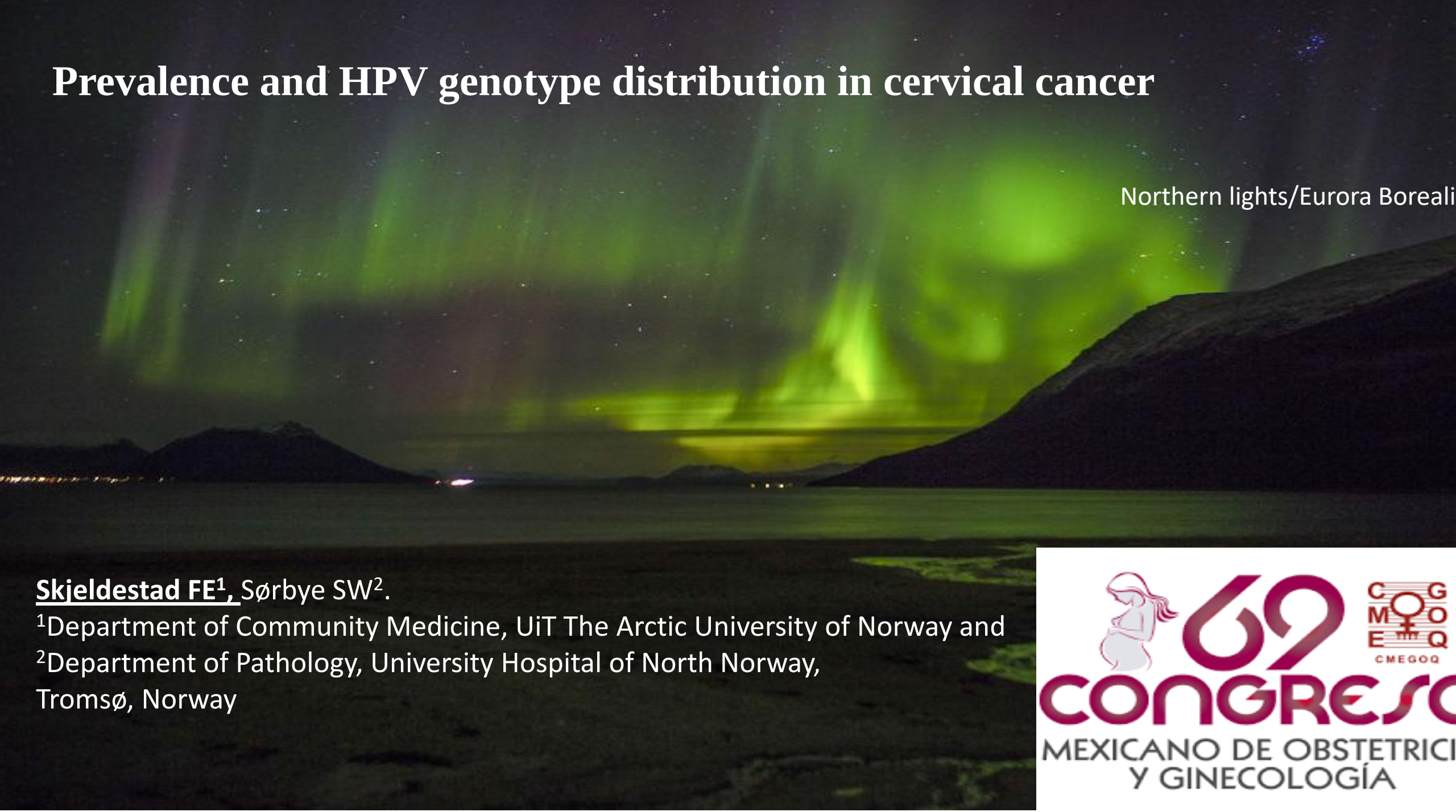
Prevalence and HPV genotype distribution in cervical cancer

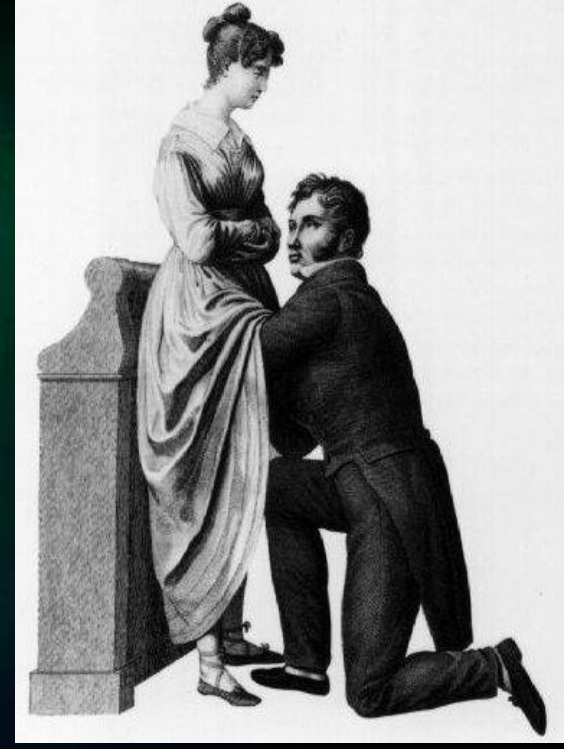


Northern lights/Eurora Boreali

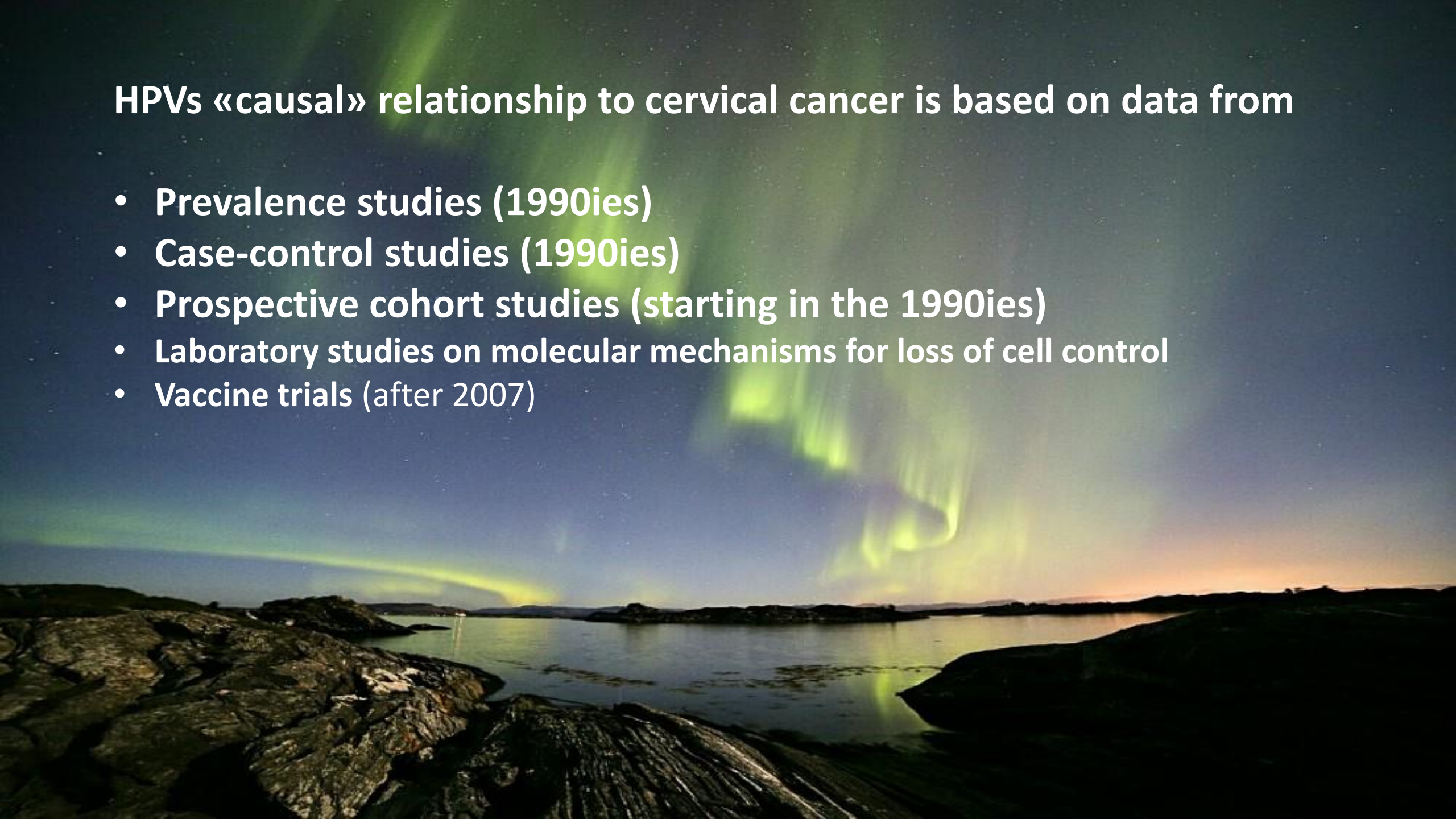
Skjeldestad FE[1], Sørbye SW[2].
[1]Department of Community Medicine, UiT The Arctic University of Norway and
[2]Department of Pathology, University Hospital of North Norway,
Tromsø, Norway

