The Future of Cervical Cancer Prevention in Europe

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ABSTRACT

Cervical cancer remains a significant source of disease and death in Europe. However, we now have the means to prevent virtually every case of cervical cancer through comprehensive, population-based, organised cervical cancer prevention programmes that effectively integrate cervical screening with the new technologies and vaccines that are now available. Given the potential health benefits of these programmes in reducing disease incidence and mortality, their establishment is now an ethical imperative for all European countries.

Key words: Cervical cancer, screening, vaccination, prevention

Introduction

Cervical cancer is the second most common cancer in women worldwide and is the most common female cancer in the Caribbean, East/Central/Southern Africa and in South-Central Asia. Globally, an estimated 471,000 women develop cervical cancer and 233,000 die from it every year (estimate for 2000)¹. The disease primarily affects younger women with the majority of cases appearing between the ages of 30 and 50², an age when many are actively involved in their careers, caring for their families or both and the impact on society as a whole is therefore greatly increased.

Cervical cancer still remains an important public health issue in Europe where it is the 7th most common cause of cancer deaths in women¹. Each year in Western Europe, 13,000 women develop cervical cancer and 6,000 women die from this disease, while the situation in Eastern Europe is much worse with approximately 31,000 women developing cervical cancer and about 17,000 dying every year³. This difference is largely due to the absence of effective cervical screening in Eastern Europe and the implementation of properly organised prevention programmes would inevitably decrease the burden of this disease in these countries.

Cervical Cancer Screening

Squamous cervical cancer is particularly amenable to screening as it has a long pre-clinical phase and identifiable precursor lesions that, if detected early, can be treated with high efficacy using simple outpatient procedures. Indeed, effective organised cervical cancer screening programmes have been proven to reduce cervical cancer incidence and mortality by more than 80%⁴. However, recent studies indicate that screening has limitations. Data available from organised screening programmes show that the initial declines in disease incidence seen following the establishment of screening have now levelled-off, indicating that the maximum effect of Pap smear-based screening has been reached in these countries⁵. Further, a meta-analysis of studies unaffected by verification bias has shown that the pooled sensitivity of the Pap smear was 77% (95% CI: 58% to 97%) when using low-grade squamous intra-epithelial lesions (LSIL) as the threshold to detect histologically confirmed cervical intraepithelial neoplasia of grade 2 or worse (CIN2+)⁶.

Given these data, an enormous amount of research effort has gone into the evaluation of new technologies such as liquid-based cytology and HPV testing, together with HPV vaccination that offer the potential to make...
further progress in the battle against this disease. However, it must be remembered that achieving reductions in the incidence and mortality of cervical cancer is entirely dependent upon the effective operation of the entire programme including primary prevention strategies such as vaccination, screening, diagnosis and treatment of pre-invasive or invasive disease. For these reasons, new technologies with the potential to be deployed must also be studied within the programme so the overall effect, including all the benefits and drawbacks, can be properly evaluated. Further, they should be evaluated within randomised controlled trials in order to obtain unbiased estimates of their effects.

The Human Papillomavirus and Cervical Cancer

There is now an overwhelming body of evidence demonstrating that persistent infection with certain types of the Human papillomavirus (HPV) is the primary risk factor for the development of cervical cancer and its precursor lesions. More than 100 different HPV types have been identified with approximately 40 of these infecting the anogenital epithelium that have been classified as either low-risk (LR) or high-risk (HR) for the development of cervical cancer based upon their identification in cervical tumour samples. A recent analysis of 11 studies has designated 15 anogenital HPV types as HR (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 68, 73 and 82), with a further 3 types designated as probably HR (26, 53 and 66) although some of these designations have been disputed by others.

This body of evidence is strong, consistent across different populations, and conclusively demonstrates that HPV is a necessary (although not a sufficient) cause of cervical cancer. On the basis of these data, it is logical to conclude that HPV testing could be a useful cervical cancer screening tool and that vaccination against HPV is a necessary (although not a sufficient) cause of cervical cancer.

