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

Slettebak MM[1], Sørbye SW[2], Skjeldestad FE[1]
[1]Department of Community Medicine, University of Tromsø and
[2]Department of Pathology, University Hospital of North Norway,
Tromsø, Norway

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.

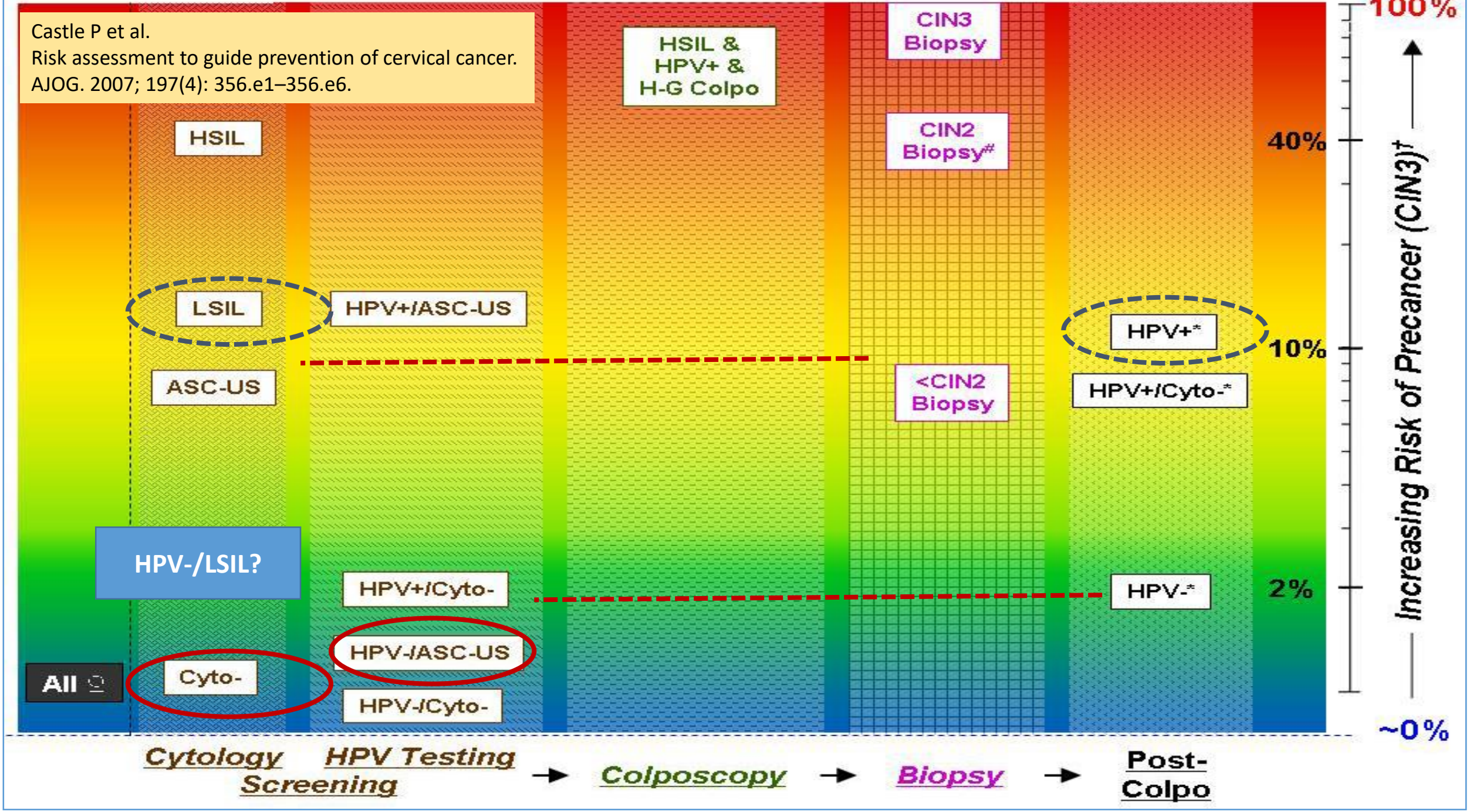
For all authors, their spouses, partners or children have no financial interests that may be relevant to the presentation.