69 CONGRESO MEXICANO DE OBSTETRICI Y GINECOLOGÍA
CMEGOQ

Cervical cancer, etiology and infections



- Bible - Circumcision
- Early 1900 - Gonorrhea
- Early 1970ies - Herpez infections
- Early 1980ies - Chlamydia trachomatis infections
- Late 1980ies - Human Pappillomavirus infections



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

- **Prevalence studies (1990ies)**
- **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)

Proc. Natl. Acad. Sci. USA
Vol. 80, pp. 3812–3815, June 1983
Medical Sciences

1983

A papillomavirus DNA from a cervical carcinoma and its prevalence in cancer biopsy samples from different geographic regions

(human papillomaviruses/low-stringency hybridization/molecular cloning/genital tumors)

MATTHIAS DÜRST, LUTZ GISSMANN, HANS IKENBERG, AND HARALD ZUR HAUSEN*

Institut für Virologie, Zentrum für Hygiene, Universität Freiburg, Hermann-Herder-Strasse 11, 7800 Freiburg, Federal Republic of Germany

Communicated by Gertrude Henle, March 21, 1983

ABSTRACT DNA from one biopsy sample of invasive cancer of the cervix contained sequences hybridizing with human papillomavirus (HPV) type 11 DNA only under nonstringent conditions. This DNA was molecularly cloned in λ phage. Under stringent conditions of hybridization it cross-hybridized to a minor extent (less than 0.1%) with HPV types 10, 14, and 15 and showed no homology with DNA of other human HPV types. We therefore propose to designate it tentatively as HPV 16. HPV 16 DNA was used as a probe to test additional cancer biopsy samples from cervical, vulval, and penile cancer, as well as benign genital warts (condylomata acuminata) and cervical dysplasias for the presence of homologous sequences. In 61.1% (11/18) of cervical cancer samples from German patients sequences were found hybridizing with HPV 16 DNA under conditions of high stringency. In contrast, only 34.8% (8/23) of cancer biopsy samples from Kenya and Brazil revealed this DNA. Vulval and penile cancer biopsy samples hybridized to 28.6% (2/7) or 25% (1/4), respectively. Only 2 out of 33 condylomata acuminata contained HPV 16 DNA. Both positive tumors harbored in addition HPV 6 or HPV 11 DNA. The data thus indicate that HPV 16 DNA prevails in malignant tumors, rendering an accidental contamination with papillomavirus DNA from adjacent papillomas rather unlikely. The rare presence in benign genital papillomas in addition to common genital papillomaviruses suggests a dependence of HPV 16 replication on helper virus.

2008

German cervical cancer samples
61% (11:18) HPV 16 positive

Samples from Kenya/Brazil
35% (8/23) HPV 16 positive

Conclusion:
The data indicates that HPV 16 prevails in malignant tumors.

Prevalence studies: HPV in Cervical Cancer (22 countries/PCR 25+ types)

HPV	Africa N=186 (%)	Central and South Ameri. N=505 (%)	Southeast Asia N=98 (%)	Europe N=83 (%)	North Ameri. N=57 (%)	Total N=932
16	43	51	43	65	58	50
16+	13	18	8	14	5	15
18	18	10	32	8	16	14
18+	15	13	11	6	16	13
56	3	0.6	3	2	4	2
51	1	1	0	0	0	0.8
26	0	0.8	0	0	0	0.4
55	0	0.4	0	0	0	0.2
6	0	0.2	0	0	0	0.1
11	0	0.2	0	0	0	0.1

1995

Bosch XF et al. Prevalence of Human Papillomavirus in Cervical Cancer: a World Perspective.
J Natl Cancer Inst 1995;87:796-802

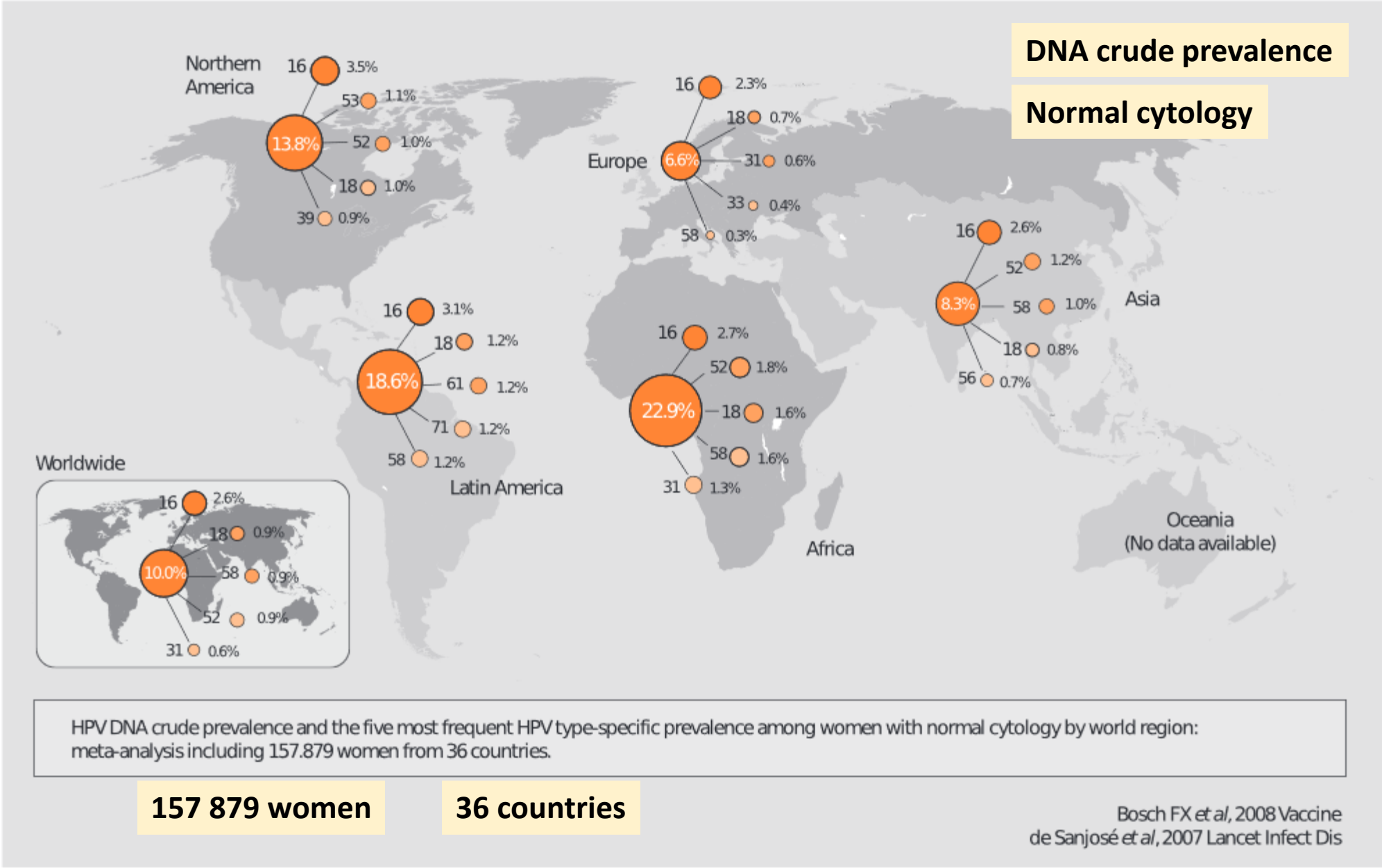
Prevalence study: HPV in Cervical Cancer (22 countries/PCR 25+ types)

