Efficacy of addition of hrHPV testing by Hybrid Capture II to conventional cytological screening for cervical cancer: 5 years follow-up.

No registrations found.

Ethical review	Positive opinion
Status	Recruitment stopped
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON21745

Source
NTR

Brief title
VUSA-SCREEN

Health condition

Cervical intraepithelial neoplasia (CIN), Cervix cancer

Sponsors and support

Primary sponsor: SALTRO - Doctor Laboratory & Thrombosis Service, VU University Medical Center, Department of Pathology
Source(s) of monetary or material Support: SALTRO - Doctor Laboratory & Thrombosis Service, VU University Medical Center, Department of Pathology

Intervention

Outcome measures

Primary outcome

The primary outcome measure of VUSA-SCREEN is the occurrence of histologically confirmed cervical intra-epithelial neoplasia grade 3 (CIN3) lesions or (micro-) invasive carcinoma of the cervix found during the follow-up of currently diagnosed abnormalties, i.e., within 5 years.
For women whose cytology results either regress to normal (in the unblinded trial of women with mild cytological abnormalities) or who clear an infection with hrHPV without cytological abnormalities (in the blinded trial of women with normal cytology diagnoses), we assume that no precursor lesions of cervical cancer are present.
They will not be referred for colposcopically-directed biopsies and therefore will not have a histological endpoint. This policy complies with regular cervical screening in The Netherlands.

Secondary outcome

As a secondary outcome measure, histologically confirmed cervical intra-epithelial neoplasia grade 2 will also be investigated, since current guidelines recommend ablative treatment for these lesions as well.

Other secondary parameters obtained include progression and regression of cytology diagnoses, clearance and acquisition of hrHPV infections and the number of referrals for colposcopically-directed biopsies.

Study description

Background summary

Cervical cancer almost exclusively develops in the presence of high-risk types of the human papillomavirus (hrHPV). A prolonged and persistent infection of the cervix with hrHPV is necessary for the development of premalignant (cervical intra-epithelial neoplasia, CIN) and finally malignant lesions. Prolonged presence of hrHPV types will lead to cytomorphological aberrations that can be detected in a cervical smear.

Research has shown that borderline and mild dyskaryotic (BMD) lesions tested positive for hrHPV significantly increase the risk for lesions ¡ÝCIN3, and that progression to lesions ¡ÝCIN3 will not occur in the absence of hrHPV. Secondly, women with normal smears (Pap 1) positive for hrHPV have a significantly increased risk for the development of lesions ¡ÝCIN3.
Thus, we will investigate the efficacy of additional testing for hrHPV in the cervical cancer screening program both for women with normal smears (Pap 1) and for women with BMD smears (Pap 2-3a1).

In this study, hrHPV testing will be performed by the Hybrid Capture II test (HCII). The HCII is a commercially available and FDA-approved test for hrHPV.
This study has been designed as a population-based cohort study with a follow-up period of 5 years, in which 50,000 women invited for program-based screening in a geographically defined region in the Netherlands will participate.
All participants will undergo at least the routine strategy for repeat smears and referrals as is

the standard level of care in the program-based screening in the Netherlands. Most participants (> 80%) will not even undergo a different treatment, as they will be diagnosed Cervical cancer almost exclusively develops in the presence of high-risk types of the human papillomavirus (hrHPV). A prolonged and persistent infection of the cervix with hrHPV is necessary for the development of premalignant (cervical intra-epithelial neoplasia, CIN) and finally malignant lesions. Prolonged presence of hrHPV types will lead to cytomorphological aberrations that can be detected in a cervical smear.
Research has shown that borderline and mild dyskaryotic (BMD) lesions tested positive for hrHPV significantly increase the risk for lesions ¡ÝCIN3, and that progression to lesions ¡ÝCIN3 will not occur in the absence of hrHPV. Secondly, women with normal smears (Pap 1) positive for hrHPV have a significantly increased risk for the development of lesions ¡ÝCIN3.
Thus, we will investigate the efficacy of additional testing for hrHPV in the cervical cancer screening program both for women with normal smears (Pap 1) and for women with BMD smears (Pap 2-3a1).
In this study, hrHPV testing will be performed by the Hybrid Capture II test (HCII). The HCII is a commercially available and FDA-approved test for hrHPV.
This study has been designed as a population-based cohort study with a follow-up period of 5 years, in which 50,000 women invited for program-based screening in a geographically defined region in the Netherlands will participate.
All participants will undergo at least the routine strategy for repeat smears and referrals as is the standard level of care in the program-based screening in the Netherlands. Most participants (> 80%) will not even undergo a different treatment, as they will be diagnosed with hrHPV negative normal cytology (Pap 1).
The extra care in this study will involve:
1. Women with hrHPV positive BMD (Pap 2-3a1) who will be referred to the gynaecologist for colposcopy immediately, as the presence of lesions ¡ÝCIN3 will be expected solely in this group, and not in the group of women with hrHPV negative BMD;

2. All women with hrHPV positive normal cytology and 12.5% of the women with hrHPV negative cytology will undergo extra cytologic control to evaluate the role of hrHPV in the development of cytologic and histologic lesion. For these women, the hrHPV results will be blinded for the duration of the study.

