

VU Research Portal

Towards a more objective way of cervical cancer screening:

Dijkstra, M.G.

2014

document version

Publisher's PDF, also known as Version of record

[Link to publication in VU Research Portal](#)

citation for published version (APA)

Dijkstra, M. G. (2014). *Towards a more objective way of cervical cancer screening: cervical cancer screening 2.0.*

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal ?

Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

E-mail address:

vuresearchportal.ub@vu.nl

SUMMARY

Cervical cancer remains an important health problem worldwide as it affects over a half a million patients each year. Currently, it is the third most common female malignancy, with the highest incidence rates reported in low resource countries. Therefore, continuing efforts for improving the prevention of cervical cancer are warranted. Cervical cancer develops through different premalignant stages (precursor lesions) which can be detected years before cervical cancer appears, and thus, offers possibilities for screening and treatment. This recognition has resulted in the organisation of population-based screening programs, which have proven to be effective as the incidence and mortality rates of cervical cancer have decreased in countries with such a screening program.

Cervical cancer is induced by a persistent infection with hrHPV. This causal link has been proven indisputably, and strong evidence now supports the use of hrHPV testing in the prevention of cervical cancer. This thesis presents recent work evaluating opportunities of hrHPV and subsequent triage testing on the way towards a more objective manner of cervical cancer screening.

Part one: increasing the screening coverage

Chapter 1 is a general introduction on cervical cancer epidemiology, human papillomavirus infections, cervical carcinogenesis, prevention of cervical cancer, and ways to improve cervical cancer screening.

In **Chapter 2**, we evaluated whether brush-based self-sampling in combination with GP5+/6+-PCR EIA hrHPV testing is equally effective for assessing CIN2+ risk, in comparison to hrHPV testing on physician-taken scrapes. In forthcoming years, self-sampling may become increasingly important since self-collection for HPV testing has shown to persuade a subset of non-attendees to participate. Targeting non-attendees is important, because they are at higher risk of developing cervical cancer. Additionally, self-sampling may make cervical screening accessible to women in developing regions. In this outpatient population, hrHPV test results showed good concordance between self-samples and physician-taken cervical scrapes. More importantly, the clinical sensitivity for detection of CIN2+ of brush-based self-sampling combined with GP5+/6+-PCR EIA hrHPV testing was non-inferior to that of hrHPV testing on physician-taken cervical samples. Therefore, this HPV self-sampling *procedure* may be considered for use in routine cervical screening.

As mentioned above, the attendance rates of cervical screening programs can be increased by offering HPV self-sampling to non-attendees. However, the effectiveness of self-sampling procedures may be influenced by the degree of acceptance by users, sample volume, DNA yield and choice of hrHPV test. Therefore, these factors possibly play a role in successfully

recruiting non-attendees. In **Chapter 3**, we studied the effect of replacing a first generation self-sampling lavage device by an ergonomically improved, second generation device on response rates among non-responders of the Dutch cervical screening program. In addition, the clinical performance of both devices was compared. We found that participation of non-attendees in cervical cancer screening is probably not predominantly determined by the type of self-collection device, as replacing the first generation lavage device by the second generation type resulted in similar response rates and equal clinical performance.

Part two: management of hrHPV positive women

Several studies have shown that primary hrHPV screening is more sensitive than cytology for detecting CIN2/3 lesions, and cervical cancer, but also that it is less specific. Most hrHPV infections will clear spontaneously and only a minority of hrHPV positive women will have or develop clinically meaningful lesions. Thus, in order to prevent over-referral and over-treatment of patients, management of hrHPV screen positives remains a clinical dilemma. In **Chapter 4**, we presented the results of a POBASCAM (POpulation Based Screening study AMsterdam) trial sub study, in which ten triage strategies were evaluated, with regard to CIN3+ detected within four years, in order to provide directives on how to manage hrHPV DNA positive women in the setting of nation-wide cervical cancer screening. The three strategies that showed the best balance between the safety of a strategy (NPV) and the burden of screening on patients and clinicians (PPV and referral rate), were: 1. cytology and HPV16/18 genotyping at baseline without repeat testing, 2. cytology at baseline with repeat cytology testing after six months, and 3. cytology and HPV16/18 genotyping at baseline followed by repeat cytology examination at 6 months. The weights placed on safety and screening-related burden in relation to the resources available, as well as the quality of cytology in a particular country, will likely determine the eventual management of hrHPV positive women.

In **Chapter 5**, we analysed the fifteen-years risks of histologically confirmed CIN3 and cervical cancer after primary hrHPV DNA testing at enrolment, for women aged 30 years and older, who participated in a population-based randomised controlled trial (the POBASCAM trial). Our aim was to evaluate the protection against CIN3+, provided by hrHPV-based screening compared with that of cytology, and to establish the safety of an extension of the screening-interval beyond 5 years for baseline hrHPV negatives and hrHPV positive, triage negative women. Our results confirm that hrHPV screen-negatives have a very low absolute long-term CIN3+ risk (12-year risk: 0.011 (95%CI: 0.0068 - 0.015)), and therefore, that an extension of the screening interval beyond 5 years seems justified. Further, the data show that the screening-interval could even be extended to 10 years for hrHPV screen-negative women aged 40 years and older. More importantly, we showed that, regardless of which strategy was used, the long-term CIN3+ risk of hrHPV positive, triage negative women was too high to justify an extension of the screening-interval; these women should be rescreened within 5 years

Part three: accurate diagnosis of screen-positive women

Accurate histomorphological grading of CIN lesions is important for clinical management of patients, because CIN1 and CIN2/3 lesions

are managed differently. CIN grading is however subjective and affected by substantial rates of discordance among pathologists, which may lead to overtreatment. In **Chapter 6**, we studied the effect of additional interpretation of p16INK4a immunostains for making a more reproducible diagnosis of CIN2/3 lesions. The data demonstrated that the combined interpretation of H&E- and p16INK4a immunostains significantly improves the accuracy of interpreting and grading cervical lesions on biopsy samples. The accuracy of CIN lesion grading by a single pathologist with the additional use of p16INK4a stains is comparable with the consensus diagnosis of an expert pathology panel. Hence, we advocate the combined use of H&E-stained and p16INK4a-stained sections in routine histopathology, to improve the accuracy of diagnosis at an acceptable cost when used in large populations.

Part four: The time has come to start implementation

Finally, in the general discussion in **Chapter 7** we presented a review, in which we discuss the arguments in favour of, and concerns on aspects of implementation of hrHPV testing in primary cervical cancer screening. Additionally, (the key-messages of this thesis are summarized and) possible future developments are discussed. We conclude that sole hrHPV testing should replace cytology as a primary screening tool in cervical screening, an extension of the screening interval is justified for hrHPV-screen negatives. Moreover, hrHPV positive women require triage testing to prevent over-referral for colposcopy, and should be screened every 5 years, as the long-term risk to develop cervical disease is too high to delay re-screening, even after negative triage testing. In future, new objective biomarkers may improve the triage of hrHPV-screen positive women.

On the basis of our and other studies, the Dutch Minister of health has recently decided to use primary hrHPV screening to improve cervical screening efficacy. This will be implemented in the Netherlands in 2016 and comprises primary hrHPV testing in 5 screening rounds, at the ages of 30, 35, 40, 50 and 60 years. Women who test positive for hrHPV at the age of 40, 50 or 60 years, and are negative for cytology triage at baseline and after 6 months, should be re-screened after 5 years.