

Cumulative five-year diagnoses of CIN 2/3 or cervical cancer after high-risk HPV and cytology testing in a primary screening setting

Final results

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Introduction: Results of the diagnostic study

(SCHNEIDER et al., Int J Cancer 2000)

- Recruitment 1996 – 1998: 4761 women
- Objective: Detection of CIN2, CIN3 or cancer by routine cytology and high-risk HPV testing

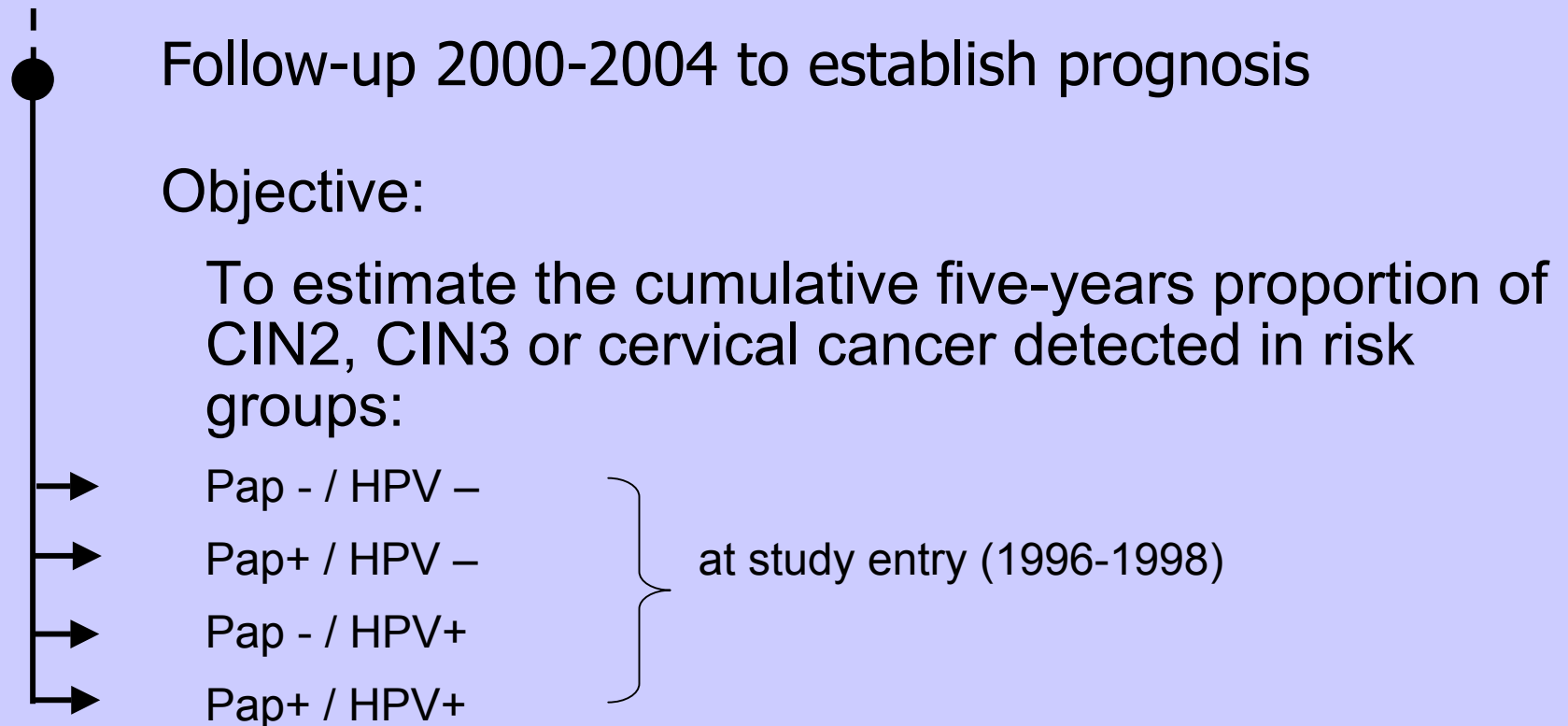
Results:

	Sensitivity	False-Positives	CIN2+ in test negatives (1-NPV)
→ HPV:	89,4%	5,2%	0,4%
→ Pap:	20,0%	0,3%	2,5%



How protective is a negative high-risk HPV test over a period of five years?

