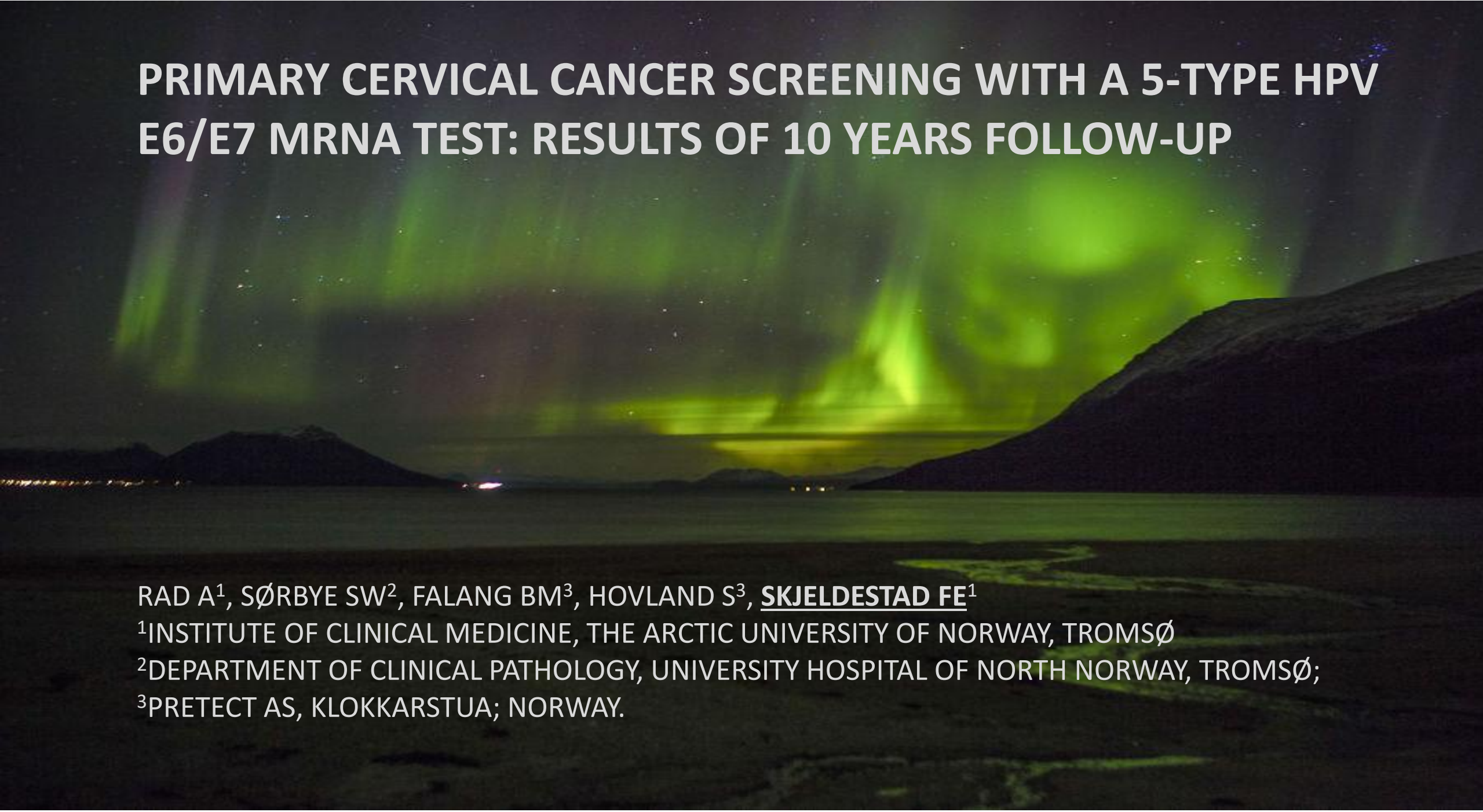
# PRIMARY CERVICAL CANCER SCREENING WITH A 5-TYPE HPV E6/E7 MRNA TEST: RESULTS OF 10 YEARS FOLLOW-UP



