HPV test introduction in the Netherlands: why and how?

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Cervical cancer screening in The Netherlands: program characteristics

- Inhabitants: 16.000.000
- Incidence 7.0/100.000 (~650 cases/year)
- Mortality 2.1/100.000 (~220 cases/year)
- Target population screening: women 30-60 year
- Screening system: call and recall, funded by Min. Health, 5 screening organizations
- Screening interval: 5 years
- Screening method: cervical cytology
- Cytological classification: CISOE-A
- Coverage: 72%, Nr. smears/year in national screening program : ~450.000-500.000
- Total nr of smears made/year: ~600.000-650.000
- Costs: 35 M €/year

Courtesy: C. Meijer

Why considering a change in the present screening programme?

- Since 2004 the incidence of cervical cancer is not decreasing anymore
- Incidence of adenocarcinoma has not decreased: adenocarcinoma and ACIS are missed
- Almost 60% cervical cancers diagnosed in screening non-attendees: Attendance to Screening programme (67%) should be increased
- It takes 18 months to triage women with equivocal (BMD) smears for colposcopy (two repeat tests)
- New manners of cervical cancer prevention: Prophylactic vaccination and better screening tests (i.e. HPV tests) have been developed

Courtesy: C. Meijer

Actions of ministry of Health

- March 20, 2007: Minister of health has asked the Health Council to advise whether “prevention of cervical cancer can be improved’
- July 10, 2007: “Committee Fighting Cervical Cancer” installed by the Health Council
- March 31, 2008: the Health Council has released its first advice:
  - HPV-DNA naïve women (12 year) should be given prophylactic vaccination with HPV16/18 L1 VLP
  - To have a catch-up for girls up to and including 16 years of age
- The second part of the advise about screening released on May 24, 2011:
  - Primary HPV screening by a clinically validated test, cytology triage
  - Offering self-sampling for HPV testing to screening non-attendees

