# 5-TYPE HPV mRNA NEGATIVE WOMEN IN TRIAGE OF ASC-US/LSIL MAY RETURN TO SCREENING AT 3-YEAR INTERVAL – AN HISTORICAL PROSPECTIVE COHORT STUDY

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Northern lights/Eurora Borealis

## DISCLOSURE

MMS and SWS have nothing to disclose.

FES has received compensation from PreTect AS for participation at Advisory Board meetings during the previous 2 years.

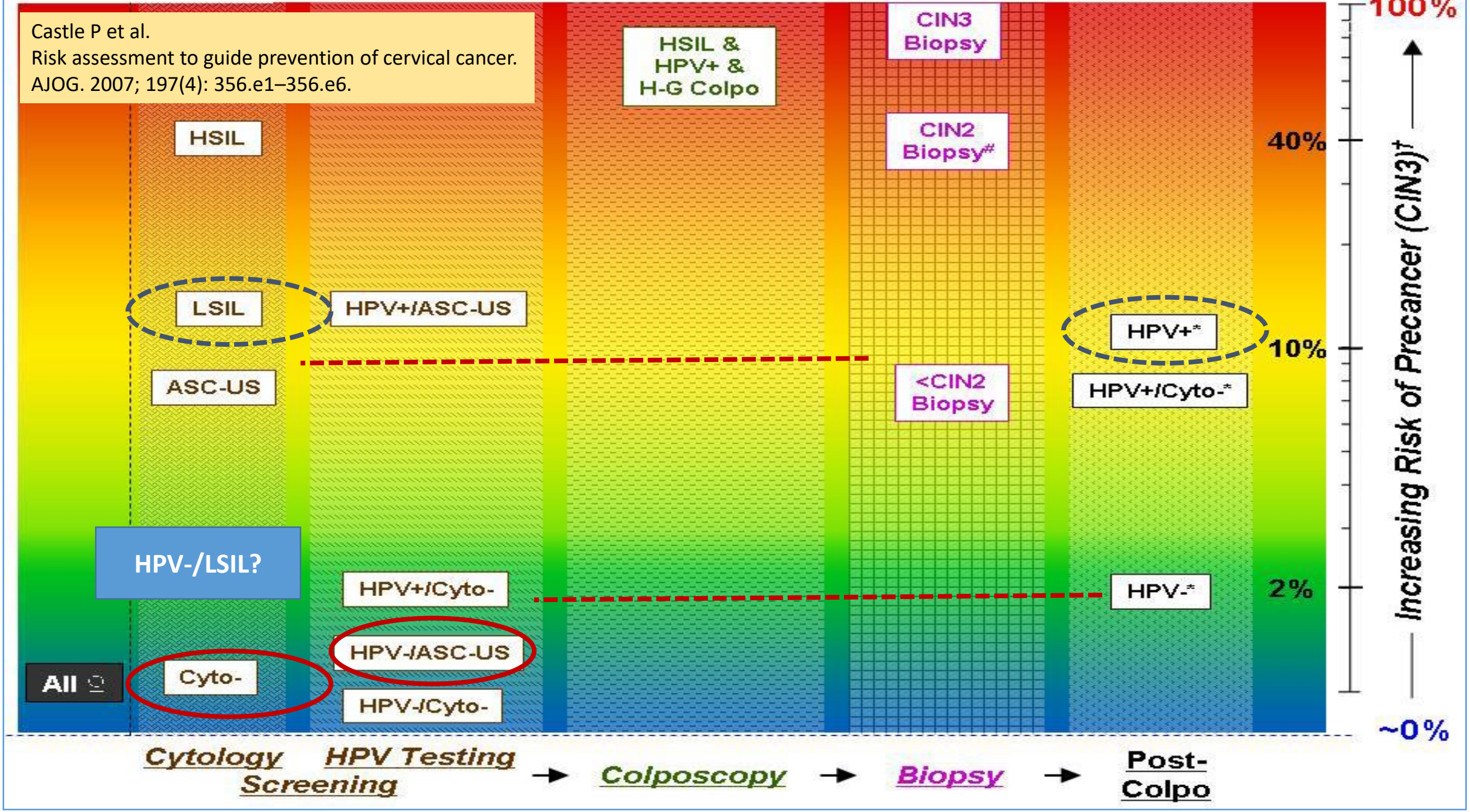
For all authors, their spouses, partners or children have no financial interests that may be relevant to the presentation.