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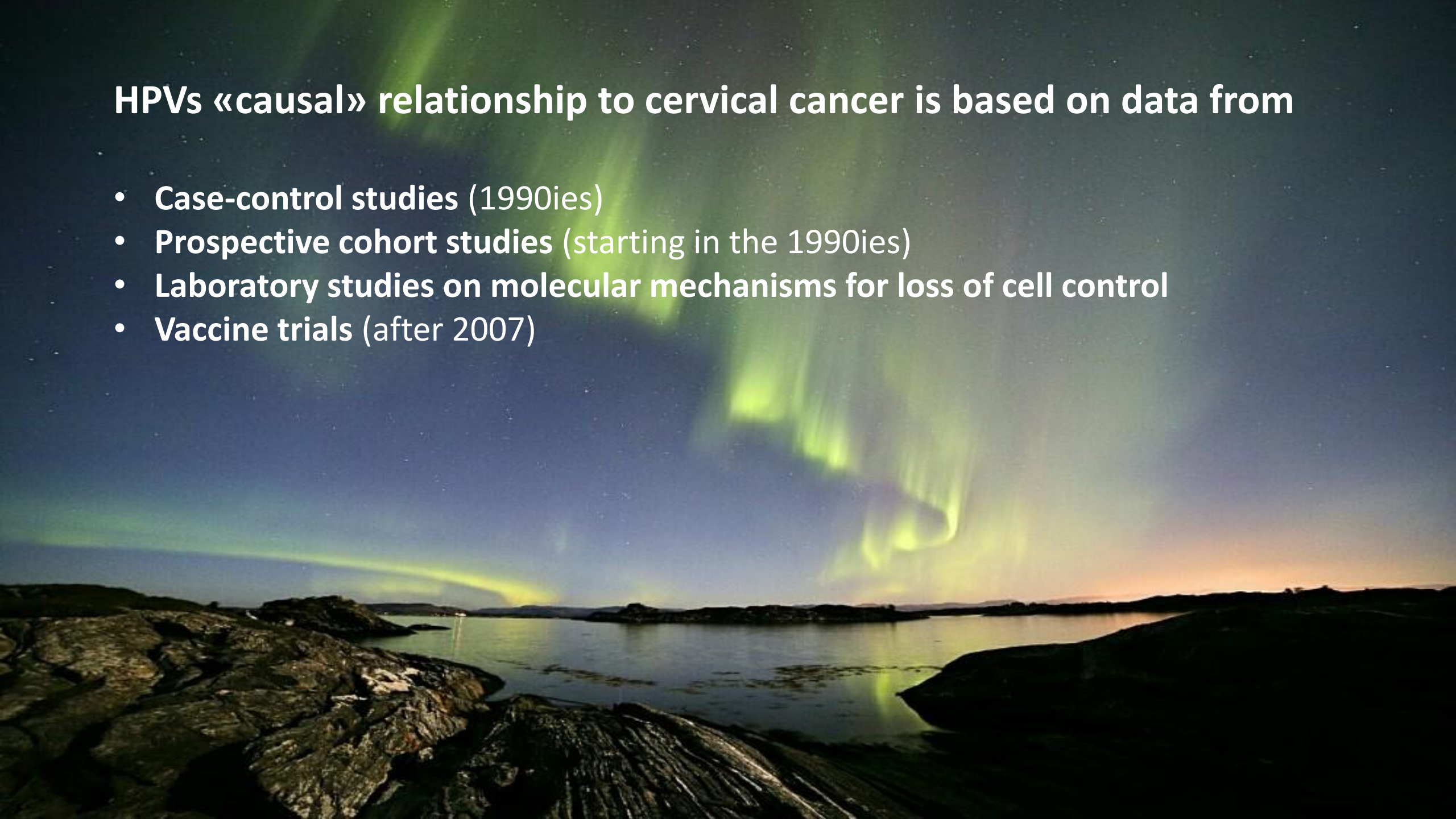
## DISCLOSURE

AR and SWS have nothing to disclose.

BMF and SH are employees at PreTect AS.