(HOYER et al., Int J Cancer 2005)



“Post-hoc design”: 5-year follow-up cohort study

Methods: Study population

- Women participating in routine screening in 7 gynaecology practices in Thuringia / Germany between 1996 and 1998
- Age of patients 18-70 years
- Normal cytology within one year prior to the study
- Exclusion criteria: pregnancy, conization, hysterectomy, unclear screening results at the beginning

- At least one follow-up according to protocol

Methods: Index tests and reference

- **Index Tests („study screening”) at practices**
 - Pap (\geq Pap III, 2nd Munich classification)
 - High-risk HPV (Consensus Primer PCR GP5+/6+,
14 types: 16 18 31 33 35 39 45 51 52 56 58 59 66 68)
 - “Routine” colposcopy (\geq CIN 1)
- Routine screening
(usually Pap, HR-HPV or colposcopy if indicated)
- **Reference (gold standard) at University Hospital Jena**
 - Colposcopy-guided punch biopsy / endocervical curettage intended to all women referred
 - Histo-pathological classification blinded to index tests

Methods: Schedule of examinations

Year of follow-up	Start	0,5	1	2	3	4	5
Data collection							
Study screening: Pap, HR-HPV, Routine colposcopy	X	(X) Control in screening negatives					X
Expert colposcopy / Biopsy / Review	ii	ii					ii
Follow-up / treatment of findings		ii	ii	ii	ii	ii	
Routine screening: Pap (HR-HPV, routine colposcopy, biopsy if indicated)			(X)	(X)	(X)	(X)	
	<div style="border: 1px solid black; padding: 5px;"> Documented in study database if positive Histology included in final review </div>						

Methods: Quality assurance - histology

- Independent review of routine diagnoses by two pathologists

Review	Number of specimens	Observed agreement* (kappa)
First	449	95,6% (88,3%)
Second	439	92,5% (74,4%)

