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REVIEW ARTICLE

A review of the use of human papilloma virus (HPV) in cervical screening

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ABSTRACT

Using key words online databases were searched to identify relevant publications to review the use of Human papilloma virus (HPV) in cervical screening. The mode of cervical screening in the UK has been decided but implementation plans have yet to be announced. The protracted uncertainty surrounding the initial announcement to move to HPV primary screening together with the lack of a national steer has resulted in a flight of staff which threatens the provision of the current and future service. The transition will be a challenging time but analysis of data from more than 176,000 women has shown clear evidence of a reduction in the incidence of cancer where HPV testing is used. There will however, be a population of women who are cytologically negative but high-risk HPV positive and the management of these women will be key to maximising the benefits of HPV primary screening. As cervical cytology becomes increasingly rare its effectiveness and role in cervical screening will come under scrutiny and we must ensure the specificity of reporting is maintained in order for it to survive.

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Introduction

With the announcement that the UK is to adopt human papilloma virus (HPV) primary cervical screening we thought it pertinent to review the use of HPV in cervical screening. To achieve this, the key words HPV, cervical cancer, primary screening and cervical cancer screening were used to search on-line databases to identify potentially relevant publications.

HPV is a small non-enveloped DNA papovavirus. The HPV genome encodes for six early proteins (E1–E7) responsible for virus replication and two late proteins, LI and L2, which are the viral structural proteins. There are over 100 different types of HPV and they are divided into low- and high-risk types. The high-risk types are associated with cervical cancer. The oncogenic HPV types include 16, 18, 31, 35, 39, 45, 51, 52, 56, 58, 59, 68 and 69. Around 50% of females acquire HPV infection of the cervix within six months of sexual 'debut', implying transmission from their male sexual partners. The virus is cleared by the immune system in the majority of cases but persistent infection by high-risk types is responsible for the development of cervical intraepithelial neoplasia (CIN) [1]. The prevalence of infection is greater in women in their twenties, at about 40% falling to around 7% in their fifties, presumably due to a higher frequency of sexual contacts in the younger women.

It was the German virologist Harold zur Hausen in the 1980s, who first linked genital warts with cervical cancer [2] but an association with papilloma virus and cancer in rabbits had been shown as early as the 1930s by Richard Shope in the United States [3]. Zur Hausen and his team went on to discover HPV-16 and HPV-18 and he shared the Nobel Prize for medicine in 2008 (Figure 1).

The International Biological Study on Cervical Cancer group found HPV in more than nine out of 10 cervical cancers from 22 countries [4]. In 1999, a group of scientists, including Professor Julian Peto, retested the samples to reveal that virtually all cervical cancer samples (99.7%) contained high-risk HPV [5].

Use of HPV in screening

The speed of progression from one milestone to another in cervical cancer screening has increased (Figure 2). It took 60 years after Papanicolaou's work was first published for the UK national screening programmes to be formalised but half that time for HPV to be used in cervical screening after it was first linked to cervical cancer in humans. In fact HPV triage was rolled out in England 13 years after it was published as the cause of invasive cervical cancer [5] in 1999. In 2002, HPV was proposed as the sole method of screening [6] and in 2003, the HART study [7] suggested a bigger role for HPV testing in cervical cancer screening. The Athena trial [8] began in 2011, followed by the English sentinel HPV primary screening pilot sites in 2013. The announcement that HPV primary screening would be fully implemented by 2019 [9] was

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CIN – Cervical Intraepithelial Neoplasia; HPV – Human Papilloma Virus; IT – Information Technology; MDT – Multi Disciplinary Team; PPV – Positive Predictive Value; UK – United Kingdom.