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

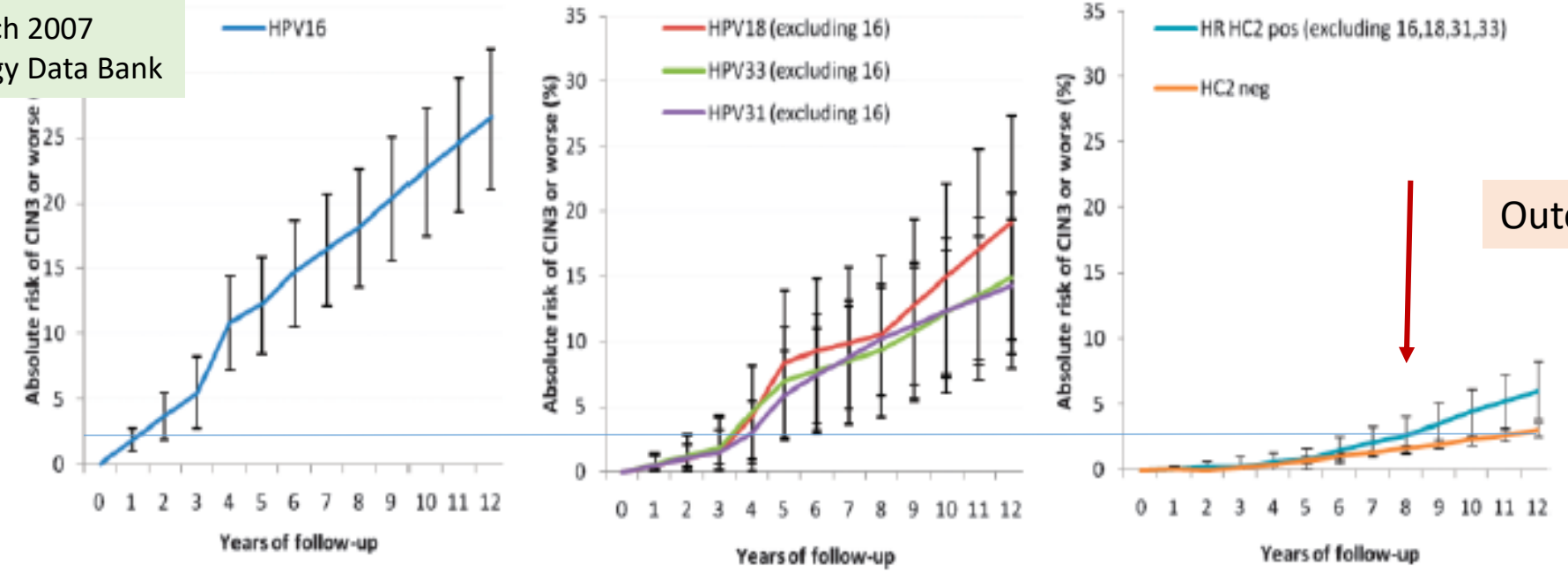


## HPVs «causal» relationship to cervical cancer is based on data from

- **Case-control studies** (1990ies)
- **Prospective cohort studies** (starting in the 1990ies)
- **Laboratory studies on molecular mechanisms for loss of cell control**
- **Vaccine trials** (after 2007)

**Cohort**
N=8 656 women
Age: 20-29 years at study start
Starting 1991
Follow-up through March 2007
Linkage Danish Pathology Data Bank

## «The Copenhagen HPV-cohort study»




Outcome: CIN 3

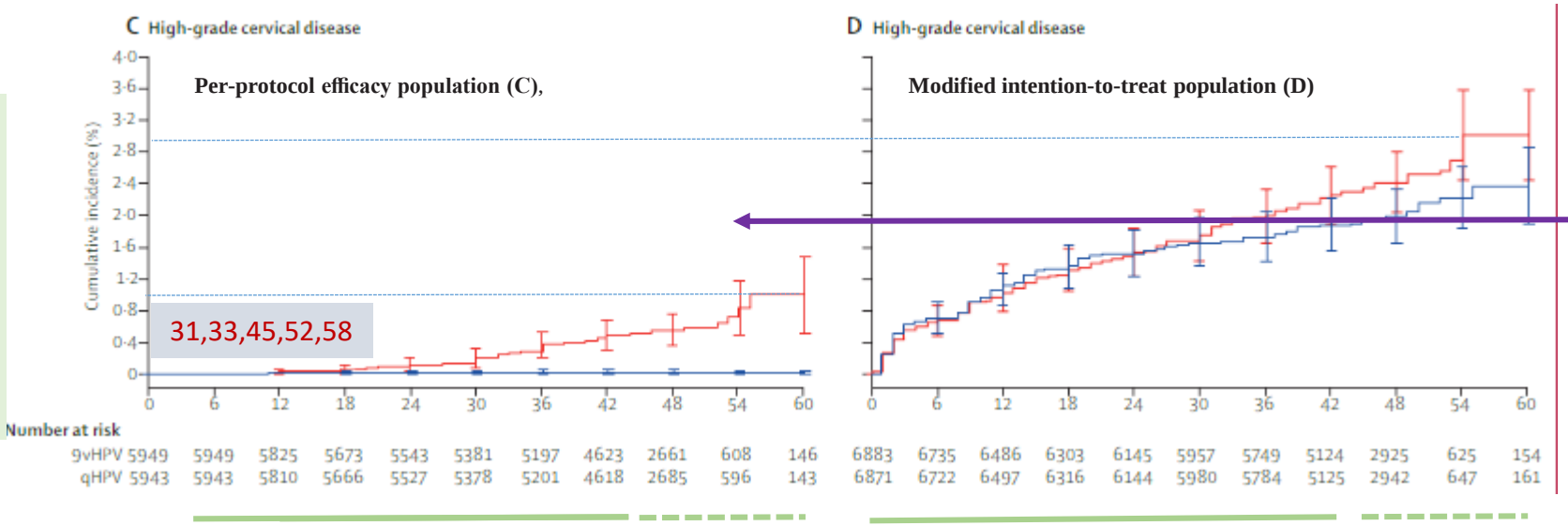
**Figure 1.** Absolute risks of cervical intraepithelial neoplasia grade 3 (CIN3) or worse after infection with different high-risk human papillomavirus (HPV) types in women with normal cytological findings at baseline. **Error bars** correspond to 95% confidence intervals. HR HC2 positive = positive to high-risk HPV types as measured by the Hybrid Capture 2 test. HC2 neg = HC2 negative.