Important issues for primary HPV screening

HPV test guidelines

HPV tests vary in their property to detect the various types of HPV infections

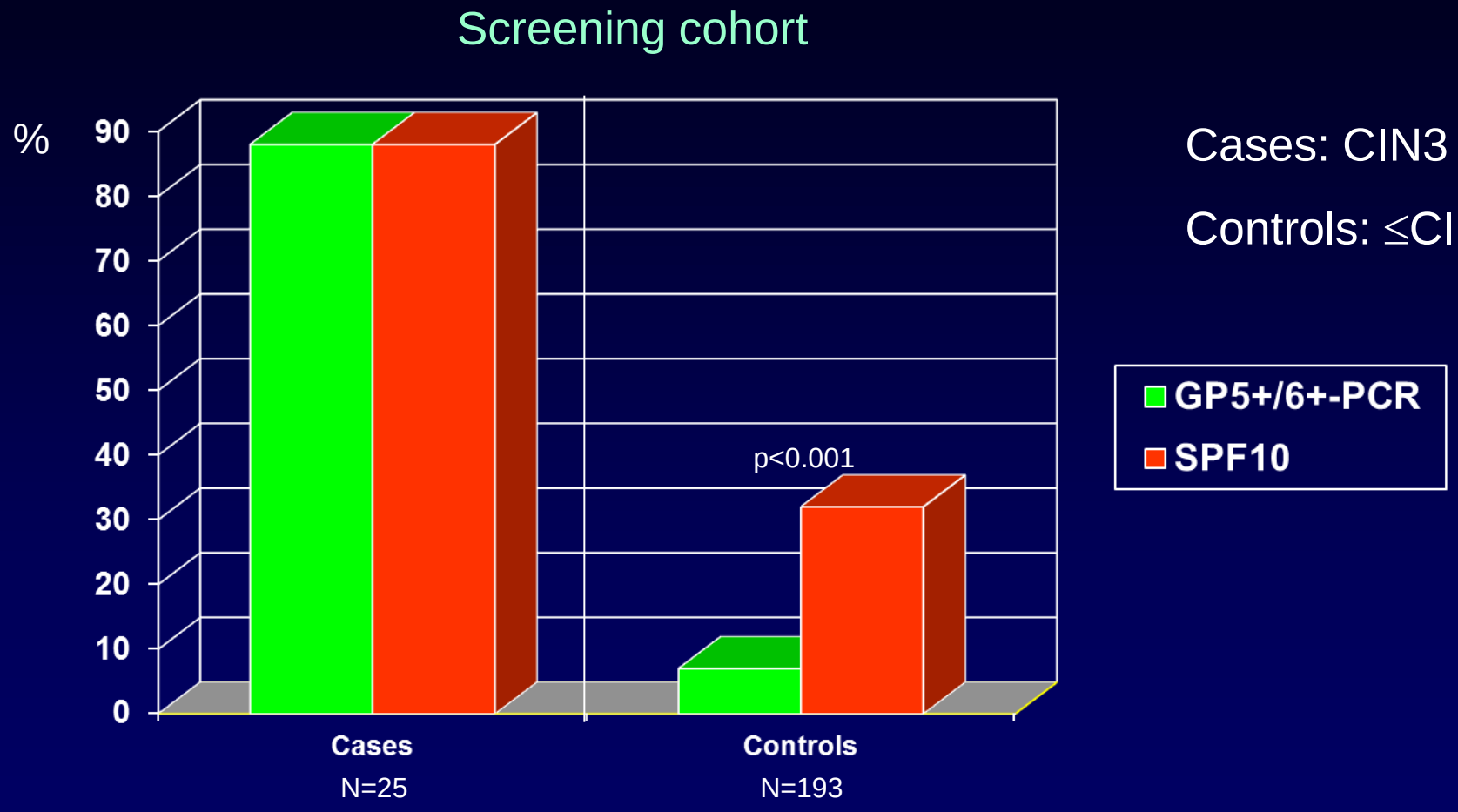
Important distinctions:

- Analytical sensitivity and specificity
  - hrHPV infections

- Clinical sensitivity and specificity
  - CIN2+ (clinically relevant hrHPV infections)

Detection of high-risk HPV infections in cervical screening is only useful when associated with presence or development of CIN2+

Nested case-control study women with normal cytology



➢ False positivity rate of SPF10 was significantly higher than that of GP5+/6+-PCR whereas true positivity rate for CIN3 was identical

Hesselink et al., JCM 2008

HPV tests should be clinically validated for screening

- Guidelines for the use of HPV tests in a clinical setting or primary screening have been developed *Meijer et al Int.J.Cancer: 2009*
- Prototype clinically validated tests are HC2 (Qiagen) and GP5+/6+ PCR-EIA (Diassay)
- Clinical validation of other HPV tests can be done by clinical equivalence analysis relative to hc2/GP5+/6+-PCR or longitudinal studies

International guidelines for HPV test requirements for primary cervical screening (formulated relative to HC2)

Candidate test should:

- Have a clinical sensitivity for CIN2+ not less than 90% of that of HC2 (women ≥ 30 years of screening population)
  - ➢ *to be tested on at least 60 samples of women with CIN2+*
- Have a clinical specificity for CIN2+ not less than 98% of that of HC2 (women ≥ 30 years of screening population)
  - ➢ *to be tested on at least 800 samples of women without CIN2+*
- Display intra-laboratory reproducibility and inter-laboratory agreement with a lower confidence bound ≥87%
- ➢ *to be tested on at least 500 samples of which 1/3 is positive with validated test*