HPV Testing for Primary Cervical Cancer Screening

For primary screening, a number of research studies (Table 1) have demonstrated that, compared to the Pap smear, HPV testing has a higher sensitivity and higher negative predictive value (NPV) for the detection of prevalent cervical cancer precursors, albeit with a lower specificity and lower positive predictive value (PPV). Importantly, some of these RCTs have moved to the evaluation of HPV testing as a single primary screening test rather than as a triage test followed by cytology for the triage of women having a positive test on the basis that:

- screening would be undertaken with the test having higher sensitivity and lower specificity, in compliance with accepted principles of screening, and as is already the case with syphilis and HIV screening;
- it would maximise specificity and PPV while achieving 95–100% of the sensitivity and NPV of the combined HPV/cytology primary test. This would provide the same level of safety but with improved cost-effectiveness by minimising the number of women with false positive results that need to be followed-up;
- it would allow 85–90% of women to return immediately to routine recall without incurring the cost of cytology, which would be reserved only for the triage of the remaining 10–15% of women with a positive HPV test;
- the high-volume testing of screening samples would be undertaken with a non-subjective test that can be automated, while the subjective, labor-intensive test would be restricted to high-risk samples only, so they could be screened more intensively because of the reduced number that need to be processed.

The interim results of these trials confirm the earlier studies with HPV testing (either alone or in combination with cytology) having a higher sensitivity and lower specificity than cytology alone for the detection of CIN2+. However, those studies reporting the performance of HPV testing as a single primary screening test with cytology triage indicate that this HPV screening algorithm
also has a higher sensitivity than cytology alone but now with a specificity that is at least equivalent to cytology. In the Finnish trial, HPV testing with cytology triage detected 1.45 times as much CIN2+ compared to cytology alone, while the specificities were not significantly different at 98.9% (95% CI: 98.6–99.2) and 99.3% (95% CI: 99.0–99.5), respectively27. Similar results were reported by Bulkmans et al. in the preliminary prospective results from the POBASCAM trial in which indicate that HPV testing followed by cytology triage compared to cytology alone can be more sensitive (92.9 vs 64.3% respectively; p=0.065) and more specific (96.8 vs 95.1% respectively; p= 0.0529). While the differences in sensitivity, NPV (99.96 vs 99.78% respectively; p=0.098) and PPV (14.6

TABLE 1
SENSITIVITY AND SPECIFICITY OF HPV TESTING COMPARED TO CERVICAL CYTOLOGY FOR THE DETECTION OF CIN2+ (USING ASC-US AS THE REFERRAL THRESHOLD)

<table>
<thead>
<tr>
<th>Study</th>
<th>Description</th>
<th>HPV</th>
<th>Pap Smear (≥ASC-US)</th>
<th>HPV/Pap Smear (≥ASC-US)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Sen</td>
<td>Spec</td>
<td>Sen</td>
</tr>
<tr>
<td>Cuzick et al.19</td>
<td>United Kingdom: n = 1,703</td>
<td>95</td>
<td>95</td>
<td>79</td>
</tr>
<tr>
<td>Schiffman et al.20</td>
<td>Costa Rica: n = 1,119</td>
<td>88</td>
<td>89</td>
<td>78</td>
</tr>
<tr>
<td>Ratnam et al.21</td>
<td>Canada: n = 2,098, 69% HC1/31% HC2, 9 ≥ 18-69 years (adjusted for verification bias)</td>
<td>85*</td>
<td>58</td>
<td>56</td>
</tr>
<tr>
<td>Clavel et al.22</td>
<td>France: n = 5,651</td>
<td>100</td>
<td>86</td>
<td>88</td>
</tr>
<tr>
<td>Petry et al.23</td>
<td>Germany: n = 8,468</td>
<td>96</td>
<td>96</td>
<td>44</td>
</tr>
<tr>
<td>Cuzick et al.24</td>
<td>United Kingdom: n = 10,358</td>
<td>97</td>
<td>93</td>
<td>77</td>
</tr>
</tbody>
</table>

ASC-US — Atypical Squamous Cells – Undetermined Significance, CIN — Cervical Intraepithelial Neoplasia, Sen — Sensitivity, Spec — Specificity; HC2 — Hybrid Capture 2 HPV test and HC1 — Hybrid Capture 1 HPV test (Digene Inc. Gaithersburg, MA), LBC — Liquid Based Cytology, * Sensitivity of HC1 was suboptimal and would have contributed to the difference seen between HPV testing alone and the combination of HPV testing with Pap