HISTOLOGICAL TYPE/	Squamous	Adeno-Ca.	Adeno-Squamous	
	N=881 (%)	N=25 (%)	N=18 (%)	
HPV/				
16	51	28	17	
16+	15	0	11	
18	12	56	39	
18+	12	12	28	
Other	6	0	0	
HPV-NEG	**7**	**4**	**6**	
Total HPV-POS	93	96	94	(in total 93%)

1995

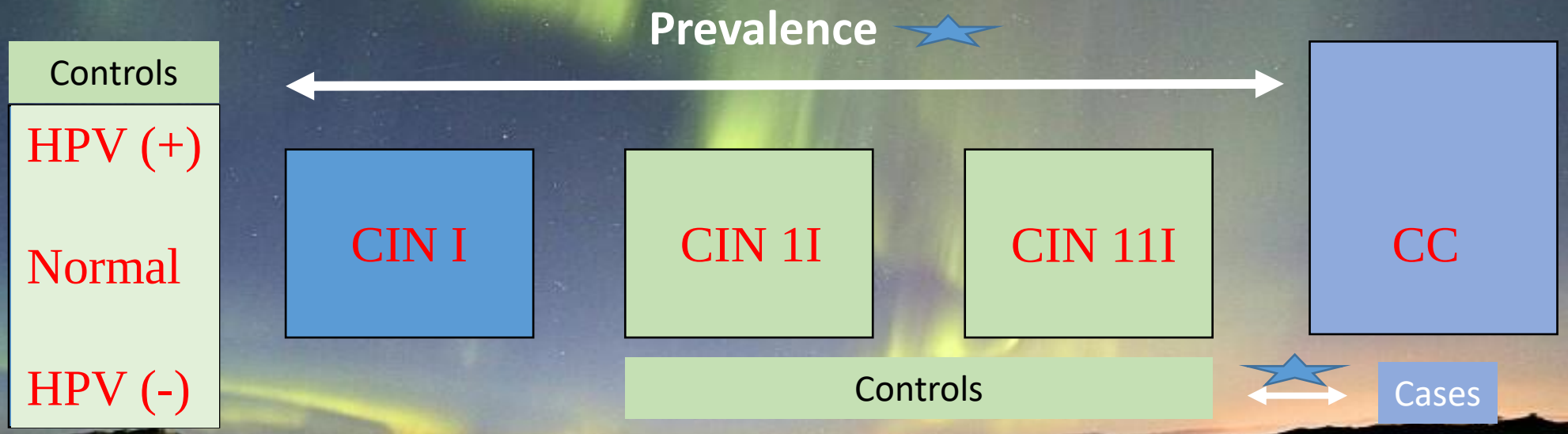
Bosch XF et al. Prevalence of Human Papillomavirus in Cervical Cancer: a World Perspective.
J Natl Cancer Inst 1995;87:796-802

Figure 1.2 HPV DNA crude prevalence and HR-HPV type-specific prevalence among women with normal cytology by world region: meta-analysis including 157.879 women from 36 countries



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

Persistent HR HPV infections - malignant cell transformation



Carcinogenesis: 15-25 years from normal cell to cancer

Table 2.5 Meta-analysis of type-specific HPV DNA prevalence in invasive cervical cancer

	Invasive cervical cancer			Normal		
	N tested	% pos	95%CI	N tested	% pos	95%CI
HPV 16	14595	54.4	53.6–55.2	76385	2.6	2.5–2.8
HPV 18	14387	15.9	15.3–16.5	76385	0.9	0.8–1.0
HPV 33	13827	4.3	4.0–4.6	74141	0.5	0.4–0.5
HPV 45	9843	3.7	3.3–4.1	65806	0.4	0.4–0.4
HPV 31	11960	3.5	3.2–3.9	74076	0.6	0.6–0.7
HPV 58	10157	3.3	2.9–3.6	72877	0.9	0.8–1.0
HPV 52	9509	2.5	2.2–2.8	69030	0.9	0.8–1.0
HPV 35	9507	1.7	1.5–2.0	74084	0.4	0.3–0.4
HPV 59	13471	1.28	1.09–1.47	64901	0.3	0.2–0.3
HPV 51	13057	1.16	0.97–1.34	67139	0.6	0.6–0.7
HPV 56	13247	0.78	0.63–0.93	68121	0.5	0.5–0.6
HPV 39	13370	1.29	1.10–1.48	64521	0.4	0.3–0.4
HPV 68	11982	0.61	0.47–0.75	63210	0.3	0.2–0.3
HPV 73	9939	0.48	0.35–0.62	44063	0.1	0.1–0.1
HPV 66	12118	0.39	0.28–0.50	59774	0.4	0.3–0.4
HPV 70	10503	0.33	0.22–0.44	35014	0.3	0.3–0.3
HPV 82	9265	0.27	0.16–0.38	42536	0.1	0.0–0.1
HPV 26	6111	0.13	0.04–0.22	44098	0.0	0.0–0.1
HPV 53	8140	0.42	0.28–0.56	44058	0.4	0.4–0.4
HPV 6	14912	0.45	0.35–0.56	58370	0.3	0.2–0.3
HPV 11	8761	0.2	0.1–0.4	58370	0.2	0.2–0.2

Nanovalent vaccine

Prevalence ratio

Table 2.5 Meta-analysis of type-specific HPV DNA prevalence in invasive cervical cancer

Invasive cervical cancer ⟷ Normal

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«Oncogenic types»

Summary -The data accumulated supports:

- **The unique carcinogenic strength of HPV 16.**
- **The importance of HPV 18 and genetically related types in causing adenoca.**
- **The weaker but still clear carcinogenic potential of six additional** types in alpha-7 (HPV 45) and alpha-9 (HPV 31, 33, 35, 52, and 58),

HPV 52 and 58 are relatively more prevalent in Asia than in other regions,
HPV 33 is most clearly prevalent in Europe
HPV 45 has particular regions where it is prominent.

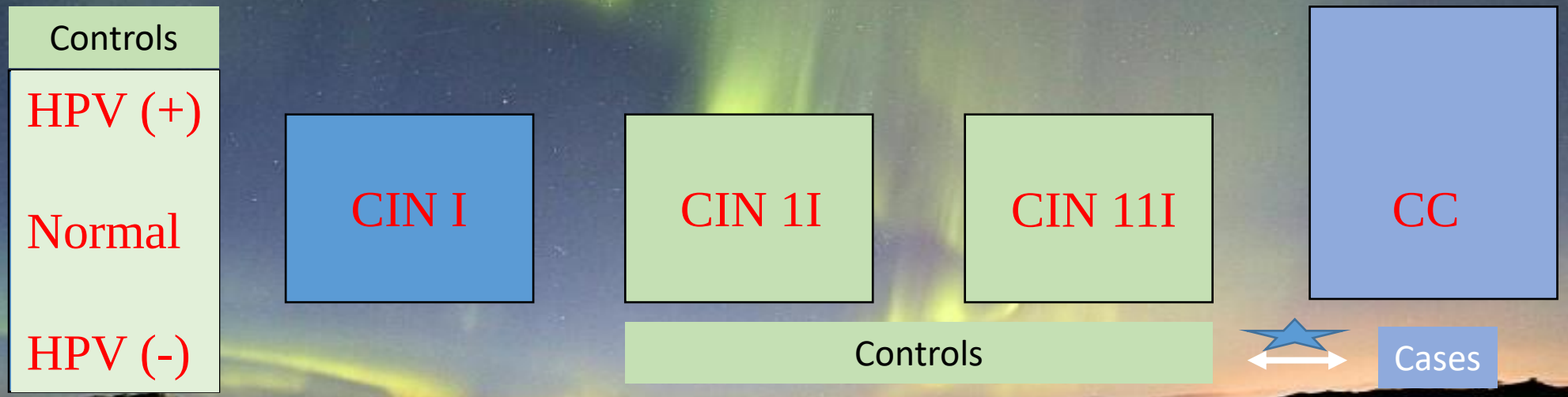
- **The small, and less certain, incremental etiological contributions**

from alpha-5 (HPV 51), alpha-6 (HPV 56), and alpha-7 (HPV 39 and HPV 59).
Each causes a few percent at most of cervical cancer cases worldwide, although regional variability has been observed.