## Screening for cervical cancer

- Age start of screening, screening interval, diagnostic test(s)
- Algorithms for follow-up of abnormal smears
- Treatment
- Post-treatment follow-up

**Paradigm shift – HPV vaccination / primary HPV-screening**

**Concept of risk stratification**


Castle P et al.
Risk assessment to guide prevention of cervical cancer.
AJOG. 2007; 197(4): 356.e1–356.e6.
HSIL
LSIL
ASC-US
HPV-/LSIL?
All
Cyto-
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HPV-/ASC-US
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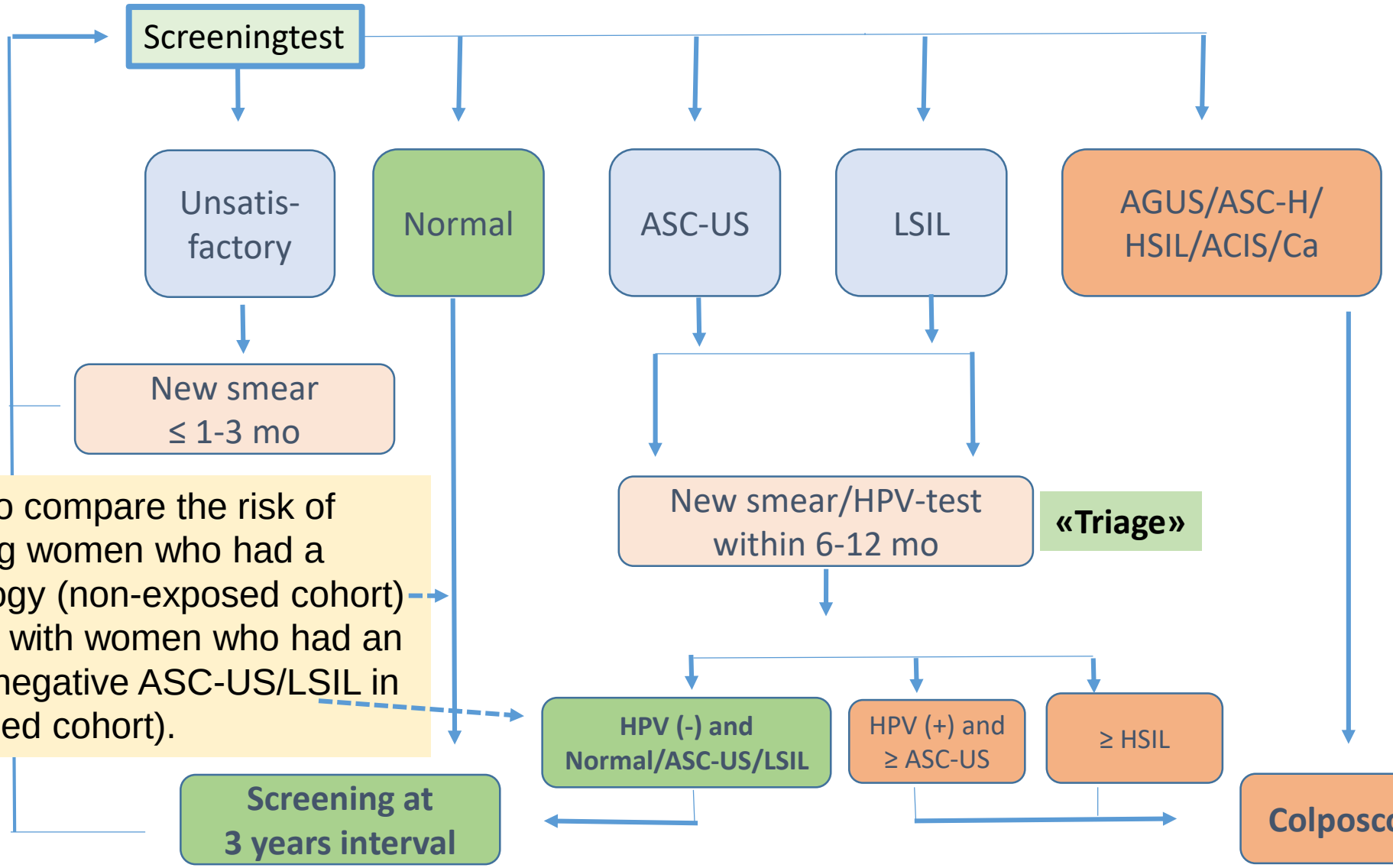
Biopsy
HPV+*
HPV+/Cyto-*
HPV-*
40%
10%
2%
100%
~0%
Increasing Risk of Precancer (CIN3)†
Cytology
HPV Testing
Screening
Colposcopy
Biopsy
Post-
Colpo

Screening for cervical cancer in Norway

- < 1995: Opportunistic screening 25-69 years at 3-year interval
- >= 1995: Nationwide screening 25-69 years at 3-year interval
- Algorithms  for follow-up have changed over time

# Norwegian screening algorithm during the study years 2006-2011




***Objective.*** To compare the risk of CIN3+ among women who had a normal cytology (non-exposed cohort) at study start with women who had an HPV mRNA negative ASC-US/LSIL in triage (exposed cohort).

