COMETH study.

No registrations found.

Ethical review	Positive opinion
Status	Pending
Health condition type	-
Study type	Observational non invasive

Summary

ID

NL-OMON23076

Source
NTR

Brief title
COMETH

Health condition

cervical (pre)malignant disease
high risk human papillomavirus

(voorstadia van) baarmoederhalskanker
hoogrisico humaan papillomavirus

Sponsors and support

Primary sponsor: VU University Medical Center
Source(s) of monetary or material Support: Nederlandse Kankerbestrijding KWF

Intervention

Outcome measures

Primary outcome

Endpoint is histology outcome; i.e. presence or absence of ≥CIN2 lesions.

Secondary outcome

N/A

Study description

Background summary

Rationale:

High-risk human papillomavirus (hr-HPV) DNA testing complementary to current cytology examination (i.e. Pap test) of cervical smears has shown an increased sensitivity and negative predictive value (NPV) for cervical cancer and its precursor lesions, high-grade cervical intraepithelial neoplasia (≥CIN2), when compared with cytology alone.However, the specificity of hr-HPV DNA testing is lower than that of cytology as a considerable number of hr-HPV positive women will clear the virus and consequently will not develop ≥CIN2 lesions. Additional biomarkers are therefore needed to reduce the number of false positive test outcomes and consequently, unnecessary follow-up procedures. Currently, cytology is the most logic option since women with a double positive hr-HPV and cytology test result have a substantial risk of ≥CIN2 lesions. Nevertheless, besides its limited sensitivity, cytological examination is also subjective and prone to variability. In this study we aim to evaluate the value of other candidate markers for triage of hr-HPV positive women in comparison with that of cytology examination.

Several studies have suggested a value of HPV transcript analysis as a risk determinant for ≥CIN2. In a pilot study conducted on cervical samples from a historical cohort, we found that a positive HPV mRNA result conferred an increased risk of ≥CIN2 compared to that of mRNA negative hr-HPV positive women. Consequently HPV transcript analysis may be suitable as a triage tool to distinguish hr-HPV positive women who need direct colposcopy because of their increased risk of ≥CIN2 lesions.

In parallel studies we discovered the potential value of detection of DNA methylation of specific genes, reflecting gene silencing, as a marker (i.e. methylation marker) for HPV-induced (pre)malignant disease. Silencing of two such genes, namely CADM1 and MAL, by promoter methylation was functionally involved in cervical cancer development and strongly associated with ≥CIN2. Moreover, promoter methylation of CADM1 and/or MAL was significantly more frequent in hr-HPV positive scrapings of women with ≥CIN2 compared to those that did not have a high-grade lesion and together, these methylation markers displayed a sensitivity for these lesions greater than cytology. Consequently, analysis of CADM1 and MAL promoter methylation might be a promising alternative clinical marker for risk stratification of hr-HPV positive women. Compared to cytology, mRNA, methylation and other molecular markers have the advantage that scoring can be performed in an objective

manner, as these are based on molecular, rather than morphologic assays.

Objective:

To compare the value of HPV transcript analysis, analysis of DNA methylation status and other molecular markers with that of cytology examination as tools for stratification of hr-HPV positive women for risk of high-grade CIN lesions and cervical carcinoma (≥CIN2). The aim is to demonstrate that the sensitivity of these alternative tests, for detection of ≥CIN2 lesions, is non-inferior to that of cytology examination. Non-inferiority of either HPV transcript analysis, DNA methylation analysis or analysis of other molecular markers would justify replacement of cytology because these tests are more objective and less prone to variability.

Study design:

Prospective cohort study, multi centre trial.

Study population:

Women, between18-70 years old, who are referred to the Obstetrics and Gynaecology outpatient clinics of the VU University Medical Center (VUmc) in Amsterdam, University Medical Center Utrecht (UMCU), Erasmus Medical Center in Rotterdam, Reinier de Graaf Groep in Voorburg, Sint Antonius ziekenhuis in Nieuwegein, Flevoziekenhuis in Almere, Alant Vrouw in Amsterdam/Bilthoven and Sint Lucas Andreas ziekenhuis in Amsterdam. Participants will be selected from the regular gynaecological outpatient population. A total of 300 hr-HPV positive women visiting the outpatient clinic will be necessary for inclusion in this study.