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

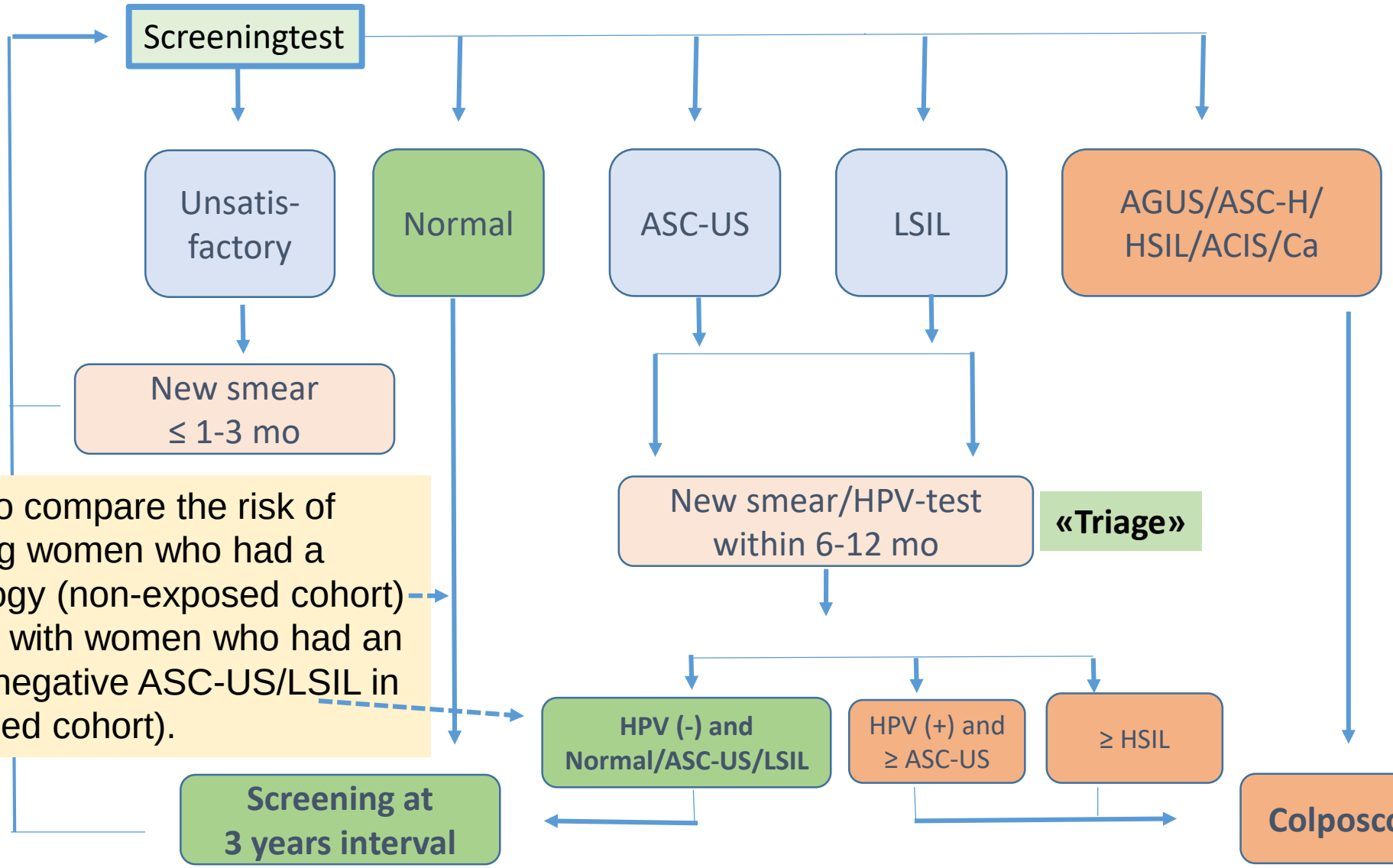
Concept of risk stratification


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-
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-*
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 %	N=1 063 %	
			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 Per 100 women	N=1 063 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:

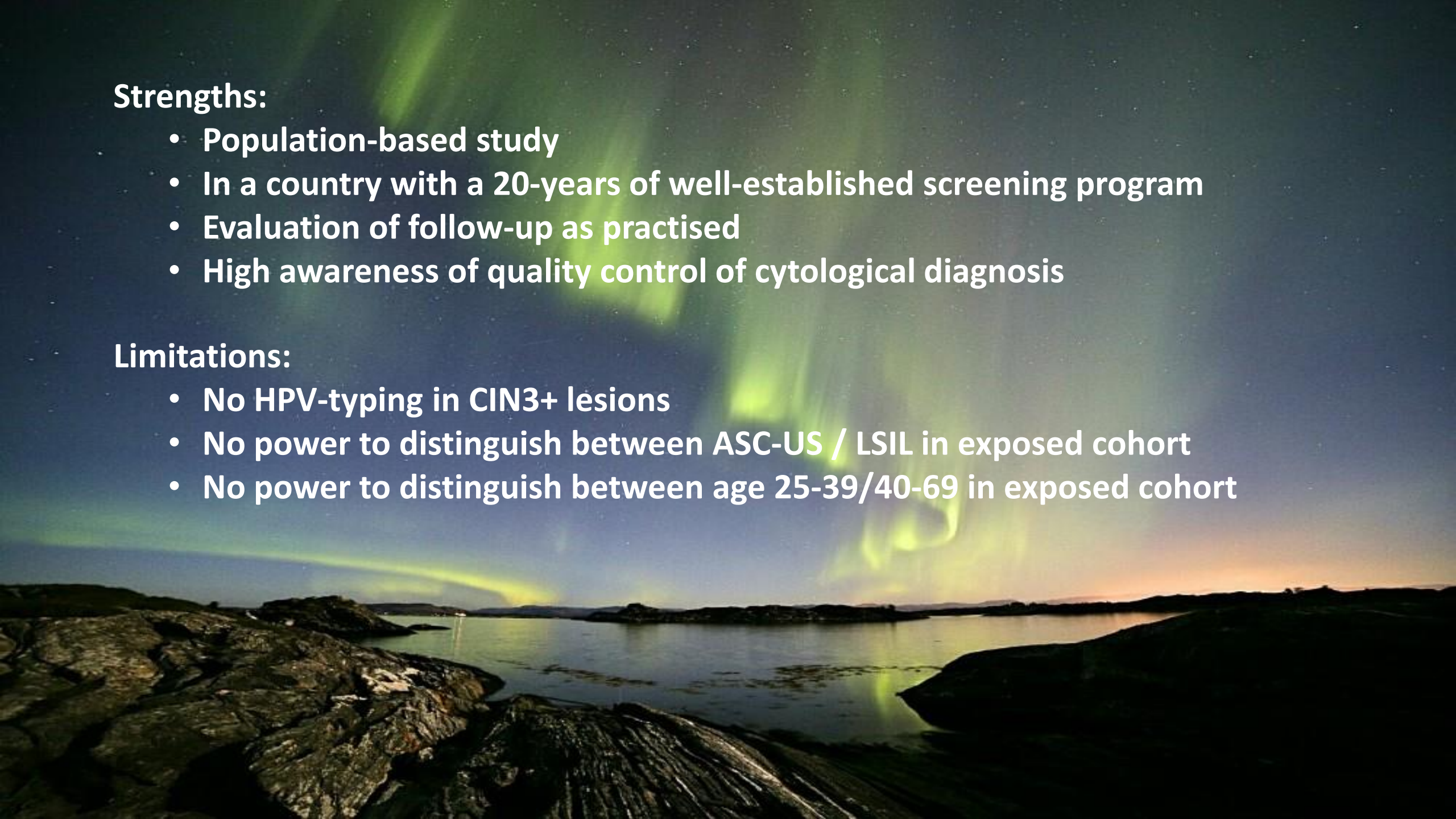
- Risk cumulative incidence of CIN3+ in first screening round is very low
  - Normal cytology: 0.24 per 100 women at 42 months
  - mRNA negative ASC-US/LSIL: 1.45

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