- **Acknowledgement of an unresolved dividing line between the HPV types with the weakest evidence judged to be sufficient**, and those with evidence judged highly suggestive yet limited (alpha-7 HPV 68 and alpha-11 HPV 73).

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

Persistent HR HPV infections - malignant cell transformation



Carcinogenesis: 15-25 years from normal cell to cancer

Tjalma WA et al. Int J Cancer 2013;132:854-67.

Europe

Table 2. Pooled estimates of HR-HPV-type prevalence among women with HG-CIN or ICC and infected with a single HPV type, overall and by histological diagnosis, in 17 European countries between 2001 and 2008

Women with HG-CIN	All HG-CIN (*N* = 2,445)		Women with ICC	All ICC (*N* = 2,715)		SCC (*N* = 2,169)		ADC (*N* = 321)		ASC (*N* = 81)		Other diagnoses (*N* = 144)	
HPV type	%[1]	95% CI	HPV type	%[1]	95% CI	%[1]	95% CI	%[1]	95% CI	%[1]	95% CI	%[1]	95% CI
16	59.9	51.5–68.1	16	63.3	58.8–67.7	66.2	65.2–67.3	54.2	45.5–62.8	35.8	12.8–63.0	66.5	49.6–81.5
18	3.6	1.4–6.9	18	15.2	8.6–23.3	10.8	9.2–12.6	40.4	29.2–52.0	48.5	41.1–56.0	12.1	5.8–20.4
31	9.0	6.0–12.6	31	3.7	1.2–7.5	4.1	1.4–8.0	1.4	0.0–27.9	5.7	0.0–54.0	6.5	0.0–34.2
33	10.5	9.4–11.6	33	4.6	2.0–8.2	5.3	2.3–9.4	1.5	0.0–26.4	5.5	0.0–54.8	6.6	0.0–35.5
35	2.5	0.9–4.8	35	1.1	0.4–2.1	1.3	0.3–3.1	0	–	0	–	2.7	0.0–43.7
39	0.4	0.0–7.0	39	1.1	0.0–6.2	1.3	0.0–7.0	1.3	0.0–29.5	0	–	2.8	0.0–42.9
45	1.9	0.1–5.9	45	5.3	2.9–8.3	5.0	1.8–9.7	8.3	1.6–16.9	10.8	0.0–43.8	4.4	0.0–35.6
51	2.0	0.1–6.3	51	0.4	0.0–3.9	0.4	0.0–4.8	1.4	0.0–28.7	0	–	0	–
52	3.9	0.7–9.5	52	1.7	0.0–6.8	2.0	0.0–8.6	0	–	4.5	0.0–59.0	3.5	0.0–38.8
56	0.9	0.0–5.8	56	0.8	0.0–6.0	1.0	0.0–7.1	0	–	4.5	0.0–59.0	0	–
58	3.2	1.6–5.4	58	1.1	0.0–3.6	1.3	0.0–5.6	0	–	0	–	3.4	0.0–40.1
59	0.4	0.0–7.4	59	0.6	0.0–5.8	0.6	0.0–6.3	0	–	4.6	0.0–57.3	0	–
66	0.4	0.0–4.6	66	0.2	0.0–9.5	0.2	0.0–10.9	0	–	0	–	0	–
68	0.8	0.0–2.7	68	1.3	0.0–6.3	1.5	0.0–7.7	0	–	0	–	3.2	0.0–41.9

Single versus multiple infections; summarizes to > 100%

mRNA and DNA diagnosed HPV types in cervical cancer in South Africa

Hierarchial analytic strategy, infections count once, only.
Ex.: 16,35=16; 18,45=18

Overall, HPV was detected in 95.2% (159/167) of specimens.

The DNA- and mRNA tests each rendered 91.6 % (153/167)

Table 2

Concordant and discordant pairs in DNA/mRNA analysis of type-specific HPV detection.

	HPV-type	Total numbers positive (N)	mRNA-positive only (N)	Both mRNA and DNA positive (N)	DNA-positive only (N)
Types present in both tests	16	67	0	66	1
	18	27	2	25	0
	45	21	2	19	0
	35	18	1	15	2
	33	9	3	6	0
	52	7	2	5	0
	31	4	0	3	1
	58	4	1	0	3
	51	3	2	1	0
Types present in the DNA-test, only	30	1	NA		1
	56	1	NA		1
	69	1	NA		1
	73	1	NA		1
	82	2	NA		2
	Total		13	140	13

9 types

44 types

DNA = deoxyribonucleic acid, HIV = human immunodeficiency virus, HPV = human papillomavirus, mRNA = messenger ribonucleic acid.

9 high-risk HPV-types included in the mRNA test, 91.6% (153/167)
DNA test, 88.0% (147/167)

Rad A et al. HPV types in cervical cancer in South Africa. Medicine (2017) 96:47(e8752)

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

- **Prevalence studies (1990ies)**
- **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)

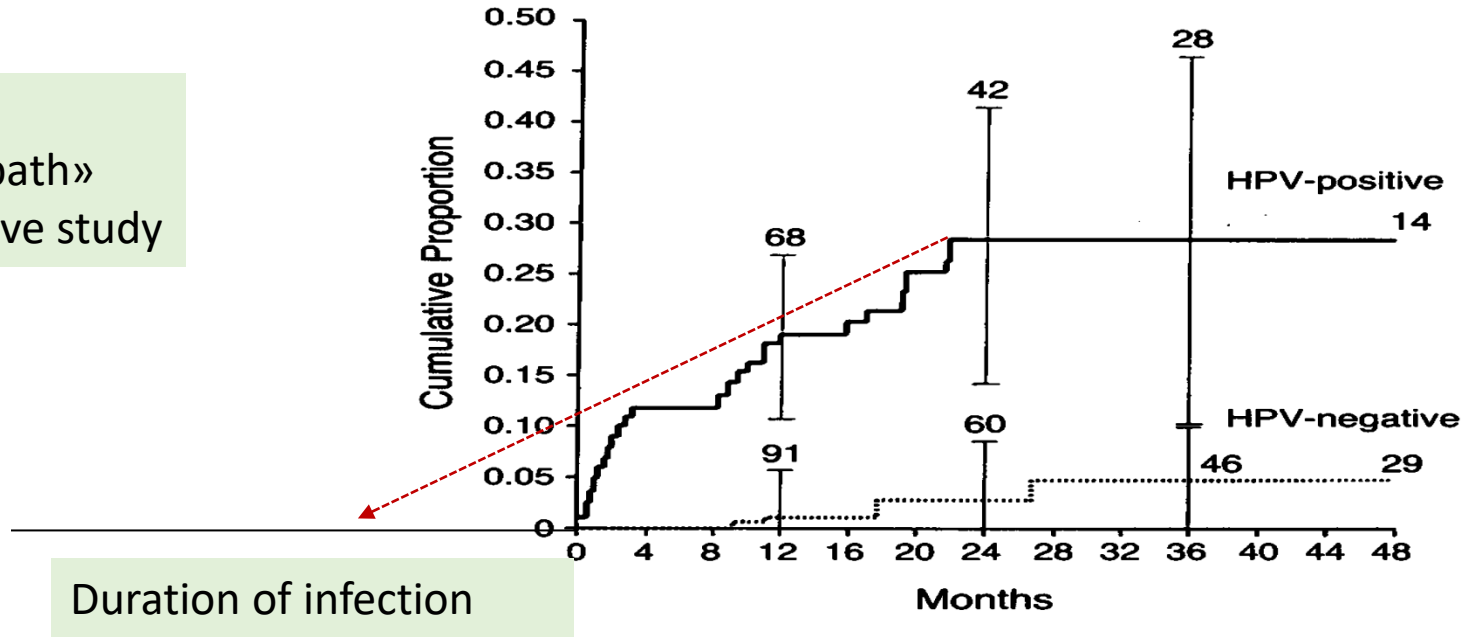
A COHORT STUDY OF THE RISK OF CERVICAL INTRAEPITHELIAL NEOPLASIA GRADE 2 OR 3 IN RELATION TO PAPILLOMAVIRUS INFECTION

Laura A. Koutsky, Ph.D., King K. Holmes, M.D., Ph.D., Cathy W. Critchlow, M.S., Claire E. Stevens, M.A., P.A., Jorma Paavonen, M.D., Anna Marie Beckmann, Ph.D., Timothy A. DeRouen, Ph.D., Denise A. Galloway, Ph.D., Debra Vernon, C.T., A.S.C.P., and Nancy B. Kiviat, M.D.