**Kjær S, Frederiksen K, Munk C, Iftner T. Long-term Absolute Risk of Cervical Intraepithelial Neoplasia Grade 3 or Worse Following Human Papillomavirus Infection: Role of Persistence. J Natl Cancer Inst 2010;102:1478–1488**

# Final efficacy analyses of a nine-valent human papillomavirus

9vHPV vaccine: 6,11,16,18,31,33,45,52,58  4vHPV vaccine: 6,11,16,18

**RCT**
N=14 215 (eligible)
Recruited:
Sept. 2007 through Dec. 2010,
105 study cites/18 countries
Age: 16-26 years
- No previous CIN
- No prev. abnormal smears
- ≤ 4 life time partners




**CIN 2 (31,33,45,52,58)**
1:5949 // 32:5943

**CIN 3 (31,33,45,52,58)**
0:5949 // **7**:5943
16.6/10 000 w-yrs.

**Time to the development of cervical disease related to HPV 31, 33, 45, 52, or 58**
**High-grade cervical disease was defined as grade 2 or 3 cervical intraepithelial neoplasia or adenocarcinoma in situ.**
**Analyses of the per-protocol efficacy population (C)**, which included participants who received all three doses of vaccine within 1 year, were seronegative at day 1, and PCR-negative from day 1 to month 7 for the HPV type being analysed, and had no protocol deviations that could affect the evaluation of vaccine prophylactic efficacy.
**Analyses of) the modified intention-to-treat population (D** including participants who received one or more doses of vaccine and had efficacy follow-up for the relevant endpoint, including participants who tested positive or negative for HPV DNA at the time of vaccination.

**Huh WK, Joura EA, Giuliano AR et al. Final efficacy, immunogenicity, and safety analyses of a nine-valent human papillomavirus vaccine in women aged 16–26 years: a randomised, double-blind trial. Lancet 2017; 390: 2143–59**

## Our cohort study:

2003-2004: Screened with a five type mRNA E6/E7 test (PreTect HPV-Proofer)

- Individual genotyping of HPV 16, 18, 31, 33, 45
- By general practitioners and gynaecologists in privat settings at Pap-smear screening

Inclusion/exclusion criteria, follow-up; data from the Norwegian Cancer Registry (NCR)

- Cancer case-report-form (clinical) (case-based reporting)
- Cytology case-report-form (from pathology departments, smear basis for reporting)
- Histology case-report-form (from pathology departments, histology basis for reporting)
- CIN treatment case-report-form (from gynecology departments/gynaecologists that treat patients, case-based reporting)

Follow-up through December 31, 2015

Merged by personal identification number (11 digits)

# Formal issues

The Regional Committee for Medical Research Ethics,
Region East, Oslo, Norway, reviewed the study.
The committee approved merging the laboratory data on HPV with clinical/cytology/histology data from NCR without informed consent from the participants (REK Sør-Øst 2010/2858)