In order to evaluate the hrHPV-based referral strategies with the regular repeat and referral recommendations, we compare the results of the study cohort with a cohort of women screened with conventional cytological testing only in the same period, region and study laboratory.

The research questions that will be answered in the study include the following:

1. Can women with BMD and a positive HCII hrHPV test be referred to the gynaecologist immediately, whereas women with a negative hrHPV test will be referred back to the regular screening program, without an increase in risk of missing lesions ¡ÝCIN3?

2. Is the risk of lesions ¡ÝCIN3 for women with hrHPV negative BMD not increased compared

to women with normal cytology (Pap 1) and an unknown result of the HCII hrHPV test (i.e. women who are at present given an advice to repeat the smear after 5 years in the Netherlands)?

3. To what extent will lesions ¡ÝCIN3 and/or cytologic progression to ¡Ý moderate dyskaryosis develop in women with HCII hrHPV positive normal cytology (Pap 1) compared to women diagnosed with HCII hrHPV negative normal cytology (Pap 1)?

4. Will the repeat and referral strategy based on classical cytology and HCII hrHPV testing not result in less women diagnosed with lesions ¡ÝCIN3 for the women with BMD, than in a historical cohort of women diagnosed with BMD in the preceding year in the program-based cervical cancer screening?

5. Can the efficacy and cost effectiveness of the cervical screening programme be improved by increasing the screening interval for women with normal cytology and a negative hrHPV test?

6. What is the 5 years risk of ¡ÝCIN3 lesions for women with normal cytology and a negative hrHPV test?

7. What is the 3 years risk of ¡ÝCIN3 lesions for women with normal cytology and a negative hrHPV test at baseline and after 2 years?

8. What is the 5 years risk of ¡ÝCIN3 lesions for women with normal cytology and a hrHPV positive test?

9. What are the HPV type specific 5 years risks of ¡ÝCIN3 lesions?

10. What is the 5 years risk of ¡ÝCIN3 lesions for baseline
additionally tested molecular markers?

Study objective

In the original study (NTR215), we assessed the 3-year risk of CIN3+ in women stratified for hrHPV and cytology at baseline. In this study, we will assess the 5-year risks. Stratification at baseline is done on hrHPV, cytology, and hrHPV genotype. The results will be used to assess the optimal screening algorithm with hrHPV testing and to determine the length of the screening interval.

Study design

N/A

Intervention

In the VUSA-SCREEN, women participating the regular cervical screening program were

offered high-risk human papillomavirus (hrHPV) test, using the commercially available and FDA approved Hybrid Capture II test, in addition to cytology or cytology only. In order to improve detection of precursor lesions of cervical cancer, hrHPV is evaluated using a cohort study of women whose smears were consecutively screened at a single laboratory in The Netherlands. Within this cohort study, we nested an unblinded trial of women with mildly abnormal screening smears and repeat and referral recommendations were based on the presence or absence of high-risk human papillomavirus.
Secondly, we nested a randomized trial of women with normal cytology whose hrHPV test results were triple blinded to participants, treating clinicians and study personnel, and advised all women with blinded test results to repeat cervical screening at earlier intervals than current screening guidelines in the Netherlands recommend in order to evaluate screening strategies for women with normal cytology and a positive hrHPV test.

Contacts

Public
D.C. Rijkaart
[default]
The Netherlands
Scientific
D.C. Rijkaart
[default]
The Netherlands

Eligibility criteria

Inclusion criteria

1. Women invited for the cervical cancer screening program (ages 30-60 years);

2. General practitioner affiliated with SALTRO laboratory.

Exclusion criteria

1. Not called for screening, i.e., ages under 30 years, or over 60 years;

2. Follow-up of previous non-normal cytology within the current screening round of the program, i.e., abnormal cytology or lesion ¡ÝCIN3 less than 2 years before inclusion;

3. Current pregnancy;

4. Status after extirpation of the uterus or amputation of the portio.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-10-2003
Enrollment:	50000
Type:	Actual

Ethics review

Positive opinion

Date:	10-06-2009
Application type:	First submission

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
NTR-new	NL1740
NTR-old	NTR1850
Other	NTR : TC 215
ISRCTN	ISRCTN wordt niet meer aangevraagd.

Study results

Summary results
N/A