Intervention:

At intake, women will receive a self-sampling device to collect a cervical smear. The self sampler will be sent to the laboratory of the VUmc and will be tested for the presence of hr-HPV DNA. Women who are hr-HPV positive are eligible for this study and will be asked to further participate. Hr-HPV negative women will be excluded from the study. Participating hr-HPV positive women will be referred for colposcopy, because they have a 20 times increased risk of developing high grade CIN lesions. Patients will visit the gynaecologist two times; A cervical smear will be collected for analysis of HPV transcripts, DNA methylation and other molecular markers, when participants visit the first time. At the second visit a colposcopy will be performed. In case no lesions are visible, two blind biopsy will be taken 96 and 12 o'clock) and in women ≥35 years of age, endocervical curettage will be performed in case the transformation zone is not visible. Cervical smear samples of study participants will be

subjected to all three tests for triaging; i.e. HPV transcript analysis, analysis of DNA methylation status (CADM1 and MAL promoter methylation), other molecular markers and cytological examination. All laboratory tests will be done at VU University Medical Center. Test results and histology outcome for all women will be matched and analysed.

Main study parameters/endpoints:

Endpoint is histology outcome; i.e. presence or absence of ≥CIN2 lesions. The short-term risk of ≥CIN2 will be assessed as a function of HPV mRNA , DNA methylation status and status of other molecular markers. The sensitivity, specificity, positive and negative predictive values of mRNA testing, analysis of DNA promoter methylation and analysis of other markers for detection of ≥CIN2 lesions in hr-HPV positive women will be determined and compared to that of cytology.

Study objective

High-risk human papillomavirus (hr-HPV) DNA testing complementary to current cytology examination (i.e. Pap test) of cervical smears has shown an increased sensitivity and negative predictive value (NPV) for cervical cancer and its precursor lesions, high-grade cervical intraepithelial neoplasia (≥CIN2), when compared with cytology alone. However, the specificity of hr-HPV DNA testing is lower than that of cytology as a considerable number of hr-HPV positive women will clear the virus and consequently will not develop ≥CIN2 lesions. Additional biomarkers are therefore needed to reduce the number of false positive test outcomes and consequently, unnecessary follow-up procedures. Currently, cytology is the most logic option since women with a double positive hr-HPV and cytology test result have a substantial risk of ≥CIN2 lesions. Nevertheless, besides its limited sensitivity, cytological examination is also subjective and prone to variability. In this study we aim to evaluate the value of other candidate markers for triage of hr-HPV positive women in comparison with that of cytology examination.

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Study design

The endpoint will be reached at the colposcopy-visit, which is 3-4 weeks after the first visit.

Intervention

N/A

Contacts

Public
VU University Medical Center, Department of Pathology,
De Boelelaan 1117
C.J.L.M. Meijer
De Boelelaan 1117
Amsterdam 1081 VH
The Netherlands
+31 (0)20 4444070
Scientific
VU University Medical Center, Department of Pathology,
De Boelelaan 1117
C.J.L.M. Meijer
De Boelelaan 1117
Amsterdam 1081 VH
The Netherlands
+31 (0)20 4444070

Eligibility criteria

Inclusion criteria

1. Women 18-70 years of age;

2. Cervical smear is hr-HPV DNA positive;

3. Intact cervix (no history of LEEP or surgical treatment involving damage to transformation zone of the cervix);

4. To be able to undergo colposcopy (according to gynaecologist);

5. Sufficient knowledge of the Dutch or English language;

6. To be able to understand the content of the research study;

7. Signed informed consent form.

Exclusion criteria

1. Women unable to take a self-sample (including a physical or mental handicap);

2. Cervical smear is hr-HPV DNA negative;

3. Cervical cancer within the preceding 2 years;

4. Presence of any cancer but cervical cancer;

5. History of surgery on cervix;

6. Withdrawal of the informed consent by the patient;

7. Pregnancy or having been pregnant in the last 3 months;

8. Breast-feeding, or breast-feeding in the last 3 months;

9. Heavy bleeding (menstruation or other cause) or excessive vaginal discharge that makes it not possible for colposcopy to be performed. Enrolment into the study will be postponed till condition is resolved and judged by gynaecologists.

Study design

Design

Study type:	Observational non invasive
Intervention model:	Parallel

Allocation:	Non controlled trial
Masking:	Open (masking not used)
Control:	N/A , unknown

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	20-08-2010
Enrollment:	300
Type:	Anticipated

Ethics review

Positive opinion

Date:	02-08-2010
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	NL2341
NTR-old	NTR2447
Other	METc VUmc : 2009/178
ISRCTN	ISRCTN wordt niet meer aangevraagd.

Study results

Summary results
N/A