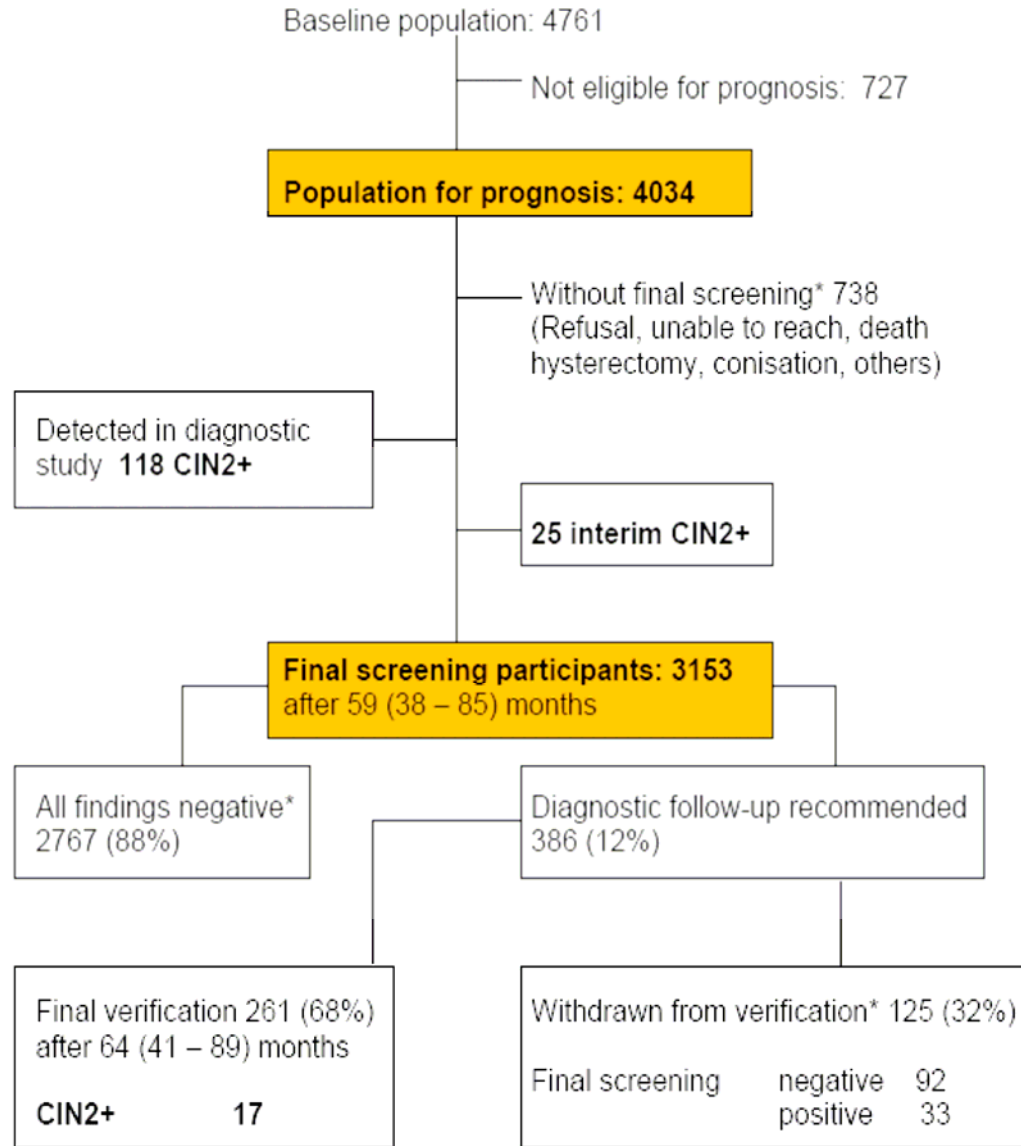
* to identify a CIN2+ case

- Overall, histology diagnoses exist for 626 women, whereas 94,4% have been reviewed (35 women with routine diagnosis)

Results: Flowchart

Age at entry in
population for
prognosis:

50% ≤ 35 years
75% ≤ 43 years



* censored at date of last acceptable information

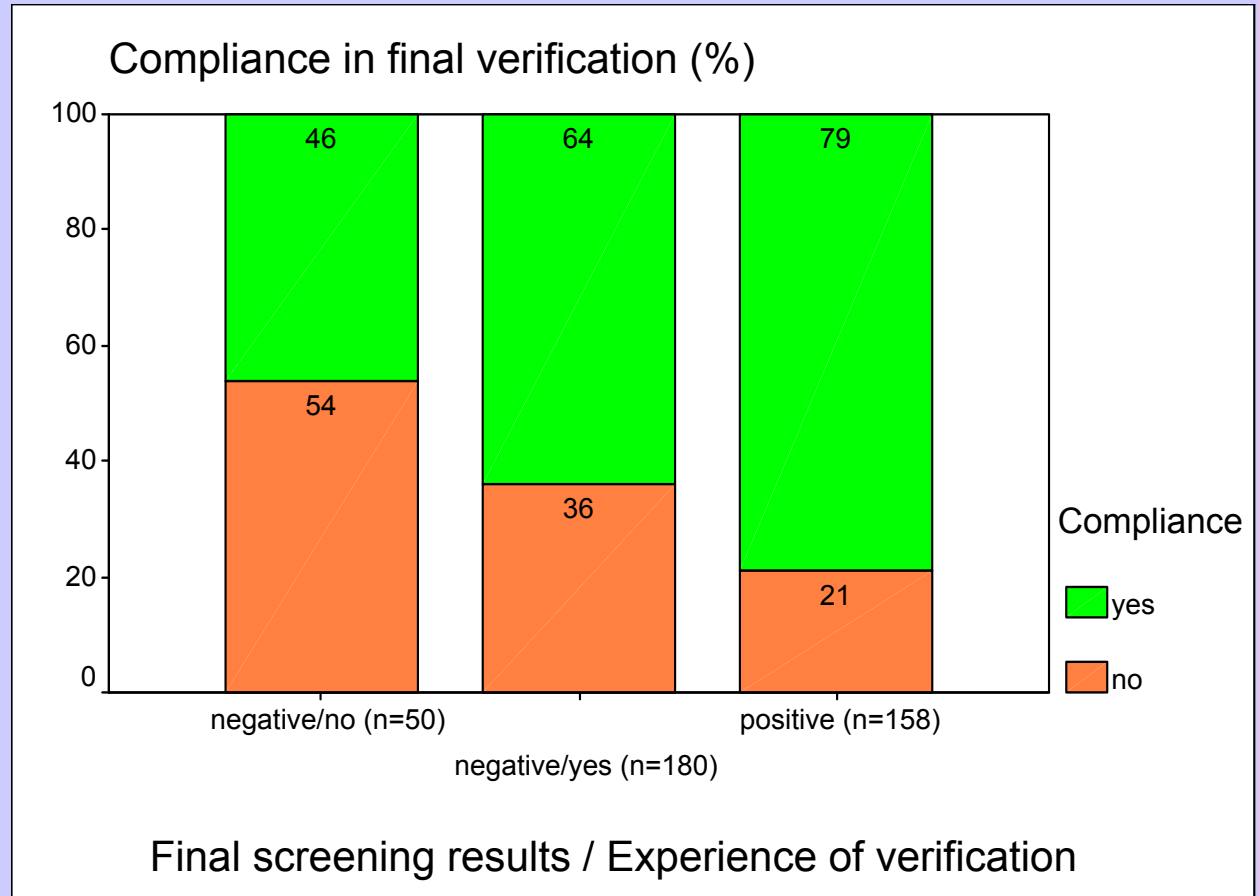
Results: Compliance in diagnostic follow-up

