European recommendations on cervical cancer screening

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INTRODUCTION

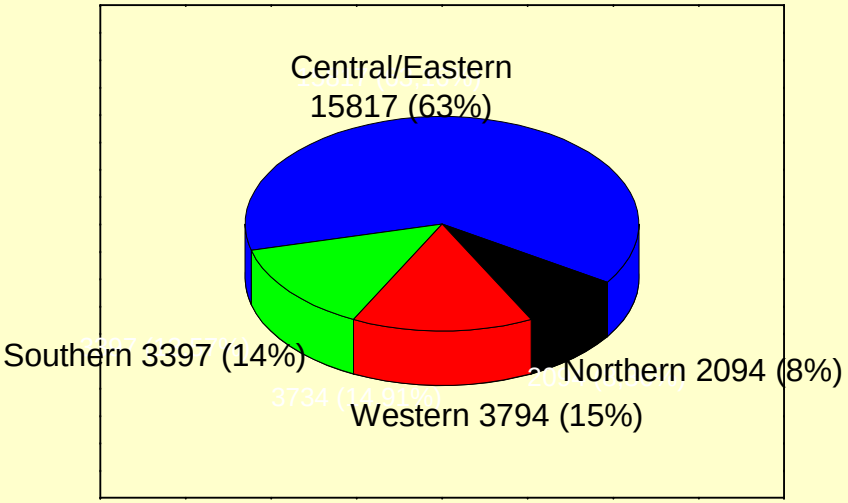
- Well-organised cytology-based screening, with histological confirmation of pre-cancers and excision of the lesions, for cervical cancer can prevent incidence and mortality from invasive cervical cancer by 80% or more (IARC, 2005)
- Evidence growing on the efficacy of novel methods in primary screening, particularly on Human Papillomavirus (HPV) testing
  - ❖ Essential: the balance between benefit and potential harm
- The Council of the European Union has recommended organised, population-based approach for cancer screening programmes

Purpose of the presentation

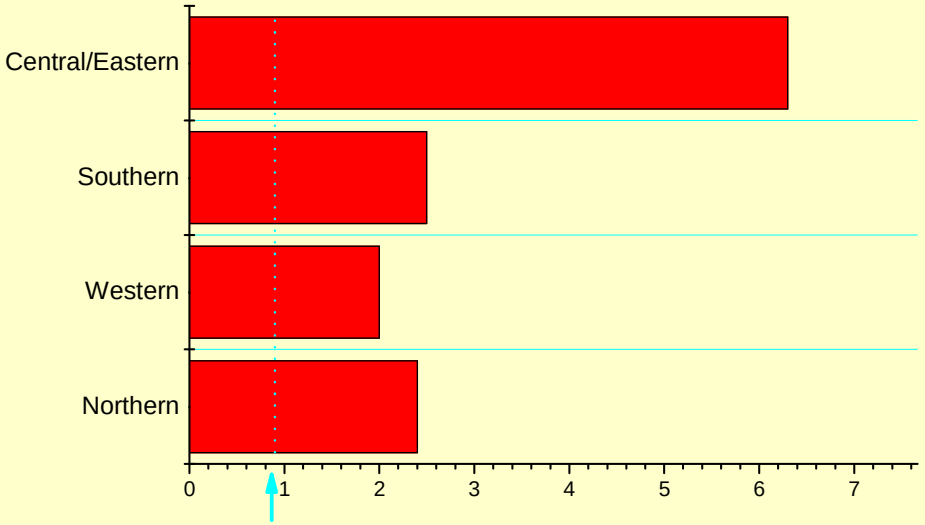
- Describe the current evidence and recommendations for cervical cancer prevention with emphasis on screening
- Discuss implementation of cervical cancer screening programmes
- Discuss implementation of new methods in cervical cancer screening

Cervical cancer in Europe

- 54,300 new cases and 25,100 deaths estimated in a year (Ferlay et al. 2010; Globocan 2008)
- In the EU countries (n=27), the estimated numbers are 31,400 and 13,600