Study design:		Cross-sectional/cohort
Selection of participants:		Random-numbers table were used to select women
Setting:		STD clinic
Recrutment years:		1984-86
Age:		16-50
Selected/eligible:		883
Enrolled:		779
Met inclusion criteria:		323 (41%)
- Previous CIN	34	
- Atypical smears	81	
- Poor quality smears	21	
Included		187
From 1987-89		60 more women included
Final study population		**247**

Follow-up: 1 , 4 and thereafter every 6 months for at least 24 months

1992
«Causal path»
Prospective study



CIN 2-3

Duration of infection

Figure 2. Cumulative Proportion of 241 Women with Negative Cervical Cytologic Tests on Enrollment in Whom Biopsy-Confirmed Cervical Intraepithelial Neoplasia Grade 2 or 3 Developed.

The analysis began at the time of the first positive HPV DNA test for the HPV-positive group, and at the time of enrollment for the HPV-negative group. Ninety-five percent confidence intervals are shown at one, two, and three years for the cumulative proportion with cervical intraepithelial neoplasia grade 2 or 3. Numbers indicate the number of women without biopsy-confirmed cervical intraepithelial neoplasia grade 2 or 3 who were included in the follow-up at the intervals shown. One woman with two negative tests for HPV DNA and a second woman with eight such tests tested positive for HPV DNA (HPV 16 or 18) on the same day that biopsy-confirmed cervical intraepithelial neoplasia grade 2 or 3 was discovered.

Long-term Absolute Risk of Cervical Intraepithelial Neoplasia Grade 3 or Worse Following Human Papillomavirus Infection: Role of Persistence

Susanne K. Kjær, Kirsten Frederiksen, Christian Munk, Thomas Iftner

Manuscript received September 23, 2009; revised January 20, 2010; accepted August 16, 2010.

Correspondence to: Susanne K. Kjær, MD, DMSc, Department of Viruses, Hormones and Cancer, Institute of Cancer Epidemiology, Danish Cancer Society, Strandboulevarden 49, DK-2100 Copenhagen, Denmark (e-mail: susanne@cancer.dk).

[J Natl Cancer Inst 2005;97:1072–9]

J Natl Cancer Inst 2010;102:1478–1488

Study design:	Cohort study – natural course of HPV
Selection of participants:	Random sample from the general female population
Recrutment years:	15 May, 1991 to January 31, 1993
Age:	20-29 yrs
Inclusion:	11 088 women - routine screening with Pap-smear
1st follow-up after 2 yrs:	8 656 women met (78% of initial sample)
Study population:	**7 482, both visits, normal smear at 1st visit**
Outcomes collected passively	Danish pathology data bank
HPV-test	HC2 (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 69) Many genotypes with other PCR-methods
HPV-stratification:	HPV-16+, HPV-18+ (not HPV-16)*, HPV-31*, HPV-33*

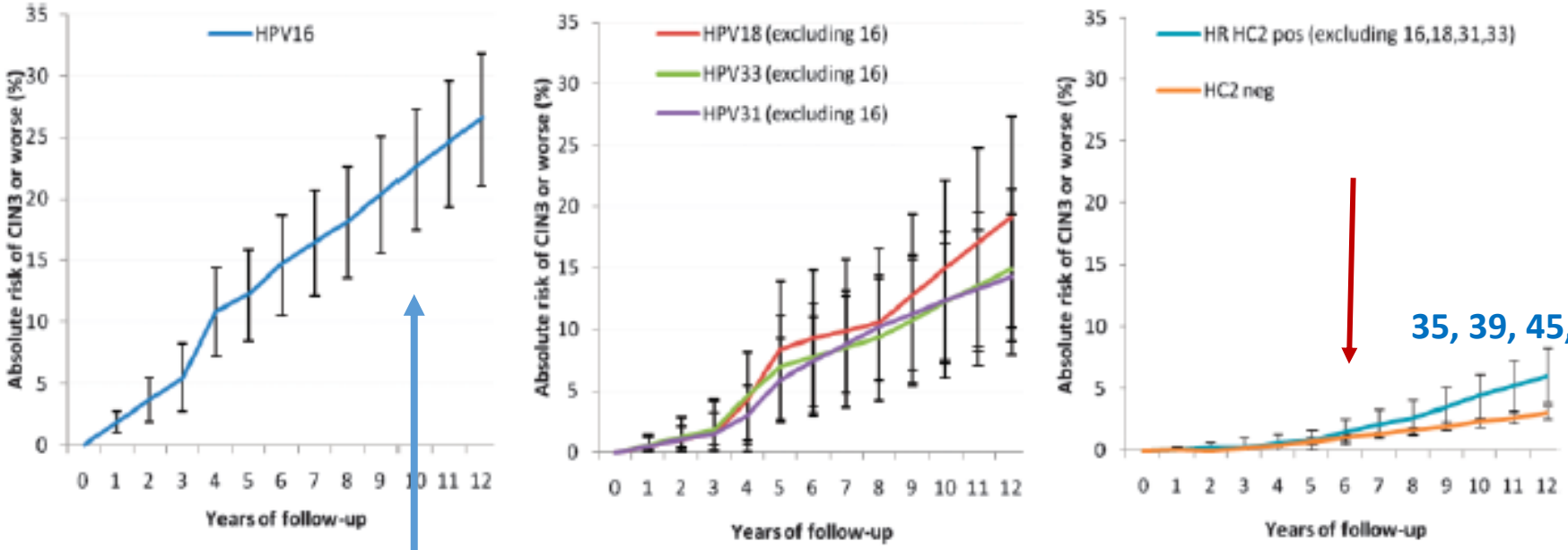


Figure 1. Absolute risks of cervical intraepithelial neoplasia grade 3 (CIN3) or worse after infection with different high-risk human papillomavirus (HPV) types in women with normal cytological findings at baseline. **Error bars** correspond to 95% confidence intervals. HR HC2 positive = positive to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

