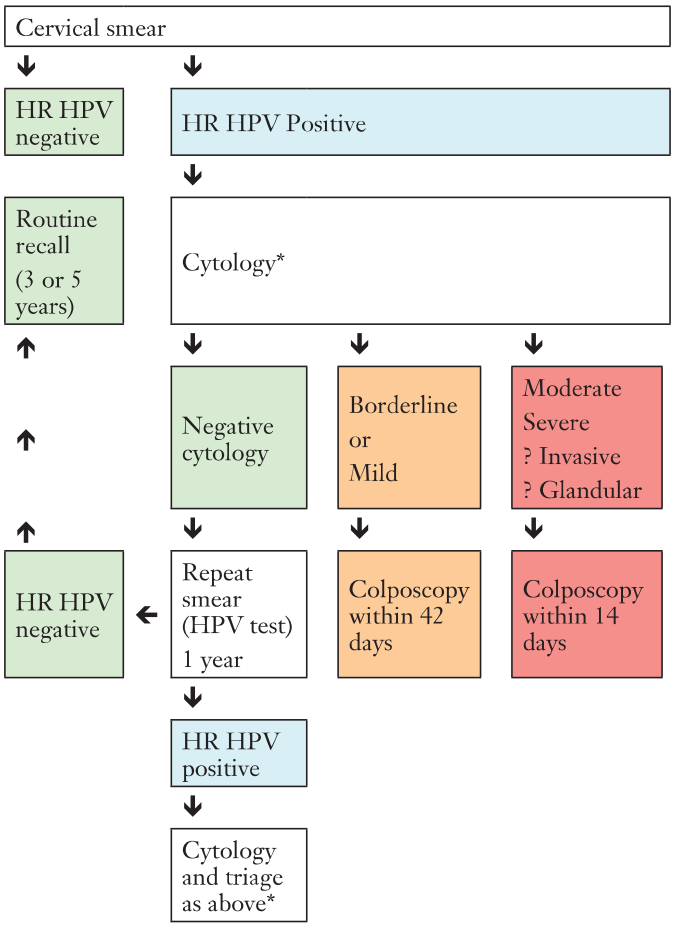

Figure 2: UHMB pathway for cervical smears where the primary investigation is HPV identification.

The rest of the UK will convert to primary HPV screening over the next few years. As a pilot site for the last 5 years we present our experience of a group of women who would not previously have been referred to colposcopy as their smear tests demonstrated normal cytology.

Human Papilloma Virus

HPV is a non-enveloped, double-stranded deoxyribose nucleic acid (DNA) virus, belonging to the family of papillomaviridae.[7, 9] Its genome capsid shell is composed of two structural proteins, one major (L1) and one minor (L2).[6, 7, 9] Recognition of HPV's structure is intrinsic to understanding its involvement in the pathogenesis of cervical intraepithelial neoplasia (CIN) through the persistent infection. In order for clearance of the virus, which is passed through skin-to-skin contact predominantly via vaginal intercourse,[8, 10] antibodies to structural protein L1 are required. However, as the infection is restricted to the superficial or intermediate cell layer(s), a relatively small immune response is mediated.[7, 9] Approximately half of women who encounter HPV will develop detectable antibodies but this does not necessarily protect against subsequent re-infection with the same HPV type; seroconversion is dependent on the individual and HPV strain involved but averages from 8 – 12 months.[7] There are more than 100 strains of HPV of varying carcinogenic classification as detailed in Table 1, below.

High-risk HPV (HR HPV) types	Probable high-risk HPV types	Unclassified or Lower risk HPV types
16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59	26, 53, 66, 67, 68, 70, 73, 82	6, 11, 40, 42, 43, 44, 54, 61, 72, 81

Table 1: Classification of HPV types with regards to risk of cervical cancer.

The natural history of chronic HR HPV related cervical changes is illustrated in Figure 3.[11-13] Those with persistent infection may develop CIN of moderate grade (CIN 2) or severe grade (CIN 3) or possibly glandular cervical intraepithelial neoplasia (CGIN) a precancerous lesion involving the glandular tissue of the cervix.[9] If untreated, CIN 2 and 3 have a high probability of progression to invasive squamous cell carcinoma within a 10 to 20-year period.[7,11] Alongside HR HPV strains being identified as risk factors for the development of squamous cell carcinoma, combined oral contraceptives (COCs), HIV type 1 and tobacco smoking have all been linked to the disease.[14]

HPV immunisation programme

In 2008, Public Health England commenced a national immunisation programme offering girls between 12 - 18 years a vaccination against the two HR HPV strains, 16 and 18.[1, 10] The current programme provides girls in Year 8 of education (12 - 13 year olds) a two-stage vaccination process to protect against four types of HPV, strains 16, 18, 6 and 11, the latter two being the commonest cause of genital warts.[1, 8, 10] It is known that the vaccine provides protection for at least 10 years, but is widely believed to be effective for longer.[1] As the first cohort of immunised girls are only just reaching cervical screening minimum age, there are yet to be definitive figures with regards to reduction in incidence of cervical cancer.