Meijer CJ, *et al. Int. J Cancer* 2009

Follow-up of HPV positive women

Several candidate triage tests evaluated

- Cytology
- HPV 16/18 genotyping
- Combinations of these tests

Rijkaart et al Int.J Cancer 2011; Dijkstra et al CEBP 2013

Four baseline triage strategies for hrHPV positive women in VUSA-screen study

Triage strategy at baseline	CIN3+ risk in case of negative test	Percentage of women with colposcopy at baseline
Cytology	4.9	21.6
HPV16,18	6.6	32.4
HPV16,18,31,33 or 45	4.9	50.7
Cytology and HPV 16, 18	2.9	43.4

CIN3+ risk is too high (> 2%) to use in cervical screening: F-up necessary

Rijkaart et al IJC 2011

10 baseline plus 12 month follow-up strategies for HPV positive women

		Endpoint CIN3+			
Baseline triage test	Follow-up triage test	NPV %	PPV %	Repeat tests %	Colpo rate %
Cytology	**Cytology**	**99.3**	**37.5**	**78.4**	**33.4**
Cytology	hrHPV	99.6	19.5	78.4	65.7
Cytology	HPV type persistence	97.5	24.1	78.4	48.2
Cytology	HPV16,18 genotyping	96.9	28.7	78.4	38.5
Cytology	**Cytology/HPV16,18**	**99.5**	**27.9**	**78.4**	**45.4**
Cytology	**Cytology/HPV16,18 persistence**	**99.5**	**30.5**	**78.4**	**41.4**
Cytology	Cytology/HPV	100	19.4	78.4	66.6
Cytology/HPV16,18	**Cytology**	**99.7**	**25.6**	**56.6**	**49.9**
Cytology/HPV16,18	HPV type persistence	98.3	21.2	56.6	57.5
Cytology/HPV16,18	hrHPV	100	17.8	56.6	72.6

Four strategies had a NPV ≥98% and PPV ≥20%

Rijkaart et al IJC 2011

Conclusions

- HPV testing is at present the best primary screening tool for primary cervical screening

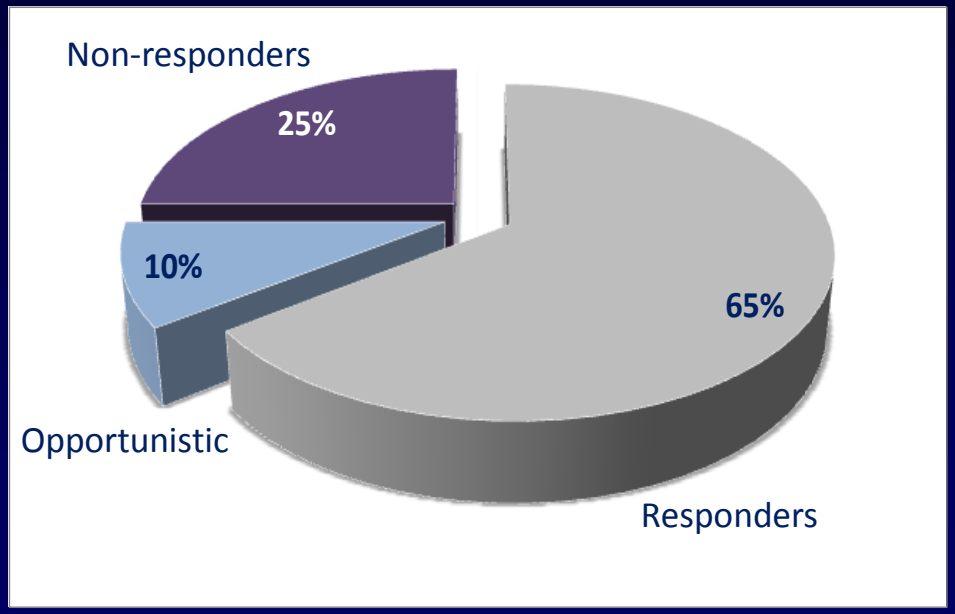
- Two follow-up strategies for HPV test positive women with normal cytology showed the best balances for negative risk stratification, colposcopy referral rates and ease of implementation:

  A) Baseline cytology and cytology in follow-up (6 or 12 months)