35, 39, 45, 51, 52, 56, 58, 59, 69

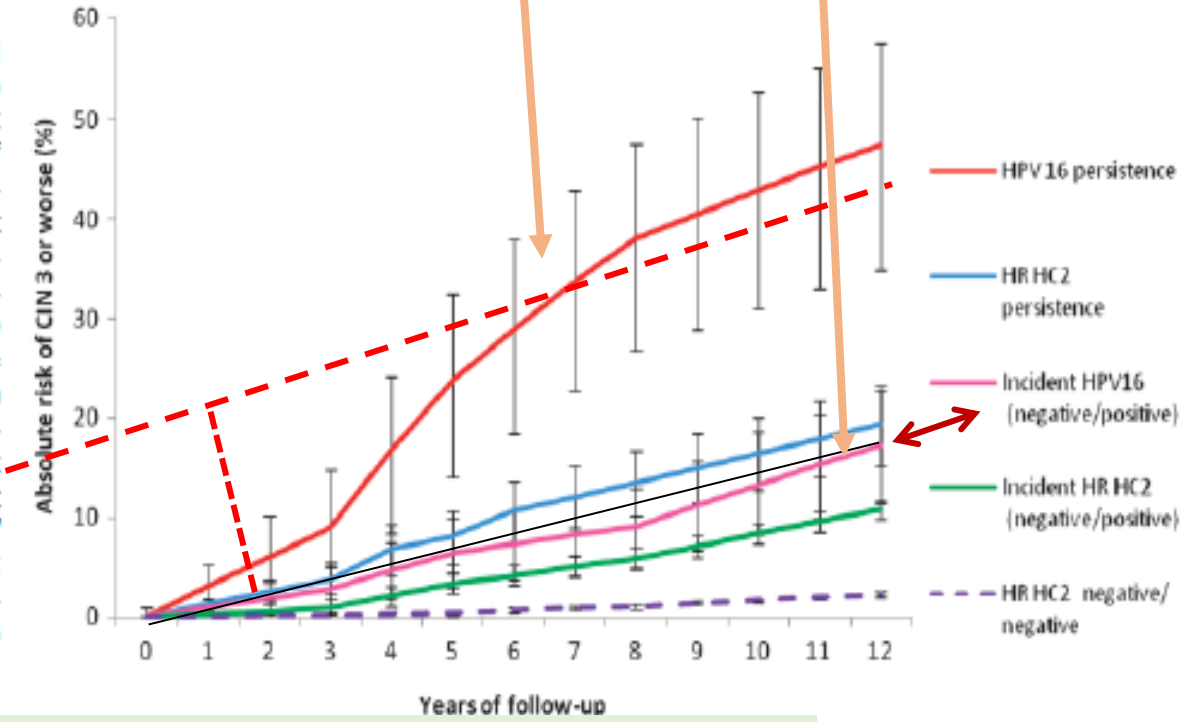
Persistent infection – duration – HPV-16: RISK for CIN3 over 12 years: ~ 26-27%

Incident infections – duration – HPV-16: spontaneous regression/latency (?) - > 70%

J Natl Cancer Inst 2010;102:1478–1488

Illustrates the progression to CIN 3 in prevalent and incident cases

Figure 3. Absolute risks of developing cervical intraepithelial neoplasia grade 3 (CIN3) or worse in women with normal cytological findings at baseline in relation to various measures of human papillomavirus (HPV) status. HPV16 persistence = positive to HPV16 at the first and at the second study examination. HR HC2 persistence = positive for high-risk HPV types as measured by the Hybrid Capture 2 at the first and the second study examination; incident HPV16 = negative to HPV16 at the first study examination and positive to HPV16 at the second study examination; incident HR HC2 = negative for high-risk HPV by the HC2 assay at the first and positive at the second study examination; HR HC2 negative/negative = negative for high-risk HPV by the HC2 assay at the first and the second study examination, **Error bars** correspond to 95% confidence intervals.



Driven by HPV 16

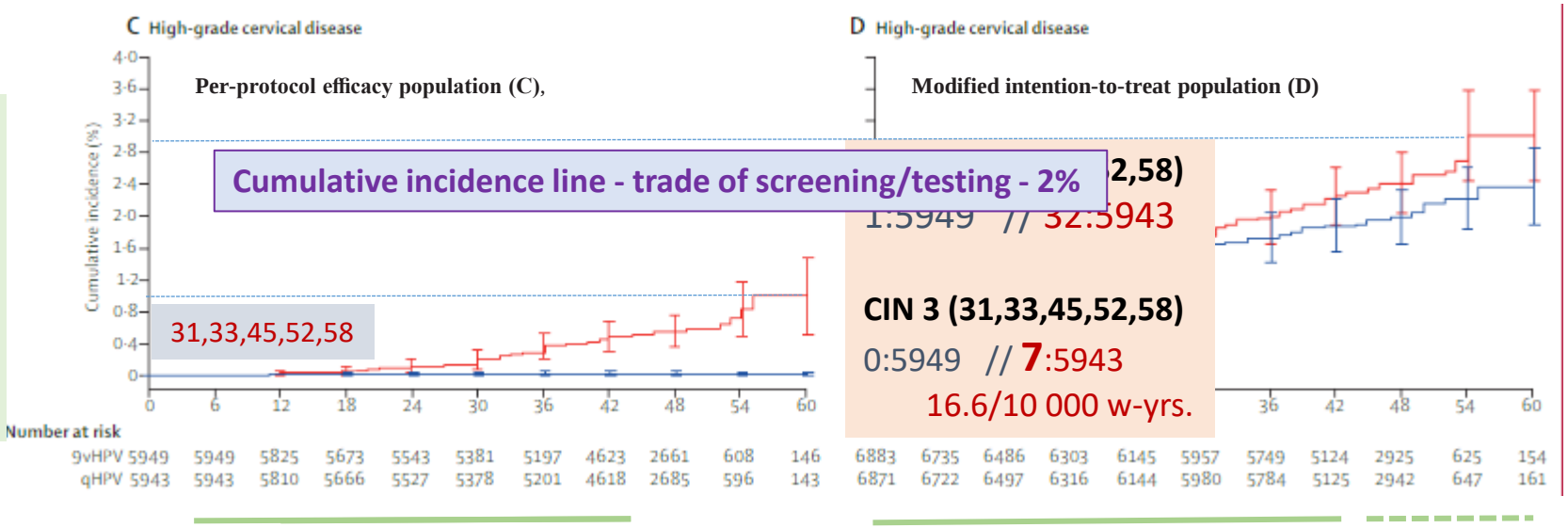
Persistent infection - HPV transmission has taken place before study start

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



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 study

In this publication follow-up through December 31st, 2009

In this presentation extended follow-up through December 31th, 2015

Primary screening with
Proofer 5
mRNA 16, 18, 31, 33, 45

Normal cytology at baseline

Open Access Research

BMJ Open

Primary cervical cancer screening with an HPV mRNA test: a prospective cohort stud

[1] Tore Jarl Gutteberg,[2,3]
destad[4]

To cite: Sørbye SW, Fismen S, Gutteberg TJ, *et al.* Primary cervical cancer screening with an HPV
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(http://dx.doi.org/10.1136/bmjopen-2016-011981).

Received 21 March 2016
Revised 20 June 2016
Accepted 14 July 2016

ABSTRACT

Obj
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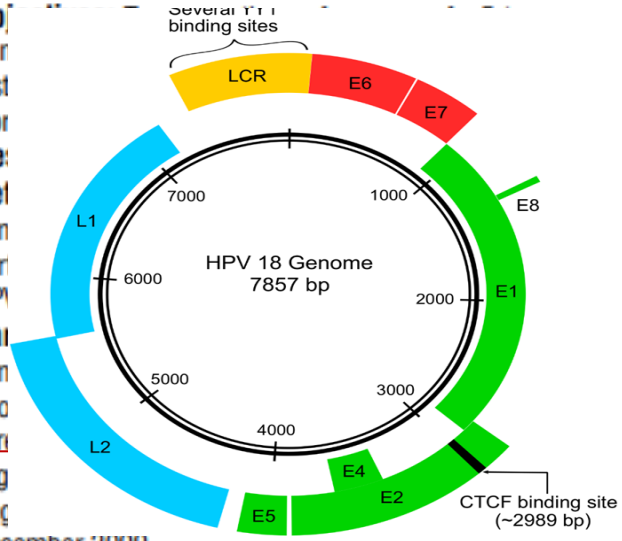
Interventions: Follow-up according to the algorithm for



Strengths and limitations of this study

- We consider studying primary screening with a 5-type human papillomavirus (HPV) messenger RNA (mRNA) test in a population of women with no previous cervical intraepithelial neoplasia grade 2 and/or abnormal smears as a strength as the HPV infections diagnosed are likely to be 'new' infections.
- We consider the follow-up within the Norwegian Cervical Cancer Screening Programme as strength, as women regardless of mobility within Norway, are captures by the surveillance system for cytology, histology and treatment.
- We consider just having one screening round with the 5-type HPV mRNA test as a limitation, in addition to follow-up based on cytology only (verification bias).

