Preventing overtreatment in CIN2/3 lesions: the role of testing methylation of FAM19A4/miR124-2 genes in predicting (non-) regression

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The primary objective of this study is to validate prospectively that testing for the DNA methylation status of some tumor suppressor genes predicts (non-)regression of a CIN2/3 lesion, and therefore can lead to prevention of overtreatment.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON45770

Source
ToetsingOnline

Brief title
Preventing overtreatment of CIN using methylation markers

Condition

- Other condition
- Reproductive neoplasms female malignant and unspecified

Synonym
cervical dysplasia, cervical precancer

Health condition

cervicale intraepitheliale neoplasie

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: ZonMw

Intervention

Keyword: Cervical intraepithelial neoplasia, methylation markers, overtreatment, regression

Outcome measures

Primary outcome

The primary study endpoint is (non-)regression at the end of the study based on

histology of the cervical exit biopsy. Regression is defined as *CIN1 on the

exit biopsy based on morphology. Non-regression is defined as CIN2 or worse

(CIN2+) on the exit biopsy based on morphology.

Secondary outcome

The secondary study endpoint is defined as HPV clearance (double negative hrHPV

test at two consecutive time points).

Study description

Background summary

Current cytology-based cervical screening programs serve to detect and treat high-grade precursor lesions (CIN2/3) to prevent cervical cancer. However, the diagnostic*treatment trajectory is associated with considerable overtreatment since CIN2/3 lesions have a high spontaneous regression rate. Pathologists are unable to differentiate between CIN2/3 lesions with a low short-term progression risk to cervical cancer (productive lesions), not in need of immediate treatment, and those with a high short-term progression risk (transforming lesions) that need immediate treatment. Recently, it has been shown that DNA methylation markers can differentiate between productive and

transforming CIN2/3.

Study objective

The primary objective of this study is to validate prospectively that testing for the DNA methylation status of some tumor suppressor genes predicts (non-)regression of a CIN2/3 lesion, and therefore can lead to prevention of overtreatment.

Study design

This study is designed as an observational longitudinal study with a follow-up of 24 months.

Intervention

Standard therapy for CIN2/3 lesions consists of excision of the lesion by either LLETZ or cold knife conisation. In this study, treatment consists of a watchful waiting policy. Participants will be monitored by an intense follow-up schedule consisting of 6-monthly visits to the colposcopy clinic for 2 years. During these visits, cervical cytology, hrHPV testing, methylation marker analysis and colposcopic evaluation of the cervix will be performed.

Study burden and risks

The main risk associated with participation in this study is the risk for lesion progression. We consider the risk of cancer within the two year period of close surveillance negligibly low since the median time from onset of CIN2/3 lesions to onset of cervical cancer is 23.5 years (95% CI: 20.8-26.6), and estimated progression rates to cancer are 1.6% within 10 years, and 12% within 20 years following onset of CIN2/3. Moreover, the treatment indication for lesions showing clinical progression (to >50% of the cervix in this study) is more stringent than was used in an earlier prospective non-intervention study (with threshold >75% of the cervix) that has been safely conducted by our group in the past (Nobbenhuis et al., Lancet 1999). Close surveillance by regular colposcopic evaluation of the lesion by a gynaecologist and, cytological and molecular evaluation of cervical cells will minimize this risk and the risk of missing a severe lesion. In case a lesion progresses into cervical cancer during the study period, this will most likely be an early stage lesion that can be treated by conisation with a very high success rate.The risk of malignant transformation of CIN2/3 lesions is 1.6% within 10 years.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

In order to be eligible to participate in the investigational treatment group of this study, a subject must meet all of the following criteria:
- CIN2 or CIN3 on a cervical punch biopsy
- CIN covering * 50% of the visible cervix
- Non-pregnant female aged 18-55 years

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:
- History of cervical pathology

- Transformation zone is not visible at colposcopy
- Prenatal diethylstilboestrol exposure
- Concomitant cancer
- Insufficient Dutch or English language skills;In case a subject falls pregnant during the study period she will not be excluded from participation. Her follow-up will not include self-sampling with the Evalyn Brush. Otherwise, follow-up will not be adjusted.

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	12-05-2017
Enrollment:	200
Type:	Actual

Ethics review

Approved WMO Date:	21-12-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-08-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

ID: 29301
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
CCMO	NL56187.029.16
OMON	NL-OMON29301