# Material and methods

**Study design:** Historical prospective cohort study

**Data source:** Database Sympathy, Department of pathology, University Hospital of North Norway

**Non-exposed cohort:** First normal cytology during January 1st 2006 - December 31st 2007

**Exposed cohort:** First ASC-US/LSIL during January 1st 2006 - December 31st 2011

**Follow-up:** Through December 31st, 2014 (36 through 108 months)

**Inclusions:** Women aged 25-69 years, residents of two most northern counties in Norway (Troms and Finnmark)

**Exclusions:** Previous screening history of ≥ HSIL and/or CIN1+

**mRNA test:** PreTect HPV-Proofer (5 types: HPV-16, -18, -31, -33, -45)

**Statistical methods:** Chi-square test, survival analysis

**Main outcome:** Cumulative incidence of CIN3+ within 1st and 2nd screening rounds (< 42 months / <78 months)

**Secondary outcome:** Compliance with screening in follow-up (< 24 months: too early, > 42 months: too late, 24-42 months: at interval)

# Selection study population

| Non-exposed cohort (01.01.2006-31.12.2007) | | Exclusions | Exposed cohort (01.01.2006-31.12.2011) | |
|---|---|---|---|---|
| N | n | | n | N |
| 31 521 | | | | 3 217 |
| | 1 927 | Age ≤ 24 år | 624 | |
| | 1 272 | Age ≥ 70 år | 53 | |
| 28 322 | | | | 2 539 |
| | 639 | ≥ HSIL before index | 109 | |
| | 343 | ≥ CIN 1 before index | 43 | |
| | 1 392 | ≥ HSIL/≥ CIN 1 before index | 168 | |
| 25 948 | | Recommended triage | | 2 219 |
| | | No follow-up | 107 | |
| | | Direct to biopsy | 88 | |
| | | No HPV test done | 629 | |
| | | mRNA positive | 257 | |
| | | ≥HSIL | 32 | |
| | | mRNA negative, unsatisfactory/normal/ASCUS/LSIL | Back to screening | 1 106 |
| | | Triage < 90 after index (1-89) | 34 | |
| | | Triage > 540 after index | 9 | |
| 25 948 | | Included in the study | | 1 063 |
| | | | | |

# Study population characteristics

| | Cohorts | | P-value |
|---|---|---|---|
| | Non-exposed | Exposed | |
| | N=25 948 | N=1 063 | |
| | % | % | |
| **Age (years)** | | | P < 0.001 |
| **25-39** | 36,1 | **44,3** | |
| **40-54** | 36,6 | **41,3** | |
| **55-69** | 27,3 | 14,4 | |
| **Timeperiod** | | | |
| **2006-07** | 100,0 | 35.7 | |
| **2008-09** | | 33.5 | |
| **2010-11** | | 30.9 | |
| **Compliance with screening prior index smear** | | | P < 0.001 |
| **No prior attendance** | 6,9 | **13,4** | |
| **Too early** | 12,1 | 11,8 | |
| **At interval** | 54,9 | 45,5 | |

| Compliance 1st screening round (≤ 42 months) | | | |
|---|---|---|---|
| | Cohorts | | P-value |
| | Non-exposed | Exposed | |
| | N=25 948<br>% | N=1 063<br>% | |
| | | | P < 0.001 |
| **No follow-up** | 14,4 | **16,9** | |
| **Too early** | 16,8 | **46,8** | |
| **At interval** | 42,2 | 24,6 | |
| **Too late** | 26,7 | 11,7 | |

## Cumulative incidence of CIN3+/CC at 1st and 2nd screening rounds (95% CI)

| | Cohorts | | P-value |
|---|---|---|---|
| | Non-exposed | Exposed | |
| | N=25 948<br>Per 100 women | N=1 063<br>Per 100 women | |
| **CIN3+** | | | P < 0.001 |
| **42 months** | 0.24 (0.17-0.31) | **1.45 (0.55-2.4)** | |
| **78 months** | 0.73 (0.60-0.86) | **2.6 (0.94-4.3)** | |
| **Cervical cancers** | Per 100 000 women | | |
| **42 months** | 19 (0-38)(n=4) | 0 | |
| **78 months** | 67 (26-108)(n=11) | 0 | |

Incidence cervical cancer 8.4 / 100 000 women-yrs (11/(1 579 830 months of observation/12))