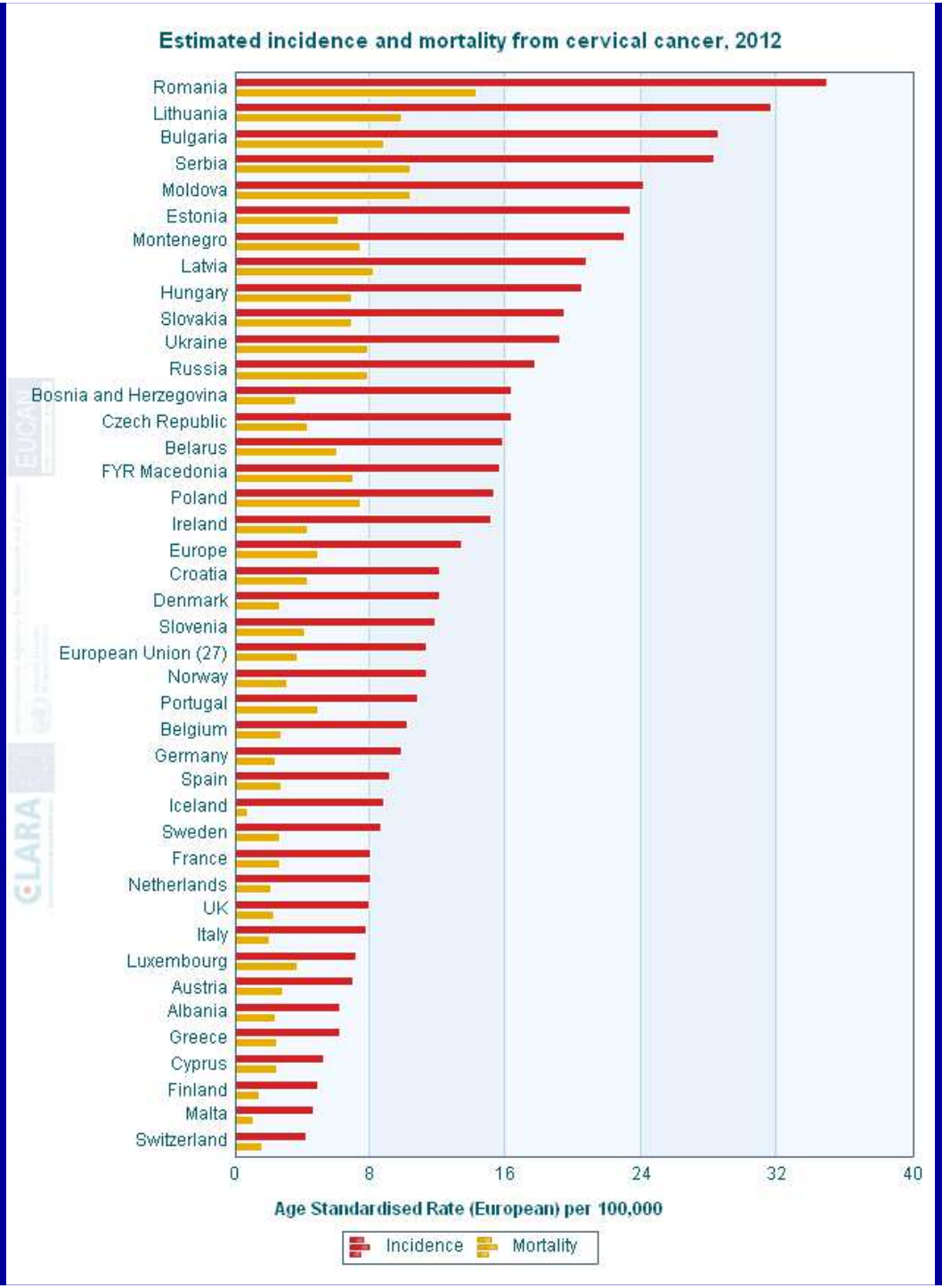


Numbers of deaths from cervical cancer in Europe (Globocan 2008)



Age-adjusted (ASR(W)) mortality rate from cervical cancer in Europe (Globocan 2002)

http://eco.iarc.fr/



Reduction in the cumulative rate of invasive Sq Cx Ca over the age range 35-64 years, with different frequencies of screening (IARC 1986)