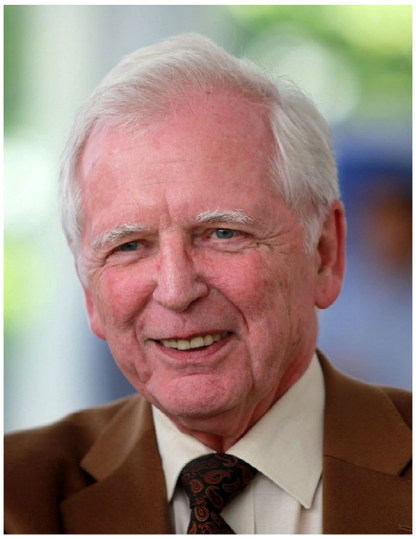

Figure 1. Harold zur Hausen.

Figure 2. George Papanicolou 1883–1962.

made 3 years later. Assuming all goes to plan primary screening will begin just 6 years after the initial pilot scheme, and only 17 years after it was first proposed. The 3 year time frame for implementation is unrealistic given we are still waiting for more detailed information for its implementation in England following the option appraisal document published at the end of January 2017. Despite knowing that HPV primary screening will be delivered as a single, seamless service, centralised with a minimum of four laboratories and a maximum of 15 [10], we do not have any information on how this will be achieved. This further work to ensure the delivery of the preferred option will include assessing costs, procurement arrangements, due diligence, the implication of each option on existing services and appropriate sign-off processes. The timescale for this work has yet to be announced. It was originally hoped that a robust plan would be in place with sufficient time to allow staff to be retrained or redeployed in order to navigate the major reduction in cytology workload ahead. It is expected that a similar streamlining of services will take place throughout the rest of the UK.

Importance of maintaining current service through transition

With HPV primary screening only the HPV positive samples are processed to cytology and consequently the reduction in cytology workload will be dramatic. The cytology workforce must be retained not only to report in the future but also to deliver the current service during transition. This is a difficult challenge as the cytology workforce has diminished over recent years, becoming more difficult to recruit and retain due to a lack of information and an ever increasing uncertainty about the future of cervical cytology. NHS England requires a cervical cytology laboratory to report a minimum of 35,000 samples each year (Service specification 25, appendix 1B) to maintain expertise amongst staff. As cytology will be reduced to around 15% of its current level this would require at least 200,000 screening samples per year to generate the required number of cytology slides. In 2015–2016, 4.21 million women were invited for screening, [11] which, given an 80% screening coverage and a workload of 200,000–300,000 suggests around 10–12 laboratories will be required. We now know that there will be a minimum of four and a maximum of 15. It had been hoped that a number of factors surrounding staffing would have mitigated the situation making the transition easier. Retirement of older staff had been suggested with retraining and redeployment for others. The protracted uncertainty surrounding the initial announcement to move to HPV primary screening together with the lack of a national steer has resulted in a flight of staff which threatens the provision of the current and future service in some areas. Previous centralisation of laboratories has resulted in shortages of both screening and reporting staff as many were unable or unwilling to travel or relocate with an uncertain future ahead. Provision of multidisciplinary team (MDT) meetings in centralised services has already proved challenging due to the number of colposcopy units covered, their location and distance from the laboratory, together with problems establishing the appropriate remote conferencing facilities. There needs to be video conferencing facilities which allow discussion with the projection of cytology and histology slide images in order for this to be successful. It is ironic, therefore, that a mitigation plan [12] has been put together to aid ailing laboratories who can no longer cope with their current workload. The plan does however, only address cytology workload and ignores any other factors that may be contributing to those 'ailing' laboratories. The remedy is to free up cytology capacity in the HPV primary screening sites by converting more women to HPV primary screening. This appears to be a cohesive, documented approach, if only the time to deliver this plan had been used to formulate a timelier implementation plan for HPV primary screening we may well have not needed mitigation. It is worth mentioning that the current climate has turned

