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Summary

Worldwide, cervical cancer is the third most common female malignancy with the highest incident rates reported in low resource countries. In countries with cervical cancer screening, the incidence and mortality rates of cervical cancer have decreased. Cytology-based screening enables cancer prevention by early detection of pre-malignant lesions, which can be treated effectively.

The recognition that a persistent infection with hrHPV is the necessary cause of cervical cancer has resulted in the development of new methods of cervical cancer prevention. These comprise secondary prevention by hrHPV testing for early detection of cervical cancer and primary prevention through HPV vaccination. This thesis presents recent work exploring the possibilities of hrHPV testing in triage of women with borderline or mildly dysplastic smears (BMD, Pap2/3a1) and the potential clinical impact of using the hrHPV test in primary screening.

Chapter 1 provided a general introduction of cervical cancer epidemiology, human papillomavirus infections, cervical carcinogenesis and cervical cancer prevention.

In **Chapter 2**, we studied whether it is feasible to use the hrHPV test as baseline triage test for women with BMD. In many European countries, including the Netherlands, women with BMD in screening are recalled for repeat testing and they are only referred for colposcopy if the cytological abnormality persists. Because the majority (>80%) of these women do not have a high-grade lesion, a significant burden is imposed on women and the health care system. Therefore, we compared repeat cytology testing at 6 and 18 months to direct referral of women with BMD and a positive hrHPV test. In this study, almost all CIN3 and CIN2+ lesions were found in hrHPV-positive women, whereas women with a negative hrHPV test had an acceptably low CIN3 and CIN2+ risk. Compared to repeat cytology testing, baseline triaging by hrHPV testing can be implemented against low costs, and leads to a faster diagnosis and less distress for women. We therefore support the strategy of referring hrHPV-positive women with BMD immediately for colposcopy and to refer those who are hrHPV-negative to routine screening.

In **Chapter 3**, we presented the main results of the population based VUSA-Screen study (VU University Medical Center SAItro laboratory population-based cervical Screening) in which 3-year follow-up results were related to baseline hrHPV testing and cytology testing to find an optimal primary screening method. In line with other studies, this study demonstrated that hrHPV testing is superior to cytology in terms of sensitivity but not in terms of specificity. Women with a double (cytology and hrHPV) negative test did not have a markedly lower CIN3+ and CIN2+ risk than women with a single negative hrHPV test. Therefore, from a health-economic perspective, cervical screening with a primary, stand-alone hrHPV test seems preferable. HrHPV-positive women have a non-negligible risk for CIN3+ (13.2%) and CIN2+ (21.9%). To prevent unnecessary colposcopy referrals, hrHPV-positive women should not be offered

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colposcopy immediately but should be further stratified by means of triage/repeat testing. Since cytology in the Netherlands has a high specificity for threshold CIN3+, we used cytology for this purpose. Women with an hrHPV-positive test and abnormal cytology had a high CIN3+ (42.2%) and CIN2+ (60.3%) risk and need immediate colposcopy. HrHPV-positive women with normal cytology have a low, but still non-negligible CIN3+ (5.2%) and CIN2+ (11.3%) risk. We showed that repeat cytology testing after 1 year for hrHPV-positive women with normal cytology at baseline is however necessary before returning women to routine screening. In present study the CIN3+ and CIN2+ risk was similar in women invited for the first time (29-33 years) and in women ≥ 34 years. Moreover, the CIN3+ risk in women with hrHPV-positive normal cytology was higher among women invited for the first time (29-33 years) than among older women.

In **Chapter 4**, we presented the final data from the POBASCAM (POpulation BAsed SCreening study AMsterdam) trial. In this randomised trial, women were randomly assigned to receive hrHPV and cytology co-testing (intervention group) or cytology testing alone (control group). At the second round 5 years later, hrHPV and cytology co-testing was done in both groups. At baseline, hrHPV testing detected more clinically relevant, CIN2+ lesions compared with screening using cytology only. This improved detection of cervical lesions at baseline led to reduced detection of CIN3+ and cervical cancers in the second round. The higher protection of CIN3+ lesions in the second round by hrHPV testing appeared to be largely attributable to HPV16. HrHPV testing in women aged 29-33 did not result in excessive detection of regressive cervical lesions. Collectively, these results support hrHPV testing in cervical screening starting at age 30.

In **Chapter 5**, we showed the results of triage strategies for hrHPV-positive women. HrHPV testing as a primary screening test requires efficient management of hrHPV-positive women. Most hrHPV infections will clear spontaneously and only a minority of hrHPV-positive women will have or develop clinically meaningful lesions. Thus, an effective triage strategy that determines which hrHPV-positive women should be referred for colposcopy is crucial to prevent unnecessary colposcopies and treatment. Our analysis of triage strategies for hrHPV-positive women based on the data from the VUSA-Screen study points to use cytological testing at baseline, followed by repeat cytology testing at 12 months. This is a feasible triage strategy because hrHPV-positive women with 2 times negative cytology have an acceptably low CIN3+ and CIN2+ risk (0.7% and 2.9%, respectively), and it is accompanied with a modest colposcopy referral rate (33.4%). Moreover, this strategy is easy to communicate to participating women and physicians.

In **Chapter 6** we studied the effect of increasing the threshold level of hrHPV testing by HC2 on the sensitivity and specificity for CIN3+ and on the colposcopy referral rate. We found that increasing the HC2 threshold could result in similar or lower colposcopy referral rates than cytology screening but only at the cost of a lower sensitivity.

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However, superior performance in terms of both sensitivity and colposcopy rate was possible if HC2 testing, at the standard threshold, was combined with cytology triage at baseline and repeat cytology testing after 1 year as earlier defined in **Chapter 5**.

Finally, in **Chapter 7** we provided a general discussion of the results presented in this thesis, and discusses possible future developments, prospects and clinical consequences of hrHPV testing. We conclude that hrHPV testing is superior to cytology as a primary screening test in cervical cancer screening programmes for women 30 years and older. Additionally, we presented feasible triage algorithms for hrHPV-positive women. In the future, new objective biomarkers may improve triage of hrHPV-positive women.