# Selection of study population

| Eligible for study participation | n | N<br>19 153 |
|---|---|---|
| Age < 25 | 2 020 | |
| Age > 69 | 223 | |
| History of CIN1+ | 883 | |
| History of >= ASC-US (no CIN1+) | 4 756 | |
| Unsatisfactory smear at HPV screening | 501 | |
| No smear collected at HPV screening | 627 | |
| No follow-up smear | 561 | |
| Total exclusions | 9 571 | 9 571 |
| Final study population (all with normal smear) | | **9 582** |

# HPV mRNA-status at study start by age (%)

| HPV-result | 25-33 yrs. N=2 610 % | 34-69 yrs. N=6 972 % | Total N= 9 582 % |
|---|---|---|---|
| HPV negative | 94.3 | 97.8 | 96.8 |
| HPV positive | 5.7 | 2.2 | 3.2 |
| HPV-16 | 2.8 | 1.0 | 1.5 |
| HPV-18 (not 16) | 0.8 | 0.3 | 0.5 |
| HPV-31/-33/-45 (not 16/not 18) | 2.1 | 0.9 | 1.2 |

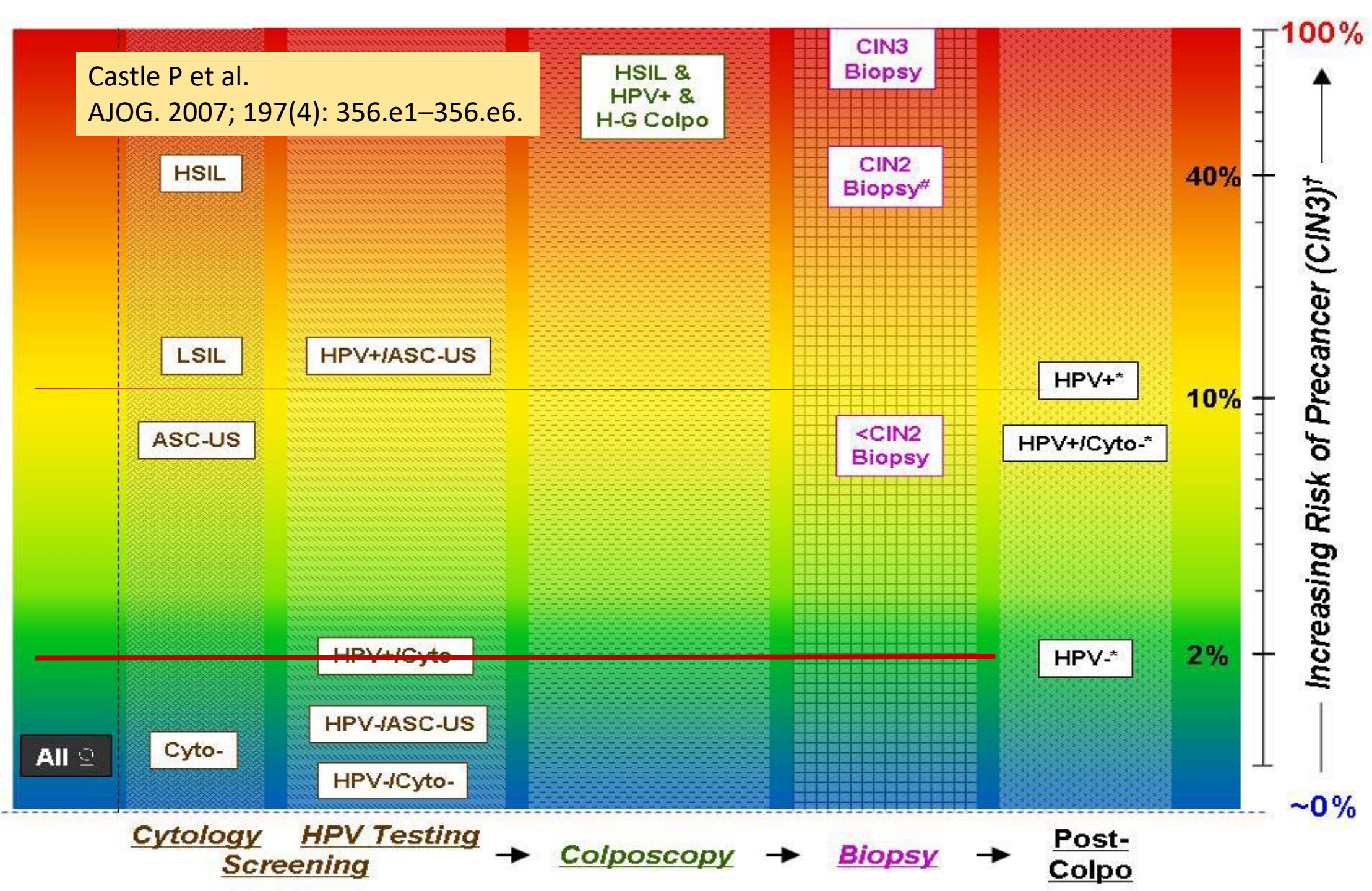
All participants had normal smear

- At least 1 follow-up reported to NCR

# Status last observation or most severe outcome ≥ CIN2 (%)

(No attrition bias)