  B) Baseline cytology & HPV16/18 genotying and cytology in follow-up (6 or 12 months)

High compliance: offering self-sampling for HPV testing

Not all women are reached for cervical screening



- In the Netherlands: 75% of women is protected (programmed & opportunistic)
- 25% is not screened at all (non-responders)
  - 57% of carcinomas in this group

Two different self-sampling devices
(used for hrHPV testing)

PROHTECT 1
N=~ 28,000 (age: 29-60 years)
Year of non-attendance: 2005

Delphi screener (cervico-vaginal lavage)

Gök et al., BMJ 2010

PROHTECT 2
N=~ 26,000 (age: 29-60 years)
Year of non-attendance: 2006

Viba brush (vaginal brush)

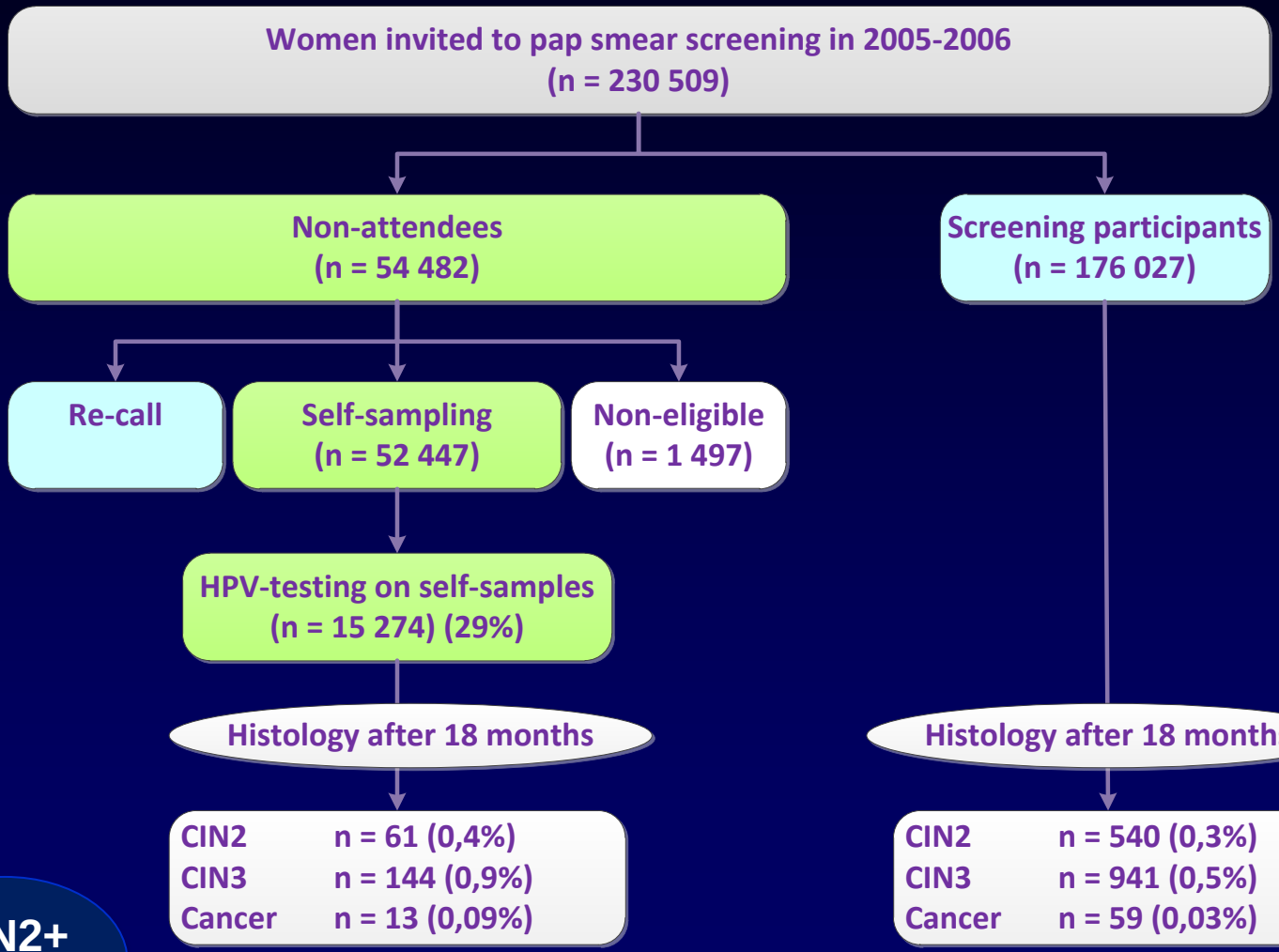
Gök et al., IntJCancer 2011

Offering self-sampling for HPV testing re-attracts non-attendees

Reference	Study design	Method (self vs clinician)	Attendance rate
Gok et al. (2010)	Self-sampling vs recall letter (99:1) 28,073 non-responders	Self-sampling (Delphi Screener) vs cervical smear	**Self: 27.7%** Recall letter: 16.6% **P<0.001**
Gok et al. (2011)	Self-sampling vs recall letter (99:1) 26,409 non-responders	Self-sampling (VibaBrush) vs cervical smear	**Self: 30.8%** Recall letter: 6.5% **P<0.001**
Bais et al. (2007)	Self-sampling vs recall letter (9:1) 2830 non-responders	Self-sampling (VibaBrush) vs cervical smear	**Self: 34.2%** Recall letter: 17.6% **P<0.001**
Sanner et al. (2009)	Self-sampling (no control group) 2829 non-responders	Self-sampling (Qvintip) on demand	**Self: 39.1%**
Virtanen et al. (2011)	Self-sampling vs recall letter (1:2.7) 4160 non-responders	Self-sampling (Delphi Screener) vs cervical smear	**Self: 29.8%** Recall letter: 26.2% **P = 0.02**