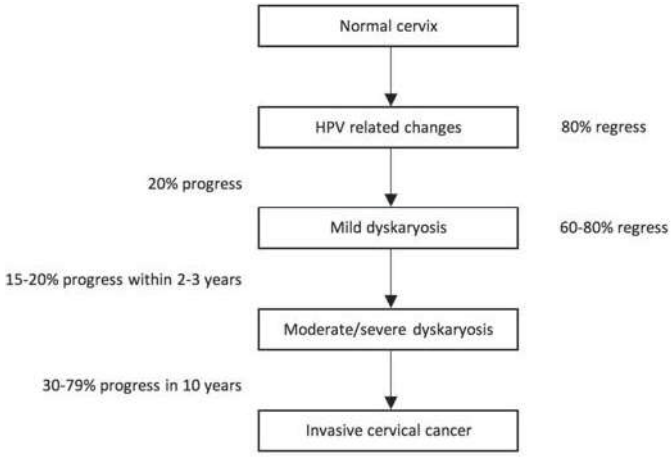

Figure 3: Progression from normal cervix to invasive cancer.

METHODOLOGY

This was a retrospective analysis of women referred to UHMB Colposcopy service due to a HPV-positive, cytology-negative smear with a first appointment date within 2012 or 2013. Compuscope™ database was utilised to identify all women who were eligible and, alongside Lorenzo™ and Manchester Cervical Sample Taker Database (CSTD), was used to collect a range of data. Information about demographic factors of age, parity, smoking status, and contraceptive use was obtained as well as any further or previous appointments and/or treatments the women had undergone. The data collection was achieved by three researchers within the Department. As this was an audit project, no ethical approval was sought. The women's confidentiality was protected at all times.

RESULTS

Forty-five women were identified in the years 2012 and 2013 as being referred to colposcopy services due to HR HPV-positive smear with no abnormal cells (cytology-negative). Age at referral appointment is demonstrated in Figure 4.

The majority of women (51%) were identified as never-smokers with 38% identified as current smokers and 11% being previous smokers. Contraceptive method utilised was noted with 31% not using any contraceptive method (n=14) and 27% using combined oral contraceptives (COCs) as their contraceptive of choice. The remainder of women used a variety of alternative methods e.g. barrier methods or coils. Thirty-one percent were nulliparous at the time of their referral appointment, this compared to 60% having had one or more live births.

Twenty-seven of the 45 women had undergone previous cervical treatment prior to the index referral consultation. The majority of these women (n=20) had a previous LLTEZ, with four women having had two LLTEZs. Two women had prior treatment by cold coagulation and one had undergone a knife cone biopsy.

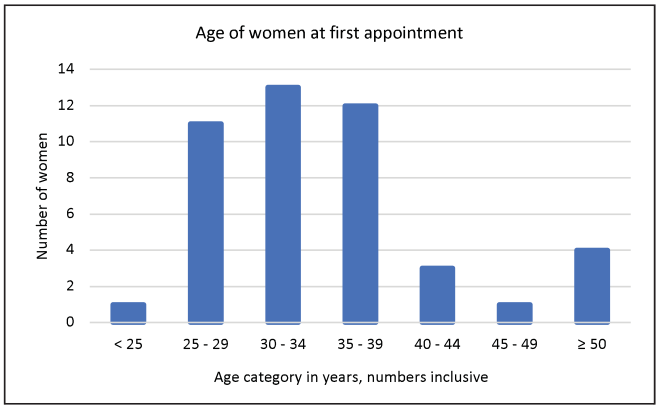

Figure 4: Distribution of age of women at first appointment.

The outcomes of the initial colposcopy visit are detailed in Figure 5.

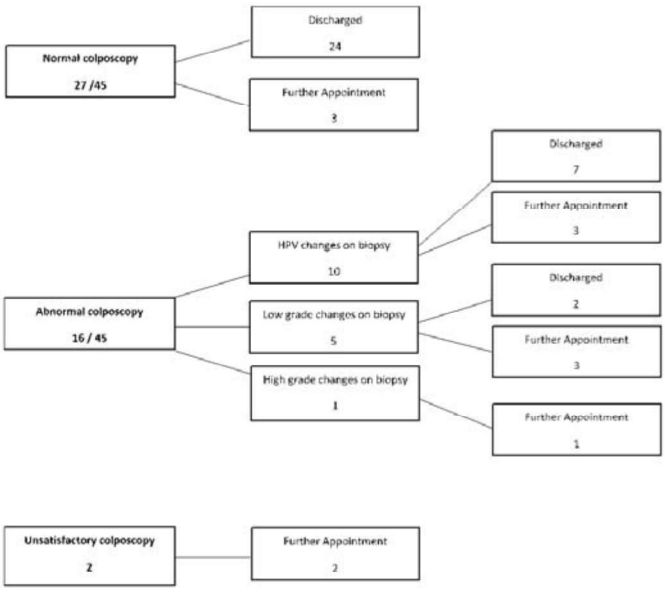

Figure 5: Opinion of the colposcopist at referral appointment, by the number of cases, and associated outcomes.