Final recall

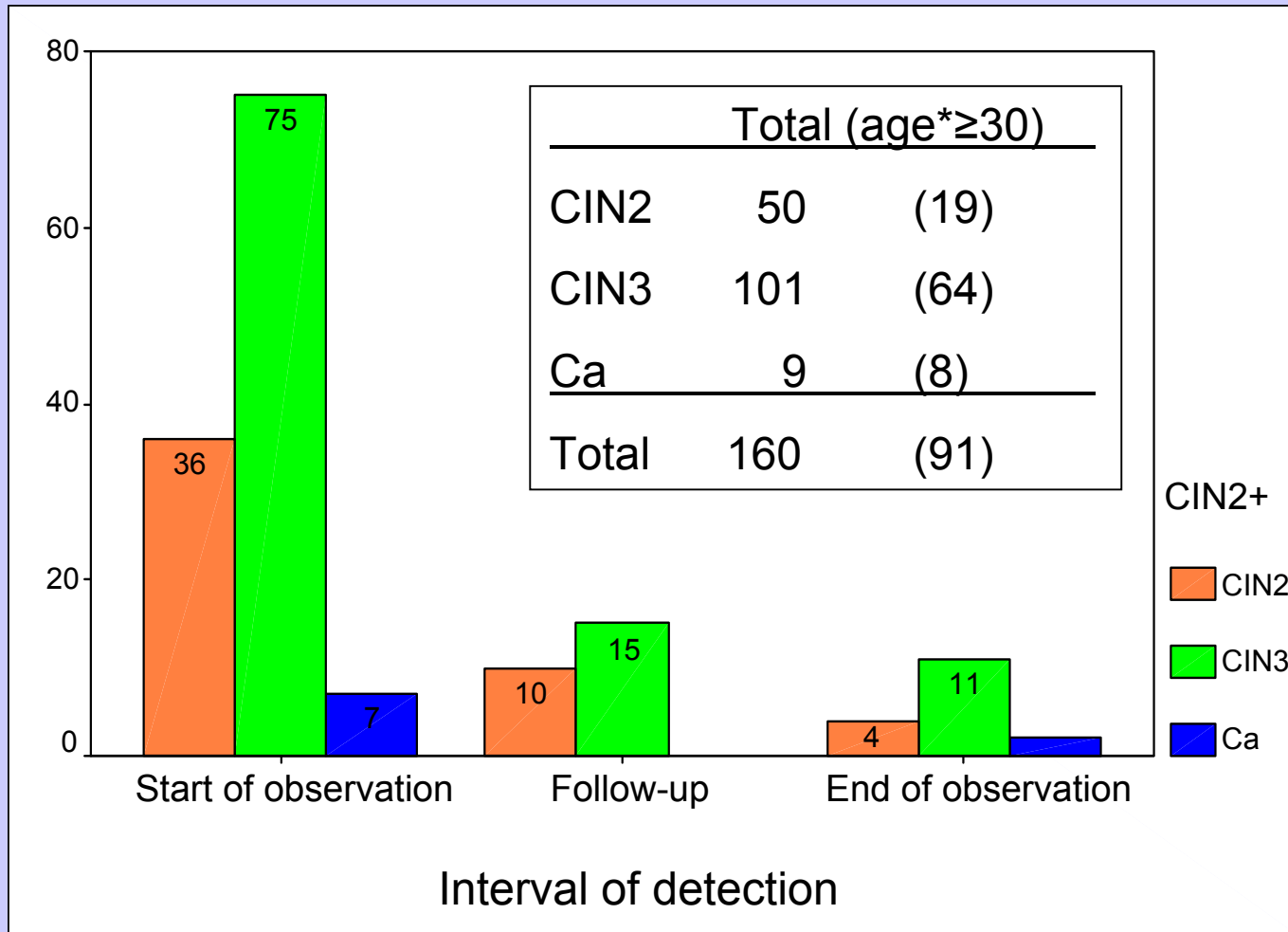
- 386 women

Final verification

- 68% due to complex recall criteria