TABLE 2
THE EUROPEAN RANDOMISED CONTROLLED TRIALS

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Total Recruitment</th>
<th>Age Range (years)</th>
<th>HPV Test</th>
<th>Cytology</th>
<th>Main Study Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finnish Randomised Public Health Trial27</td>
<td>Finland</td>
<td>200,000</td>
<td>25–65</td>
<td>HC2</td>
<td>Conventional Pap smear</td>
<td>Cumulative incidence of CIN2, CIN3 and cancer after initial screening</td>
</tr>
<tr>
<td>Swedescreen26</td>
<td>Sweden</td>
<td>12,527</td>
<td>32–38</td>
<td>PCR (GP5+/6+ primers)</td>
<td>Conventional Pap smear</td>
<td>Comparative prevalence of histologically confirmed CIN2+ at the exit screen</td>
</tr>
<tr>
<td>POBASCAM29,30</td>
<td>The Netherlands</td>
<td>44,102</td>
<td>30–60</td>
<td>PCR (GP5+/6+ primers)</td>
<td>Conventional Pap smear</td>
<td>Proportion of histologically confirmed CIN3+ found at any time during the trial from recruitment to exit screen</td>
</tr>
<tr>
<td>ARTISTIC31</td>
<td>United Kingdom</td>
<td>25,000</td>
<td>20–64</td>
<td>HC2</td>
<td>LBC</td>
<td>Comparative prevalence of histologically confirmed CIN3+ at the exit screen</td>
</tr>
<tr>
<td>NTCC32</td>
<td>Italy</td>
<td>95,000</td>
<td>25–60</td>
<td>HC2</td>
<td>LBC or conventional Pap smear</td>
<td>Comparative detection of histologically confirmed CIN2+ from the recruitment screen up to and including the exit screen</td>
</tr>
</tbody>
</table>

CIN — Cervical Intraepithelial Neoplasia, HC2 — Hybrid Capture 2 HPV test, PCR — Polymerase Chain Reaction, LBC — Liquid Based Cytology
Vaccination Against HPV for Primary Prevention of Cervical Cancer

A number of studies have now been conducted on the two first generation prophylactic HPV vaccines33–38. Both vaccines target HR-HPV types 16 & 18 (which are together responsible for over 70% of cervical cancers worldwide), while one (GARDASIL®, Merck and Co.) also includes types 6 and 11 which are non-oncogenic but still responsible for a substantial proportion of lower-grade cervical disease and the other (CERVARIX®, GlaxoSmithKline) has demonstrated to provide a degree of cross-reaction to HPV types 31 & 45 (which are the next most common oncogenic HPV types after 16 & 18)39. The result of the phase IIb and III trials have shown these vaccines to be safe, well tolerated and highly immunogenic. Further, both vaccines have been shown to offer HPV naïve women high levels of protection against HPV infection with the HPV types contained in the vaccine as well as their resulting cervical lesions35–38. However, the GARDASIL licensing submissions filed with both the US Food and Drug Administration and the European Medicines Agency included data to show there was no clear evidence of protection from disease caused by HPV types which subjects were DNA positive and/or seropositive for at the time of vaccination39,40. Further data were presented to show that in the general public where a proportion of women will have prior or current HPV infections, GARDASIL can be expected to reduce the overall rate of CIN2/3 or adenocarcinoma in situ caused by vaccine or non-vaccine types by 12.2%39.

The results of these trials have now led to the licensure of one of the vaccines in many countries with the second expected to follow shortly and it is anticipated that these vaccines will play a very important role in the prevention of cervical cancer going forward. However, the availability of these vaccines raises several implementation issues that must be addressed if the vaccines are to achieve their full potential in Europe where cervical cancer screening is already widespread and substantially efforts are underway to ensure the uniform implementation of properly organised cervical cancer screening programmes. In Europe, the enormous potential of HPV vaccination must be considered together with its limitations which are chiefly 1) its high cost (currently around €450 per person in France), 2) that the first-generation vaccines do not protect against all HR HPV types, and 3) inability to protect women who are already infected with HPV types 16 and 18. In addition, an important question remains about whether HPV vaccination will provide any supplemental protection against the development of cervical cancer in women who have been exposed to HPV 16 or 18 but subsequently mounted their own effective immune response and cleared the virus. This is a particularly important question for public health programmes where the cost for the vaccine must be taken from finite healthcare budgets and which will therefore lead to a diminution in other services. Clearly, there is an ethical concern about the implementation of vaccination programmes for women who may derive little or no additional benefit over that provided by their own immune system when the money must come from other programmes with clear and proven health benefits.

Under these conditions, there is little dispute that the vaccination of girls before the commencement of sexual activities is not only a public health priority but an ethical imperative. However, the use of vaccination in older girls and women will yield diminishing public health returns as the proportion of women exposed to HPV 16 & 18 increases, and this needs to be balanced against the clearly established protective effect of cervical screening in these populations. Unfortunately, it is not possible to have a single formula and each country must undertake its own cost-benefit analysis to establish the appropriate balance depending on their national priorities, healthcare budgets and the status of existing resources such as screening programmes. But what is clear that all European countries now need to implement comprehensive cervical cancer prevention programmes which integrate cervical screening together with HPV vaccination as it is the combination of these that will offer the most effective long-term protection against cervical cancer. Further, these new measures of cervical cancer prevention must be offered within population-based organised prevention programmes to ensure that the protection is equitably available to all women in the population.