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

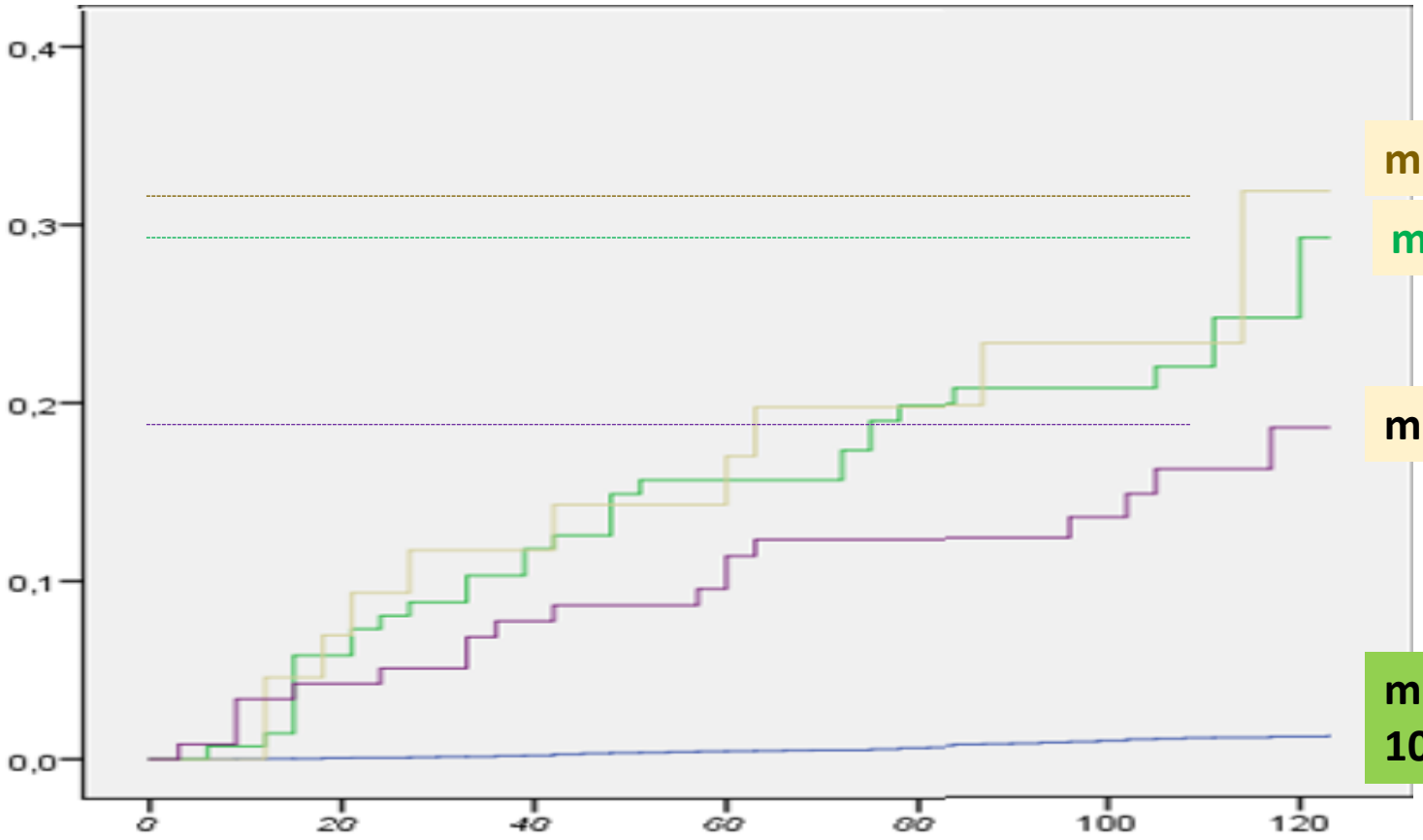
HPV-result	25-33 yrs. N=2 610 %	34-69 yrs. N=6 972 %	Total N= 9 582 %
HPV negative	94.3	97.8	96.8
HPV positive	5.7	2.2	3.2
HPV-16	2.8	1.0	1.5
HPV-18 (not 16)	0.8	0.3	0.5
HPV-31/-33/-45 (not 16/not 18)	2.1	0.9	1.2

Hierarchial analytic approach

All participants had normal smear

- At least 1 follow-up reported to NCR

Cumulative incidence of CIN 3 by mRNA HPV-types



mRNA 18 (not 16)

mRNA 16

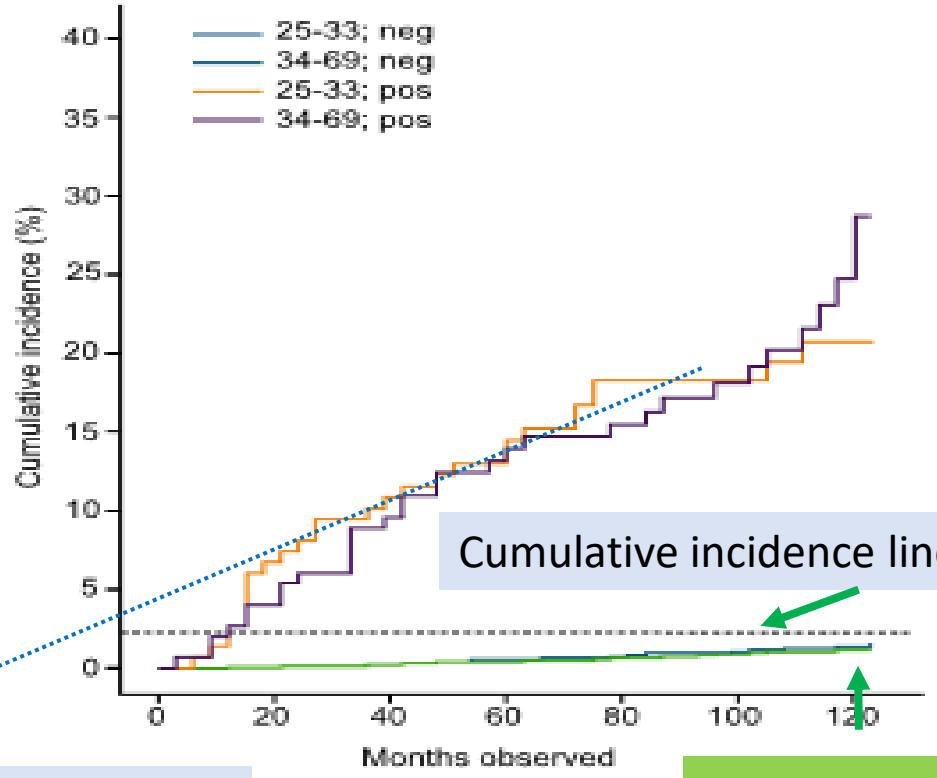
mRNA 31,33,45 (not 16, not 18)

mRNA/cytology negative at baseline
10-year risk of CIN 3 = 1.0%

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 line - trade of screening/testing - 2%

Duration of infection?

10 years risk of CIN 3 - cumulative incidence – 1.0% for mRNA/cytology negative at baseline

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

Open Access Research

BMJ Open

Primary cervical cancer screening with an HPV mRNA test: a prospective cohort study

Baseline – 2003/04 – extended update through December 31sth, 2015; analysis through 10 years

Conclusions:

The present cum. inc. of CIN3+ is similar to rates reported in primary screening studies with HPV DNA

Owing to differences in biological rationale and test characteristics, there is a trade-off between sensitivity and specificity that must be balanced when decisions on HPV tests in primary screening are taken.

HPV mRNA testing may be used as primary screening for women aged 25–33 years and 34–69 years.

visit the journal online (http://dx.doi.org/10.1136/bmjopen-2016-011981).

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neoplasia grade 2 (CIN2+) before or until 3 months after screening, 11 220 women aged 25–69 years were eligible for study participation. The Norwegian Cancer Registry completed follow-up of CIN2+ through 31 December 2009.