- 79% due to positive final screening tests



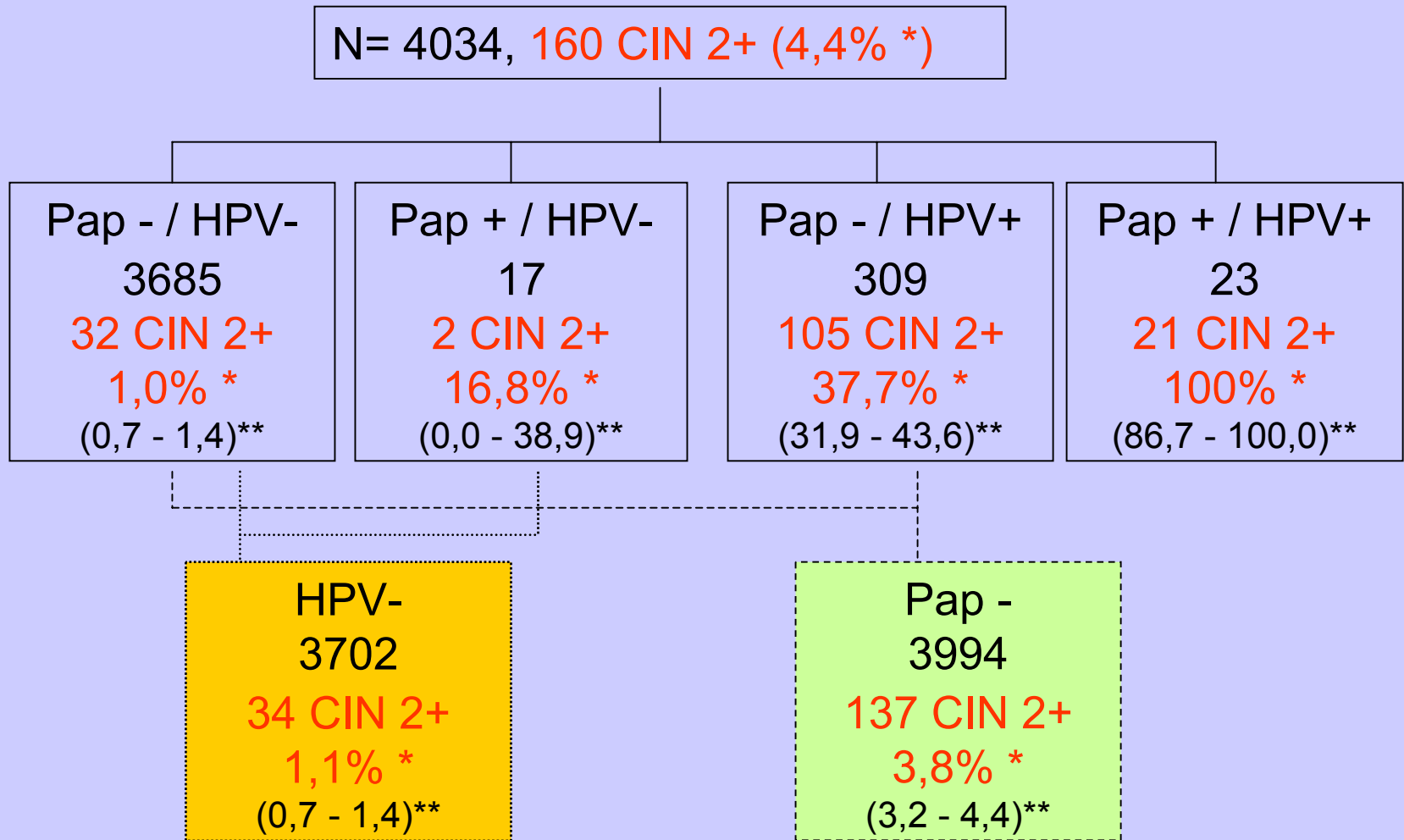
Results: Detected CIN 2+ cases in the total population for prognosis (n=4043)