The long-term outcomes to date for women with abnormal colposcopy were reviewed.

Sixteen percent (7/45) of women required further treatment (either LLETZ / hysterectomy or cold coagulation) during the years following their initial HR HPV-positive, cytology-negative smear. All of these women had abnormal colposcopy at initial colposcopy examination.

The most recent smear results were known for 44 of the total 45 women, demonstrated in Figure 6.

Of those with smears indicating long-term HR HPV infection most, 44% (n=4), identified as being smokers; smoking status was not recorded for two of the women. In relation to contraceptive choice, there was a mix of those in use. Thirty-three percent used a range of long-acting reversible contraceptives (LARCs), 22% had long-term irreversible methods in use, 22% utilised COCs and 22% used no contraceptives according to history recorded. Finally, obstetric history was considered with all nine

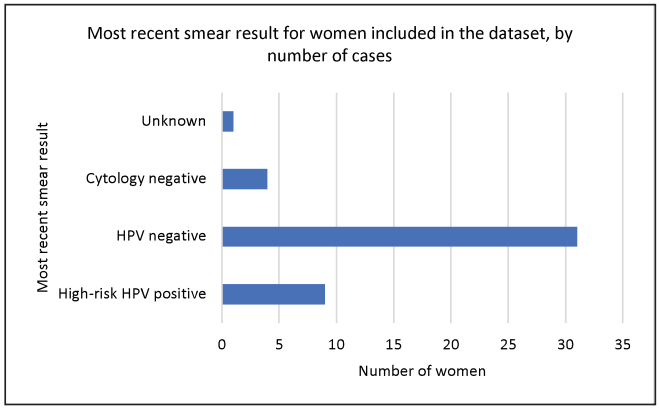

Figure 6: Result of most recent smear for women in the dataset, by number of cases.

having data recorded; three were nulliparous, however, the majority (n=5) had reported two or more live births.

Six of the nine women with current HR HPV on their most recent smear sample were either unable to have satisfactory colposcopy (n=1) or viewed as having abnormal changes (n=5) at referral smear appointment; of these, four required further treatment.

DISCUSSION

The introduction of primary HPV screening approximately doubled referrals to UHMB colposcopy. This had a huge impact on the service, so the question arises was it worth it?

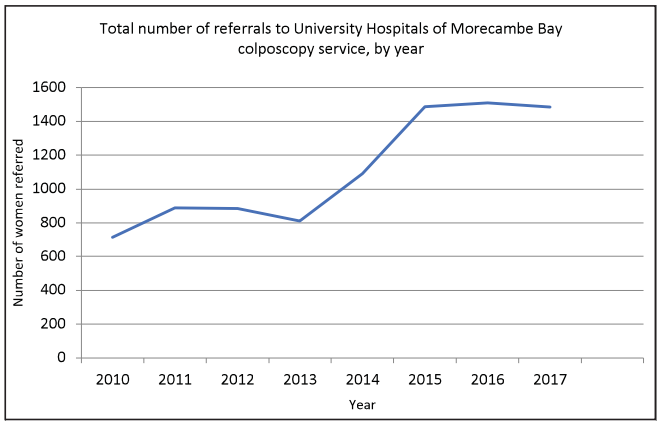

Figure 7: Number of referrals to UHMB colposcopy service since 2010.

This study looked at a relatively small cohort of women from 2012-2013 so little meaningful conclusions can be drawn from the demographic data. In this group of women there appeared to be no correlation between use of a particular contraceptive type and risk of persistent HR HPV or further treatment.

Smoking is likely to be related to the development of squamous cell carcinoma of the cervix (14, 15); however, there is limited supportive evidence from this audit.

HPV persistence following previous treatment for CIN formed a distinct group in this cohort. LLETZ biopsy is known to clear HPV in approximately 70% of cases, but even in women who do not clear the virus

a degree of protection against further abnormalities occurring is found.[16] Traditional follow up for these women was annual smears for ten years. Another change following introduction of HPV screening is that a HPV test at six months following treatment (test of cure) now dictates future management. Those women who are HPV negative return to routine screening while those who test HPV positive are referred back to colposcopy services.

We conclude that primary HPV screening has increased the detection of precancerous changes when compared with primary cytology alone.[17] Thirteen percent of the cohort had an abnormal colposcopy. This group of women would have had routine recall for their next smear in either 3 or 5 years dependent on their age on the previous cervical screening pathway where HPV testing was not utilised.

A HPV vaccination programme was introduced in the UK in 2008 for girls aged 12 – 13 years old. We can see that primary HPV testing of smears increases colposcopy referral. In the future, women who are fully vaccinated may require fewer routine smears in their adult life.

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