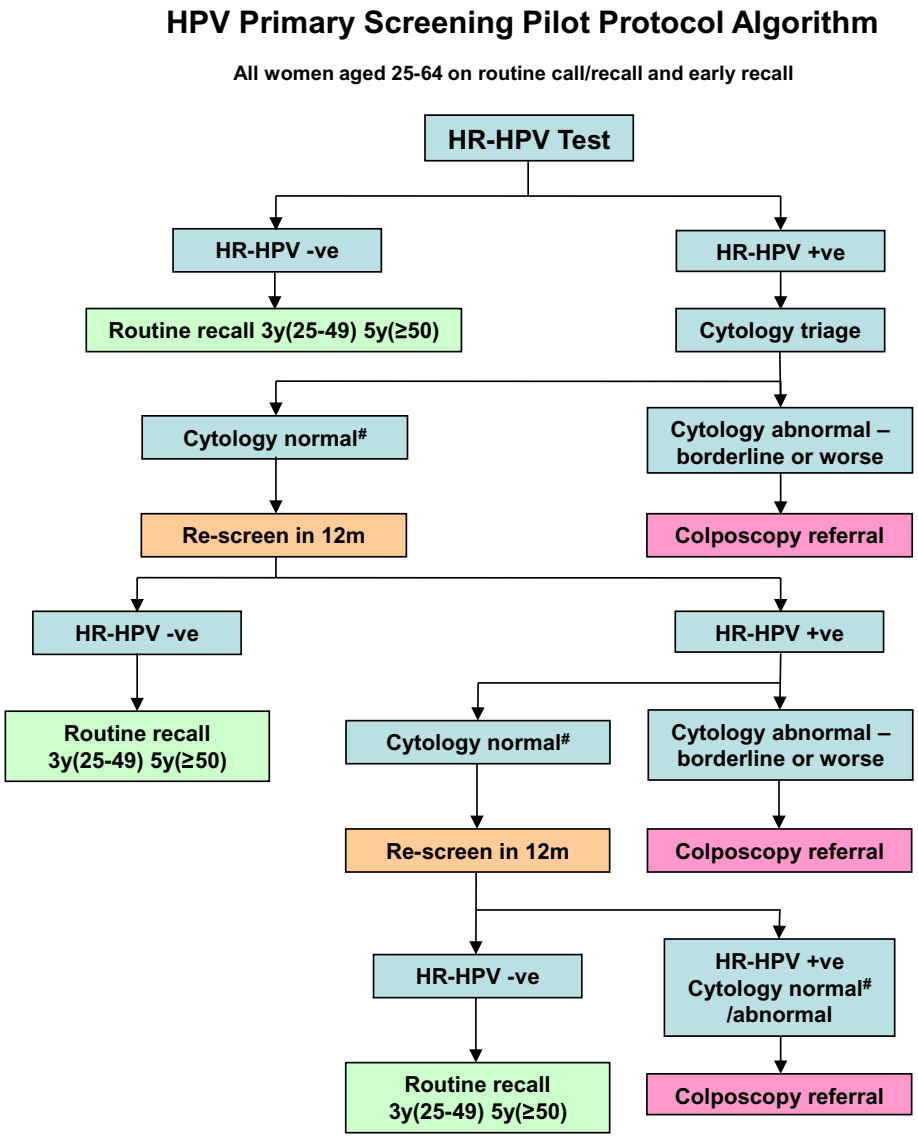

Figure 3. HPV primary screening algorithm.

neighbouring laboratories into rivals that will be bidding against each other to become a provider in the national roll-out of HPV primary screening, but in the meantime are expected to provide unilateral assistance. The current cervical screening programme uses a call/recall information technology (IT) programme developed 25 years ago. It was identified as a critical area for implementation as it will need to be much more flexible and able to cope with future developments. These developments may include differing screening intervals and personalised pathways dependent upon HPV genotyping. The system will also need to cope with the phased introduction of longer screening intervals and a more complex invitation and management system of women. It is imperative that the IT system works from the outset, otherwise there will be a loss of confidence in the screening programme.