| Baseline characteristics | | Within screening | Awaiting cytology follow-up | Awaiting colposcopy/ biopsy | CIN2 | CIN3 | Cervical cancer |
|---|---|---|---|---|---|---|---|
| Age group | N | % | % | % | % | % | % (n) |
| 25-33 | 2 610 | 95.3 | 2.0 | 0.04 | **0.5** | **2.2** | 0.0 (0) |
| 34-69 | 6 972 | 95.7 | 2.2 | 0.12 | **0.5** | **1.4** | **0.07 (5)** |
| HPV mRNA types | | | | | | | |
| Negative | 9 279 | 96.3 | 2.2 | 0.09 | **0.4** | **1.0** | **0.02 (2)** |
| 16 | 140 | 69.3 | 1.4 | 0.7 | **5.0** | **22.9** | **0.7 (1)** |
| 18 (-16) | 44 | 65.9 | 6.8 | 0.0 | **4.5** | **20.6** | **2.3 (1)** |
| 31/33/45 (-16, -18) | 119 | 79.8 | 1.7 | 0.0 | **2.5** | **15.1** | **0.8 (1)** |
| Total | **9 582** | **95.6** | **2.2** | **0.09** | **0.5** | **1.6** | **0.05 (5)** |


Castle P et al.
AJOG. 2007; 197(4): 356.e1–356.e6.
HSIL
LSIL
ASC-US
All
Cyto-
HPV+/ASC-US
HPV+/Cyto-
HPV-/ASC-US
HPV-/Cyto-
HSIL &
HPV+ &
H-G Colpo
CIN3
Biopsy
CIN2
Biopsy#
<CIN2
Biopsy
HPV+*
HPV+/Cyto-*
HPV-*
100%
40%
10%
2%
~0%
Increasing Risk of Precancer (CIN3)†
Cytology
HPV Testing
Screening
Colposcopy
Biopsy
Post-
Colpo

**Cumulative incidence of CIN3+ by age and HPV mRNA-status at study start**

**Study population**

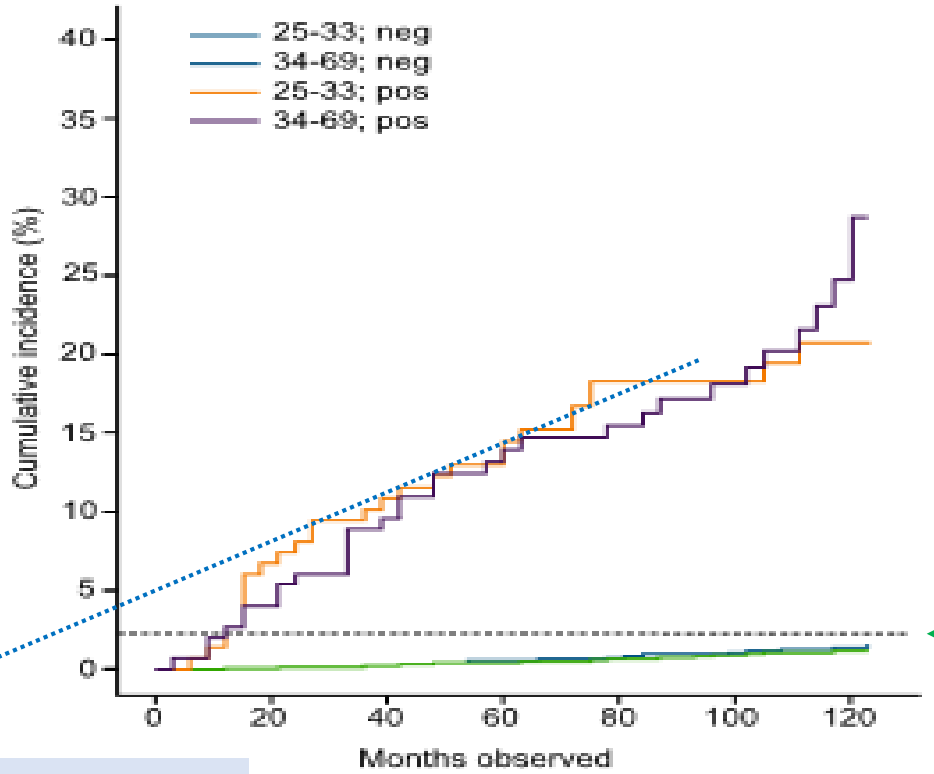
N=9 582 women (eligible)