Avoided selection bias

Attrition bias

Detection bias

## Conclusions:

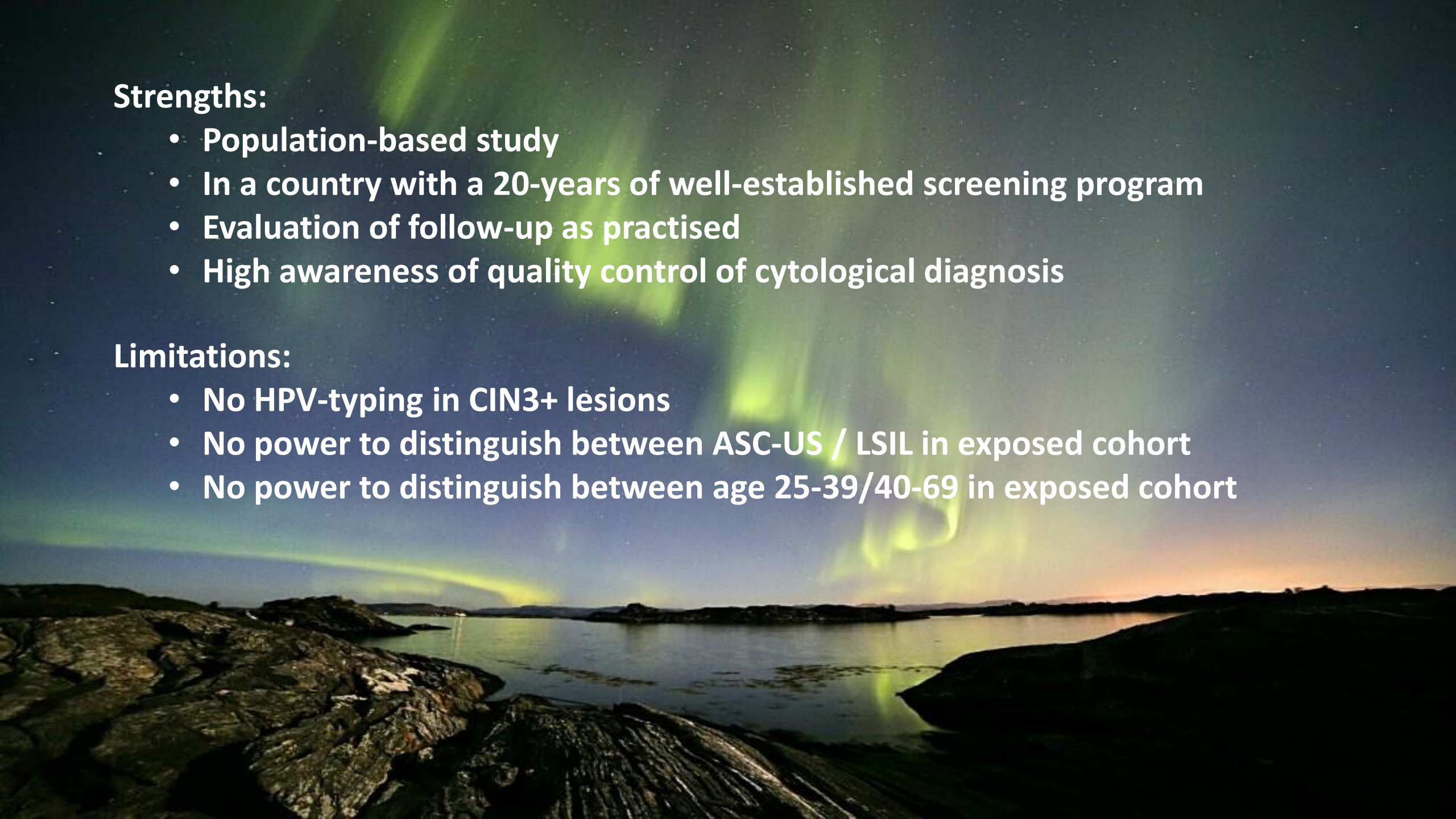
- Risk cumulative incidence of CIN3+ in first screening round is very low
  - Normal cytology: 0.24 per 100 women at 42 months
  - mRNA negative ASC-US/LSIL: 1.45

Castle P et al. Risk assessment to guide prevention of cervical cancer. AJOG. 2007; 197(4): 356.e1–356.e6.

- Rescreening at 2-3 years intervals when CIN3+ risk < 2% (2 per 100 women...)

- The mRNA PreTect HPV-Proofer test provides acceptable safety for prevention of CIN3+ (HPV-16, -18, -31, -33, -45) in women mRNA negative at triage of ASC_US / LSIL
  - Prevent overscreening/reducing numbers of women in short-term f-up
  - Prevent overtreatment

**From past to future: Primary HPV-screening – Cytology triage – rescreening ASC-US/LSIL with a mRNA test**



**Strengths:**

- Population-based study
- In a country with a 20-years of well-established screening program
- Evaluation of follow-up as practised
- High awareness of quality control of cytological diagnosis

**Limitations:**

- No HPV-typing in CIN3+ lesions
- No power to distinguish between ASC-US / LSIL in exposed cohort
- No power to distinguish between age 25-39/40-69 in exposed cohort