Discussion

As the causative agent for cervical cancer is high-risk HPV and primary prevention is now provided by vaccination it is logical to use HPV testing in routine screening. The use of HPV testing offers improved sensitivity when compared with cytology for the detection of significant cervical disease, and provides longer protection allowing extended screening intervals. HPV testing will also allow the monitoring of the efficacy of the vaccination programme (Figure 3).

The use of high-throughput HPV testing platforms needed to cope with the number of primary screening tests, together with reducing the number of samples processed to cytology and extending the screening intervals will make the programme more cost-effective. Also worthy of note is a negative HPV test at exit of the programme may offer protection to an older age than a negative cytology sample in the current programme. Analysis of data from HPV trials [13] involving more than 176,000 women has shown clear evidence of a reduction in the incidence of cancer where HPV testing is used, when compared with cytology alone. The randomised trials of HPV testing used co-testing with cytology, but it is clear from the ARTISTIC trial that co-testing is not cost-effective for primary screening.

Currently, a negative cytology result means routine recall (3 years to age 49 and then every 5 years until exit aged 64) HPV triage of borderline and low grade dyskaryosis allows women who are HPV negative to be returned to routine recall, with women who are positive being referred immediately to colposcopy. In the triage pilot the positive predictive value (PPV) for CIN 2+ was around 16%.The PPV of women directly referred with a high grade abnormality was 75–90% [14]. With screening intervals extended to 6 years the PPVs are expected to remain the same.

With the relatively high prevalence of HPV infection when compared to significant cervical disease, HPV primary screening will inevitably result in a group of women who are HPV positive and cytology negative. Contrary to a major benefit of HPV triage and test of cure which reduced repeat testing, these women will require more frequent testing until resolution of the infection or colposcopy referral. This group accounted for around 9% of women aged 20–64 in the ARTISTIC trial, but this number will fall with screening beginning at 25 and more dramatically in a vaccinated population. Those women who are HPV positive and cytology negative are, based on ARTISTIC data, and considered to be at twice the base population risk of developing CIN2+ [15]. The management of these women will be key to maximising the benefits of HPV primary screening. There are potential biomarkers to improve the specificity for underlying CIN2+ which are being evaluated but there is no reason to suggest that lesions detected by HPV and triaged by cytology should be different from those detected by cytology and triaged by HPV. HPV primary screening is not only expected to reduce the incidence of cervical cancer and deaths but to be cost saving as well. This will primarily be achieved by reducing the number of women who require cytology through vaccination and then targeting colposcopy services to women at greater risk [16]. If the screening interval is increased there will also be a reduction in the number of screens in a lifetime, likely to reduce by half to around six. It is probable that screening will be further de-intensified in a fully vaccinated screening population [17].

As cervical cytology becomes increasingly rarer its effectiveness and role in cervical screening will come under scrutiny and question. We must ensure that the interpretation and categorisation of cytology samples does not change when the HPV status of the woman is known to the reporter. Several studies have previously reported that the sensitivity of cervical cytology significantly improves when it is interpreted with knowledge of HPV status [18–20]. More importantly however, is that as we will be using cytology as a triage tool, we must ensure the specificity of reporting is maintained

Conclusion

The mode of cervical screening in the UK as we move into the next decade has been decided. There will be many challenges facing the providers including covering even more colposcopy MDT meetings, and trying to manage workforce levels with unknown future workloads. Undoubtedly within the next two years there will be winners and losers. Some laboratories will see their screening sample workload (not cytology) increase substantially, while others will cease to exist. There will be a substantial number of individuals who will no longer have a role in cervical screening due to relocation of services and the diminished number of cytology samples produced in HPV primary screening. It will be the responsibility of those who remain within cervical screening to ensure that the winner is the UK cervical screening programmes and the women who are served by them are not the losers. Cytology must remain relevant as a cost-effective triage tool otherwise HPV positive women will simply be referred to colposcopy and cervical cytology will not only be a loser but will be lost.

Disclosure statement

No potential conflict of interest was reported by the authors.

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