The Effective Integration of Technologies for the Prevention of Cervical Cancer

Although the Pap smear has been the mainstay of cervical cancer prevention for more than 50 years, it now must be recognised that the ongoing uptake of HPV vaccination against HPV 16 & 18 will have a progressively detrimental effect on cytology based screening. Evaluations of the prevalence of HPV 16 & 18 among women with abnormal cytology indicate that ASC-US, LSIL and HSIL rates could be reduced by as much as 30%, 36% and 55% respectively in a population that was fully vaccinated with a vaccine having 100% efficacy31–43. If HPV 6 and 11 are also included, ASC-US, LSIL and HSIL could eventually be reduced by a total of 40%, 46% and 60% respectively41–43. Here, it is important to note that the reductions are likely to be greater for HSIL than for ASCUS or LSIL. Therefore, vaccination will both reduce the overall prevalence of cytological abnormalities and...
shift the balance to the lower grades which have a lower PPV. These characteristics mean that vaccination will inevitably lead to a substantial deterioration in the efficacy of cytology-based screening because:

1) A decrease in disease prevalence will produce a direct and simultaneous decrease in the PPV of screening. Even with current disease rates in adequately screened populations, the PPV of cervical cancer rates from only 10 to 30% for the detection of CIN2+ in well-screened populations18-24 a situation that is only tolerated because of the seriousness of the disease that cervical screening prevents. However, reductions in disease rates subsequent to widespread vaccination, together with the shift to the lower-grades of cytological abnormalities, will further reduce the PPV of cytology-based screening programmes, eventually to a point where the stress, morbidity and costs involved in the follow-up of these false-positive women may no longer be either ethically or financially justifiable relative to the yield of true disease.

2) Reductions in disease rates would also mean that cytology screeners would have less exposure to cytological abnormalities during the course of their working day with two possible outcomes. First, regular exposure to cytological abnormalities is necessary for the maintenance of cytology screening skills. Therefore, reductions in disease rates could be accompanied by a simultaneous reduction in the sensitivity of the cytology screeners’ ability to recognise these abnormalities and a reduction in the sensitivity of the screening program. Second, a reduction in the number of true abnormalities could lead cytology screeners to compensate by over-classifying inflammatory changes or reactive atypias leading to further decreases in specificity and PPV of the screening programme.

Although these changes will only be seen with the progressive implementation of HPV vaccination and the gradual expansion of the vaccinated cohort, it is nonetheless essential for screening programmes to make plans for the changes that will be required to maintain proper levels of protection against cervical cancer. One way this could be achieved is by stratifying the population to be screened according to their risk and then applying cytology-based screening only to the subpopulation of women that is at increased risk of having clinically relevant cervical disease, i.e. those women who are HPV positive. On this basis, the uptake of HPV vaccination will necessitate a shift to HPV testing for primary screening together with cytology for the triage of women with a positive result in order to maintain the efficacy of screening in an environment with a reduced prevalence of cervical disease.

Conclusions
In Europe, cervical cancer remains a significant source of disease and death although we now have the means to prevent virtually every case through comprehensive cervical cancer prevention programmes. However, if we are to achieve this goal, it is essential that these prevention programmes effectively integrate cervical screening together with the new technologies and vaccines to ensure that the optimal protection is afforded to all age groups. In addition, they must be population-based to ensure that the protection is equally available to all women and they are run in the most cost-effective fashion. The science has been done and the tools are now available to effectively prevent cervical cancer in Europe. What we now need is the political will to make this a reality.

REFERENCES


BUDUĆNOST PREVENCIJE RAKA VRATA MATERNICE U EUROPI

SAŽETAK

Rak vrata maternice je i dalje značajna izvor bolesti i smrti u Europi. Međutim, danas postoji način prevencije gotovo svakog slučaja rak vrata maternice kroz opsežne organizirane programe prevencije, temeljene na populaciji, koji učinkovito spajaju probir za rak vrata maternice s novim metodama koje su danas dostupne. Pridajući zasluge u smislu mogućih zdravstvenih dobrobiti ovom programu u smanjenju stope pojavnosti i smrtnosti od ove bolesti, njegovo uspostavljanje je danas etički imperativ za sve europske zemlje.