Virtanen et al. (2011)	Self-sampling vs recall letter (1:2.7) 8699 non-responders	Self-sampling (Delphi Screener) vs cervical smear	**Self: 31.5%** Recall letter: 25.9% **P<0.001**
Szarewski et al. (2011)	Self-sampling vs recall letter (1:1) 3000 non-responders	Self-sampling (cotton swab, Qiagen) vs cervical smear	**Self: 10.2%** Recall letter: 4.5% **P<0.001**
Giorgi Rossi et al. (2011)	Self-sampling vs recall letter. 2480 non-responders	Self-sampling (Delphi Screener) vs cervical smear	**Self: 19.6%** Recall letter: 13.7% **P=0.007**
Wikström et al. (2011)	Self-sampling (n=2000) vs recall letter (n=2060)	Self-sampling (Qvintip) vs cervical smear	**Self: 39.0%** Recall letter: 9.0% **P<0.001**

Snijders et al Int J Cancer 2012

Comparing yields CIN2+/3+ in non-responders with screening responders



CIN2+ 1.4%

CIN2+ 0.8 %

Gök et al., Eur J Cancer 2012

HPV screening strategy as proposed by the Health counsil for the Netherlands

- Clinically validated HPV test as primary screening test
- Triage by cytology (threshold ≥BMD or ASC-US/LSIL) at baseline and 6 months and referral for colposcopy if cytology is positive
- Preferred screening scenario: HPV test at 30, 35, 40, 50, 60 years of age
  - Women (at 40,50 or 60 years) who are HPV positive and 2x cytology negative should be re-screened after 5 years by HPV and cytology testing (~2.5%)
- Vaginal self-sampling for HPV testing for non-attendees in screening program

Current status

- 2013: Performance test executed by the RIVM, the oranisation that is responsible for screening
- 2013: Minister has approved cervical screening ‘new style’ with primary HPV testing
- 2016: Implementation expected

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