Recruited: 2003/2004

Age: 25-69 years

- No previous CIN
- No prev. abn. smears
- Normal smear at screening

Follow-up: 31st Dec., 2015




Cumulative incidence 2%

Duration of infection?

Norway: has implemented a 5-years interval in HPV DNA primary screening

**Cumulative incidence of CIN3+ by HPV mRNA-status at study start**

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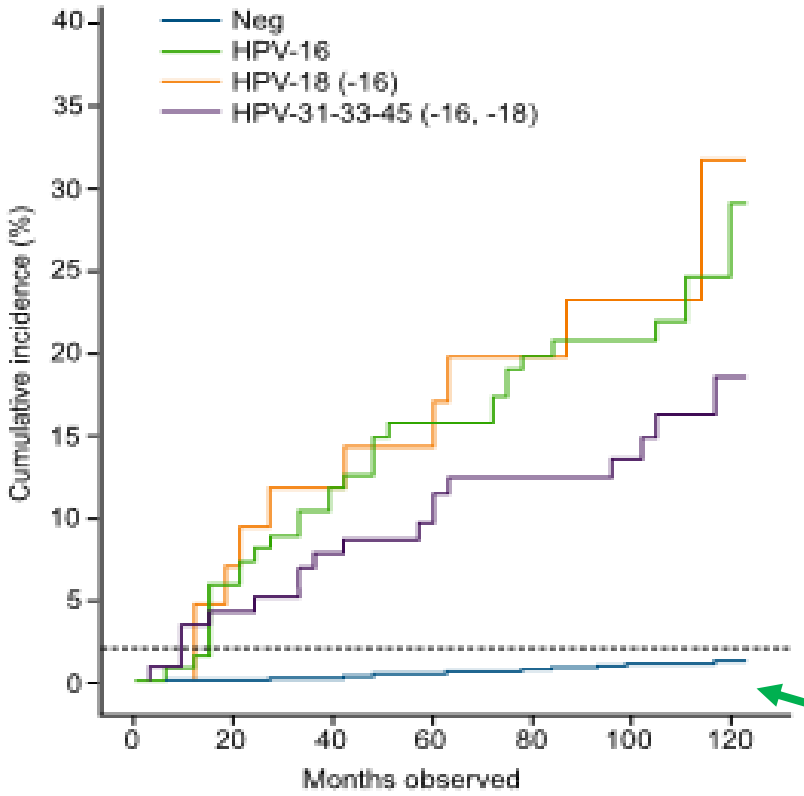