* at diagnosis

Results: Cumulative five-year detection rates*

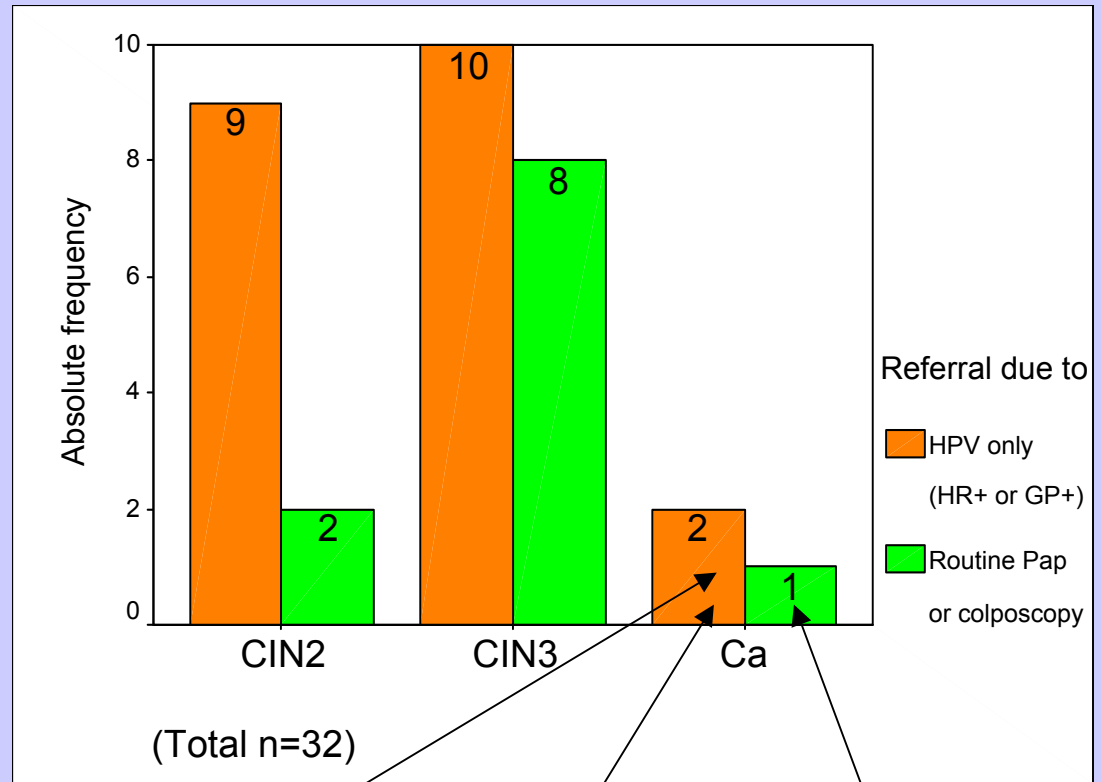
(* Lifetable estimate ** 95% confidence interval)



Results: CIN2+ in Pap- / HPV- group

Reason for referral (not at random!)

- 21 (66%) detected by HPV only
- 11 (33%) detected by routine test (irrespective of HPV)



Age 63
HPV+ at final screening
FIGO Ia2

Age 34
HPV+ at control
FIGO IIb

Age 34
colp. CIN3
FIGO Ib1

Results: Focused on more relevant ...

Cumulative five-year detection rates

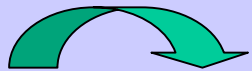
Age-range	18-70	30-70	30-70
Endpoints	160 CIN2+	91 CIN2+	72 CIN3+
(N)	(4034)	(2623)	(2623)
• Pap - / HPV -	1,0 %	0,6 %	0,5 %
• Pap + / HPV -	16,8 %	17,5 %	17,5 %
• Pap - / HPV +	37,7 %	38,7 %	30,8 %
• Pap + / HPV +	100,0 %	100,0 %	100,0 %
• Total	4,4 %	3,4 %	2,7%

Comments: Feasibility of HPV-testing

- PCR based HPV testing is feasible
(about 12.500 HPV-tests: 92% screening and follow-up, 8% diagnostic verification)
 - Follow-up of women with positive screening tests is, as expected, more complex
 - 4034 HPV-tests during first screening round and
 - 3248 HPV-tests as control in screening negatives to reduce workup-bias
- “produced”
- 1121 HPV-follow-up-tests over 5 years