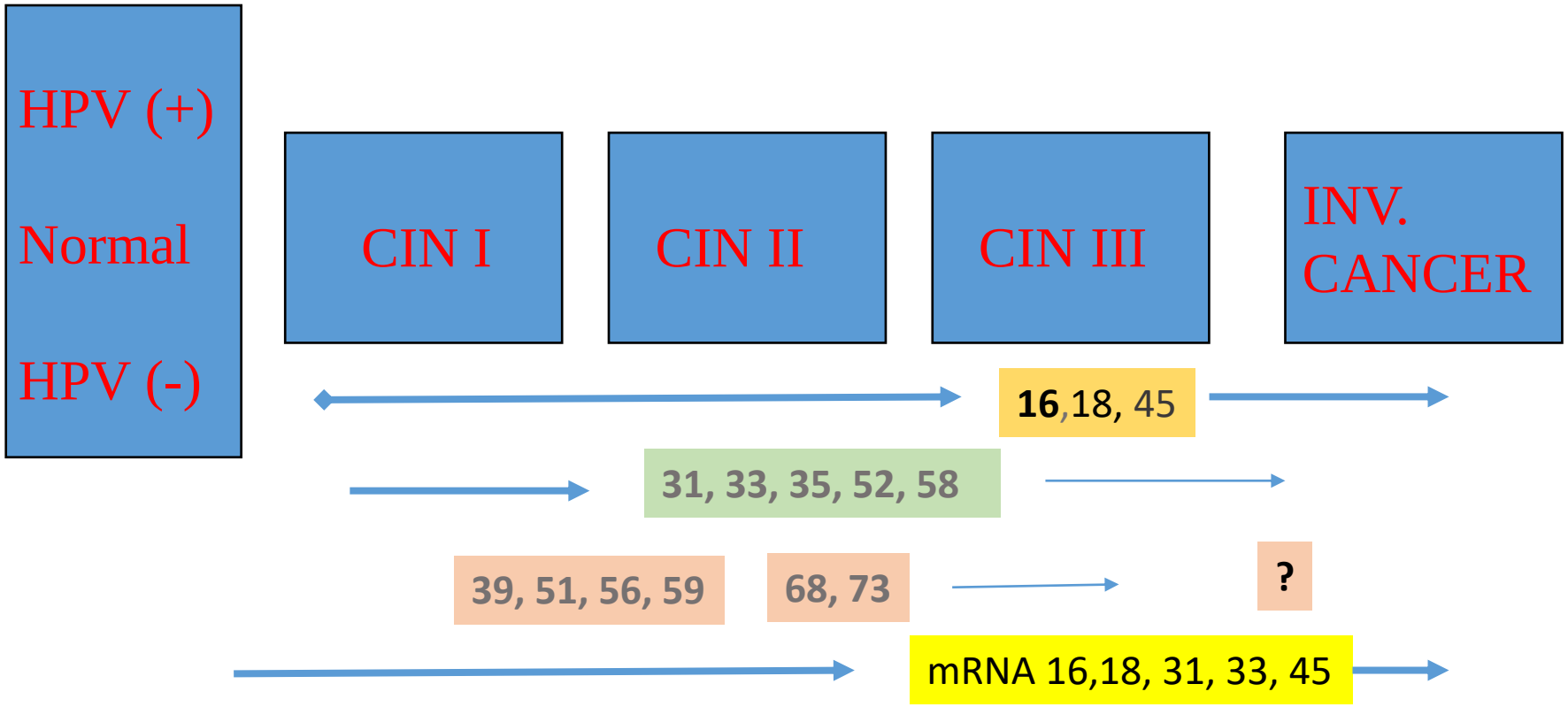
Interventions: Follow-up according to the algorithm for

Norway, are captures by the surveillance system for cytology, histology and treatment.

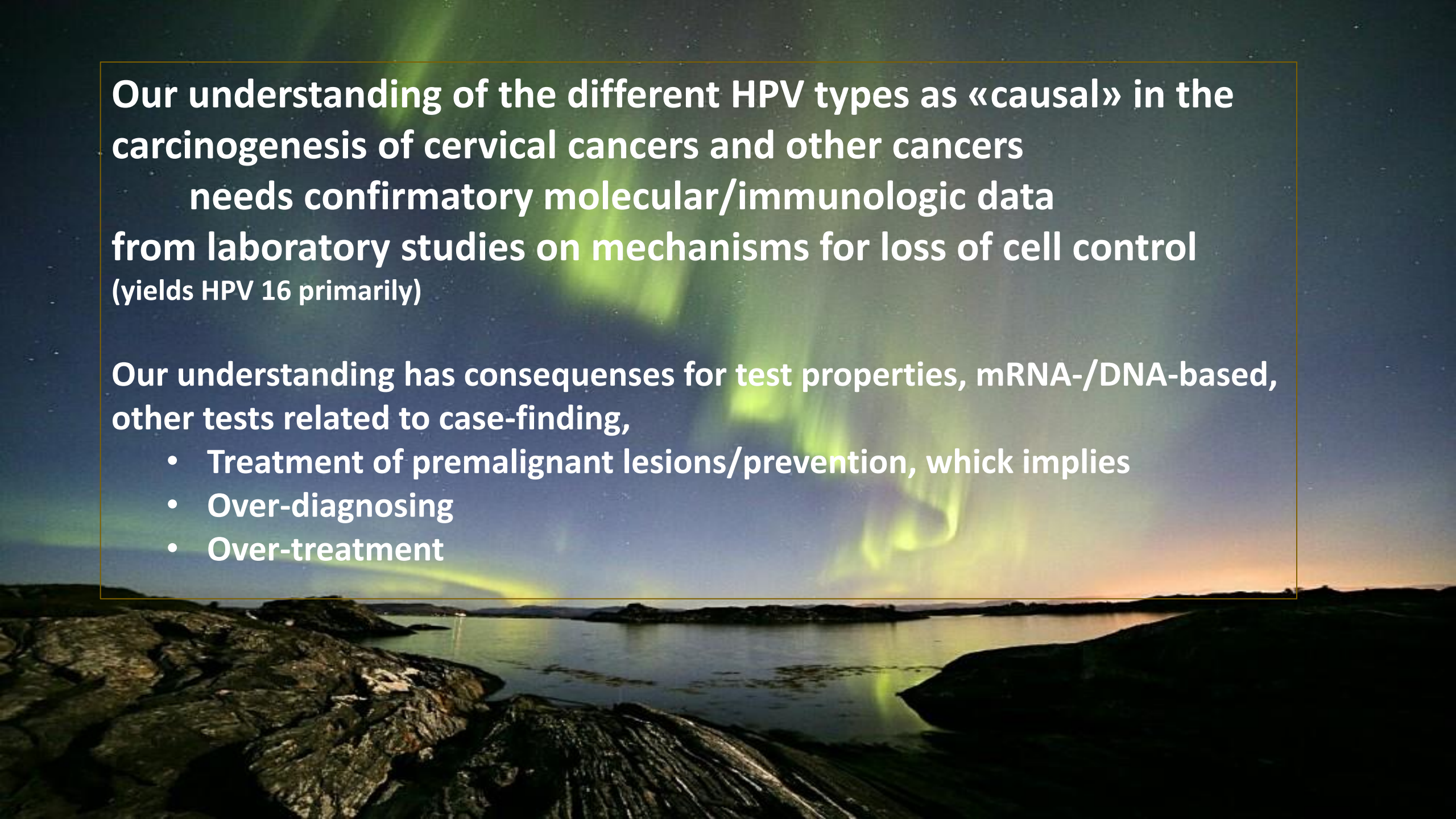
- We consider just having one screening round with the 5-type HPV mRNA test as a limitation, in addition to follow-up based on cytology only (verification bias).

In conclusion

Malign cell transformation – persistent HR HPV infection – oncogenic properties of types from Case-control and cohort studies



Carcinogenesis: 15-25 years from normal cell to cancer



Our understanding of the different HPV types as «causal» in the carcinogenesis of cervical cancers and other cancers
needs confirmatory molecular/immunologic data
from laboratory studies on mechanisms for loss of cell control
(yields HPV 16 primarily)

Our understanding has consequenses for test properties, mRNA-/DNA-based, other tests related to case-finding,

- **Treatment of premalignant lesions/prevention, whick implies**
- **Over-diagnosing**
- **Over-treatment**