Cumulative incidence 2%

HPV 52, 58 and other
low risk «oncogenic» types

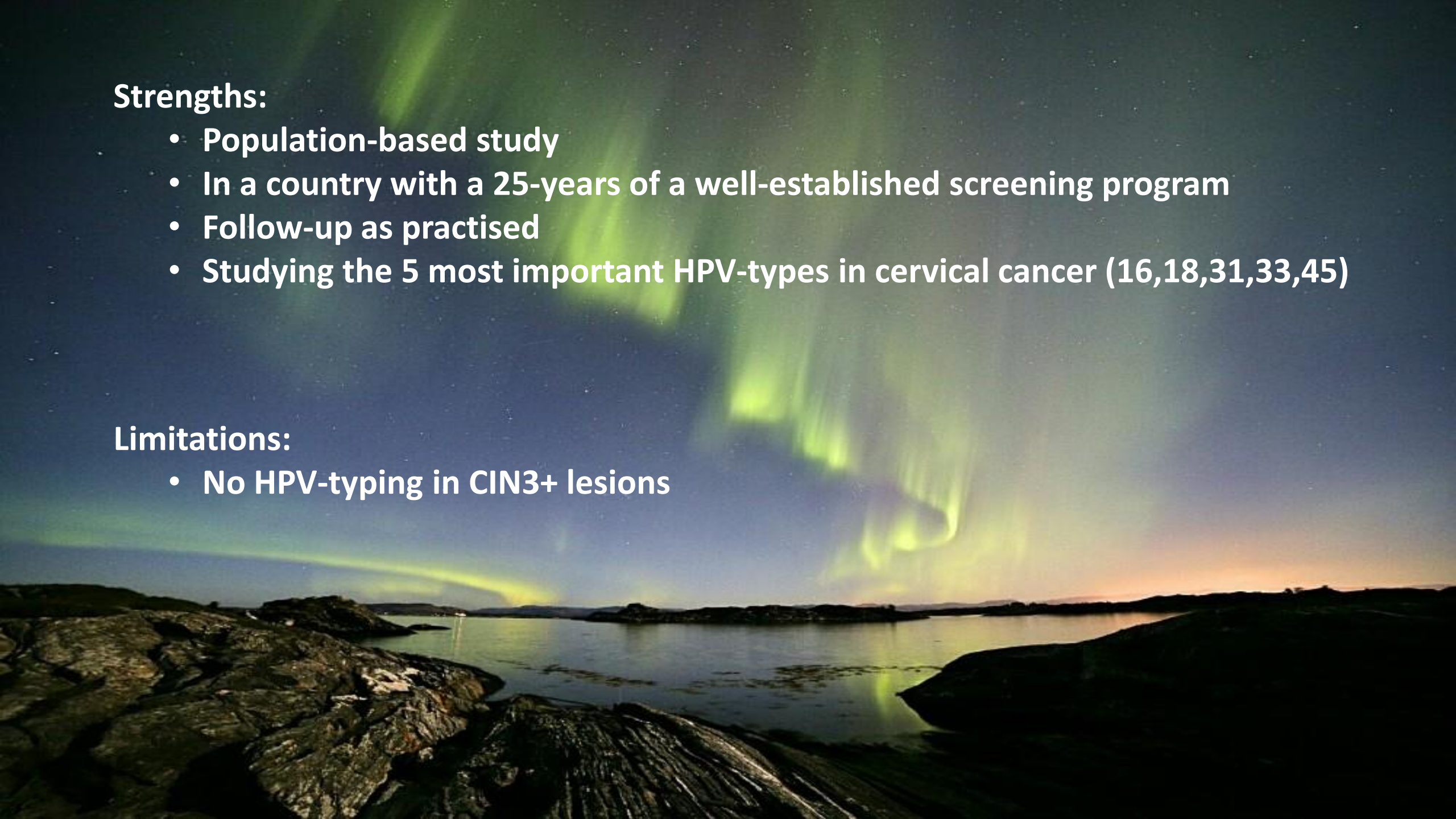
Norway: has implemented a 5-years interval in HPV DNA primary screening

# 5 cases of cervical cancer:

## Characteristics at study start and clinical features at time for diagnosis

| Case no. | At study start | | | At diagnosis | | | |
|---|---|---|---|---|---|---|---|
| | Age (yrs.) | HPV type | Screening history (months to last smear prior study start) | Diagnosed in | Months from study start | Histological type | Stage |
| 1 | 38 | 45 | 1 normal smear, only (32 mo.) | Regular scr. | 94 | Sq. cc. | 1A |
| 2 | 39 | 16 | 8 normal smears (23 mo.) | Regular scr. | 38 | Sq. cc. | 1A |
| 3 | 41 | 18 | 3 normal smears (34 mo.) | Delayed scr. | 58 | Adenoca. | 2b |
| 4 | 48 | Neg. | 4 normal smears (33 mo.) | Regular scr. | 28 | Sq cc. | 1b |
| 5 | 51 | Neg. | 6 normal smears (27 mo.) | Delayed scr. | 65 | Sq cc. | 1A |

**False negative smears**



**Strengths:**

- Population-based study
- In a country with a 25-years of a well-established screening program
- Follow-up as practised
- Studying the 5 most important HPV-types in cervical cancer (16,18,31,33,45)

**Limitations:**

- No HPV-typing in CIN3+ lesions

## Conclusions:

- 5-type HPV mRNA negative women have low risk of CIN3 in subsequent 10 years
  - extended screening interval

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...)

- 5-type HPV mRNA positive women can be referred directly to colposcopy/biopsy*
  - In comparison with a DNA-screening test the mRNA test has potential
    - to prevent overscreening
    - to reduce numbers of women in short-term f-up with very low risk of CIN3
    - to prevent overtreatment

- **The results need to be confirmed in future prospective studies (which is ongoing)**