Comments: Risk of CIN2+

- 1,1% after HPV- in five years compared to 2,6% after Pap- in the first and 3,8% in five years
- Increased significantly if HR-HPV was involved



Implication

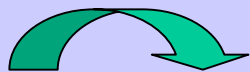
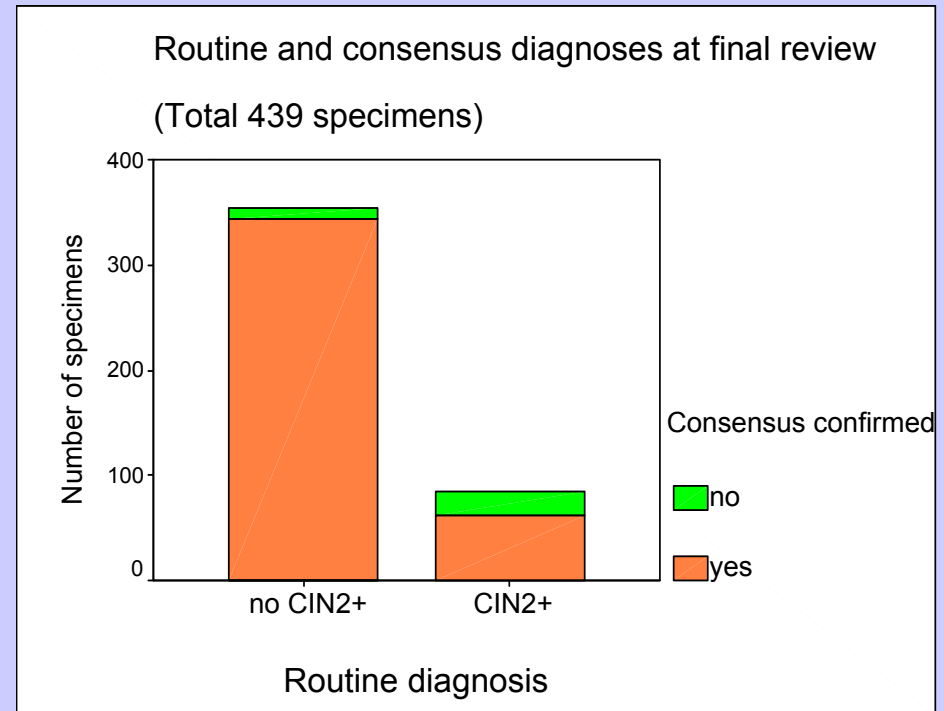
Risk-adapted screening with longer intervals after
Pap- / HR-HPV- results

Comments: 151 CIN2/3 cases detected



626 (15,5%) women underwent expert colposcopy / biopsy

- Problem of misclassification of histology (more frequent false-positive)
- CIN2/3 which do not progress to cancer („pseudo-disease“)



Undesired implication:
Probably increase of over-diagnostic and over-treatment

Comments: Limitations of our study...

...for evaluation of HPV test in primary screening

- Study cohort not population based / exclusion of women without follow-up information
- Participation rate of routine interim screening unknown due to “post-hoc” design (test-positives only)
- Comparison of test performance between Pap and HPV test probably biased by „pseudo-diseases“

Comments: Our study design corresponds...

...approximately to a screening setting of

- Yearly Pap at the discretion of the woman and the gynaecologist
supplemented by
 - Five-yearly PCR based HR-HPV test with individual invitation
- **To establish a screening which benefits from higher sensitivity of the HPV-test without an increasing risk of over-treatment will be a challenge.**

Acknowledgement:

Research group/ collaborators

- Adriaan van den Brule
- Christine Bergeron
- Chris Crum
- Matthias Dürst
- Ullrich Endisch
- Christiane Greinke
- Johannes Haerting
- Heike Hoyer
- Rosemarie Kühne-Heid
- Sabine Leistritz
- Beatrix Lotz
- Beate Ludwig
- Bernhard Müller
- Ingo Nindl
- Cornelia Scheungraber
- Achim Schneider
- Volker Schneider
- Karin Teller

Study centres

- Ulrike Baumbach
- Marlis Glaubrecht
- Gudrun Götz
- Dagmar Menzel
- Reinhard Möller
- Alexandra Mönch-Hering
- Karin Pfützenreuter
- Martin Riefenstahl
- Gabriele Wetzel