Changing the concept of cervical cancer screening in Europe –
The example of HPV DNA introduction

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HUMAN PAPILLOMAVIRUS

- Large family of virus affecting many species.
- HPV types are linked to benign diseases but also to CANCER
- There is no treatment available

Bravo et al. 2010
• HPV is a common sexually transmitted infection with high prevalence in young adults, generally asymptomatic and spontaneous cure.

• When HPV persists the risk of cancer is very high.

• HPV is the primary cause of cervical cancer.
CERVICAL CANCER

MAIN RISK FACTOR: LACK OF SCREENING
HPV 16/18 are most common oncogenic types
CERVICAL CANCER BURDEN IN EU-27

Europe/EU new cases x year 54,323/31,038

Each hour **2** women die from invasive cervical cancer in the EU

Each hour **4** women are newly diagnosed with invasive cervical cancer in the EU

Estimates derived from IARC Globocan 2008: 31,038 annual new cases of CC and 13,430 annual deaths in the EU-27 during 2008
Top 20 European countries in incidence and mortality of cervical cancer, 2008

Lowest in Europe 2.06 Malta

ASR (W) per 100,000

Ferlay J, Shin HR, Bray F, Forman D, Mathers C and Parkin DM.
GLOBOCAN 2008, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 [Internet].
MAIN PREVENTION STRATEGIES

HPV INFECTION

PRIMARY PREVENTION: VACCINATION

SECONDARY PREVENTION: SCREENING

15 years old 30 years old 45 years old 60 years old
Cervical cancer is an appropriate disease for screening

- Important public health issue
  - > 500,000 new cases x year
- Precursor lesions can be treated in
  - a safe, effective and acceptable way
- Long latency
- Acceptable and valid screening tools
1928-Improving cervical cancer screening -2011

Morphology

normal

HSIL CIN2

LSIL

HSIL CIN3

ASC-US
1990s “the DNA era”

HPV DNA

High Risk DNA:
Positive/Negative
HPV DNA testing up to 2011

- Large studies & randomized trials
- FDA /CE approved: HC2; COBAS 4800, Cervista
- High sensitivity and high NPV
- Highly standardized.
- Indication: primary screening and triage
- Outcome: predicts advanced precursors and can reduce mortality
• Detection of infection although predicts precursors of cancer.
• Referral to colposcopy can be higher than with cytology
• Need target age constraints to avoid detection of acute HPV infections
Detection of CIN2+ by standard cytology or HPV testing (HC2) is significantly higher with HPV.

- Point estimates and 95% CI. The size of the box is proportional to the size of the study.
- Summary estimates of all studies

HPV testing predicts disease. HPV negative with or without cytology behave similar.

At entry:
HPV +ve & Normal PAP

Fig 2 | Kaplan-Meier plots of cumulative incidence rate for CIN3+ for women according to baseline test results in first 72 months of follow-up, excluding Denmark and Tübingen.

Dillner et al 2008
Clinical validation studies: Over 180,000 women!

- UK, ARTISTIC, Kitchener et al. 2009
- Finland, PTH, Kotaniemi-Talonen et al. 2005
- Sweden, Swedscreen
- The Netherlands, POBASCAN, Bulkmans NW et al. 2007
- Italy, NTCC trial, Ronco et al. 2006
- India, Sankaranayanan et al. 2009
- Canada, Mayrand et al. 2009

- US, ATHENA, Stoler et al. 2011 (ASC-US)  Cobas
- CHINA, SHENNCAST, Belison et al.  Cervista

Cuzick et al 2006; Lynge E et al. 2009
Implementation of HPV screening in the general population and risk-adapted strategies

• In Wolfsburg, Germany
  – Women are offered **concomitant cytology and HPV DNA (HC2)**.
  – Among 16724 women, 104 CIN3 cases were detected in 3 years all of them in the HPV +ve branch, Cytology captured only half of them.

• In Catalonia, Spain,
  – Women >40 y.o. with poor screening history women are offered **concomitant cytology and HPV DNA (HC2)**.
  – HC2 predicted over 18 times more CIN2+ and 8 times more invasive cancer than observed in the general population. Sensitivity was 100% for HC2 and 46% for Pap.

• The Netherlands a nation wide program introducing HPV DNA as primary screening.

Luyten et al. 2009; Ibañez et al. 2012, HPV TODAY
Number of cases detected at first and second screening rounds with HPV or PAP

- CIN2
- CIN3/AIS
- Cancer

Graph showing the number of cases detected at each round.
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VACCINATION

SCREENING
HPV available vaccines could help to reduce a major burden of HPV related disease

- ANUS: 87% HPV-16, 6% HPV-18, 93% HPV 16/18
- VULVA: 80% HPV-16, 11% HPV-18, 91% HPV 16/18
- VAGINA: 77% HPV-16, 11% HPV-18, 88% HPV 16/18
- PENIS: 60% HPV-16, 13% HPV-18, 73% HPV 16/18
- CERVIX: 61% HPV-16, 10% HPV-18, 71% HPV 16/18

References: de Vuyst 2009 Int J Cancer, Miralles 2009 J Clin Pathol; de Sanjosé 2010 Lancet Oncology
Percent reduction in Cervical Cancer Incidence in Spain

- **VACCINATION + SCREENING**
  - Cytology-HPV combined: 93%
  - Cytology with HPV triage: 90%
  - Cytology alone: 89%
  - 5-year

- **VACCINATION ALONE**
  - at age 11: 62%

- Strategies with a favorable cost/effective ratio

*Diaz et al. 2010*
Investigators from The Netherlands, Finland, UK, Italy, Spain, Belgium, France

- To provide **to policy makers, scientists and other cancer prevention stakeholders** with the best available relevant data to facilitate decisions on current and novel options for the prevention of cervical cancer and other HPV-associated diseases in Europe.
Conclusions

• HPV cause major burden of disease
• Prevention is possible through screening and vaccination
• Interventions have to be valued in terms of:
  – Equity
  – Affordability
  – Cost-benefit
• The best option in developed countries is population based screening with wide intervals and highly validated screening test and vaccination of young girls.
• In countries with poor infrastructure, vaccination may be the unique acceptable option.
Thank you for your attention!