Screening frequency	% reduction in the cumulative rate	Number of tests
1 year	93.5	31-44
3 years	90.8	12-15
5 years	83.6	7-8
10 years	64.1	4

Assuming a negative screen occurring at age 35 years, and that a previous negative screen had been performed

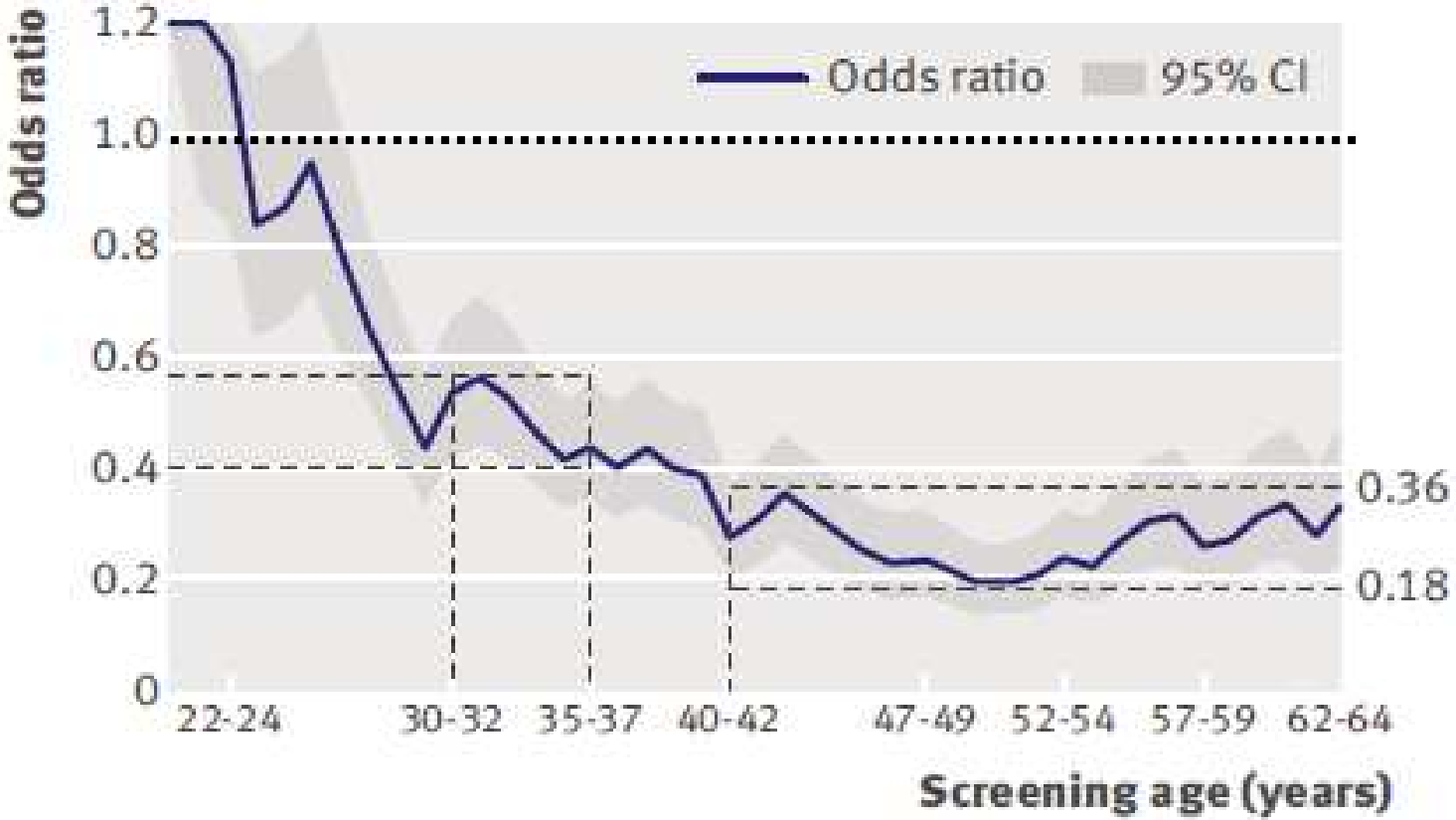
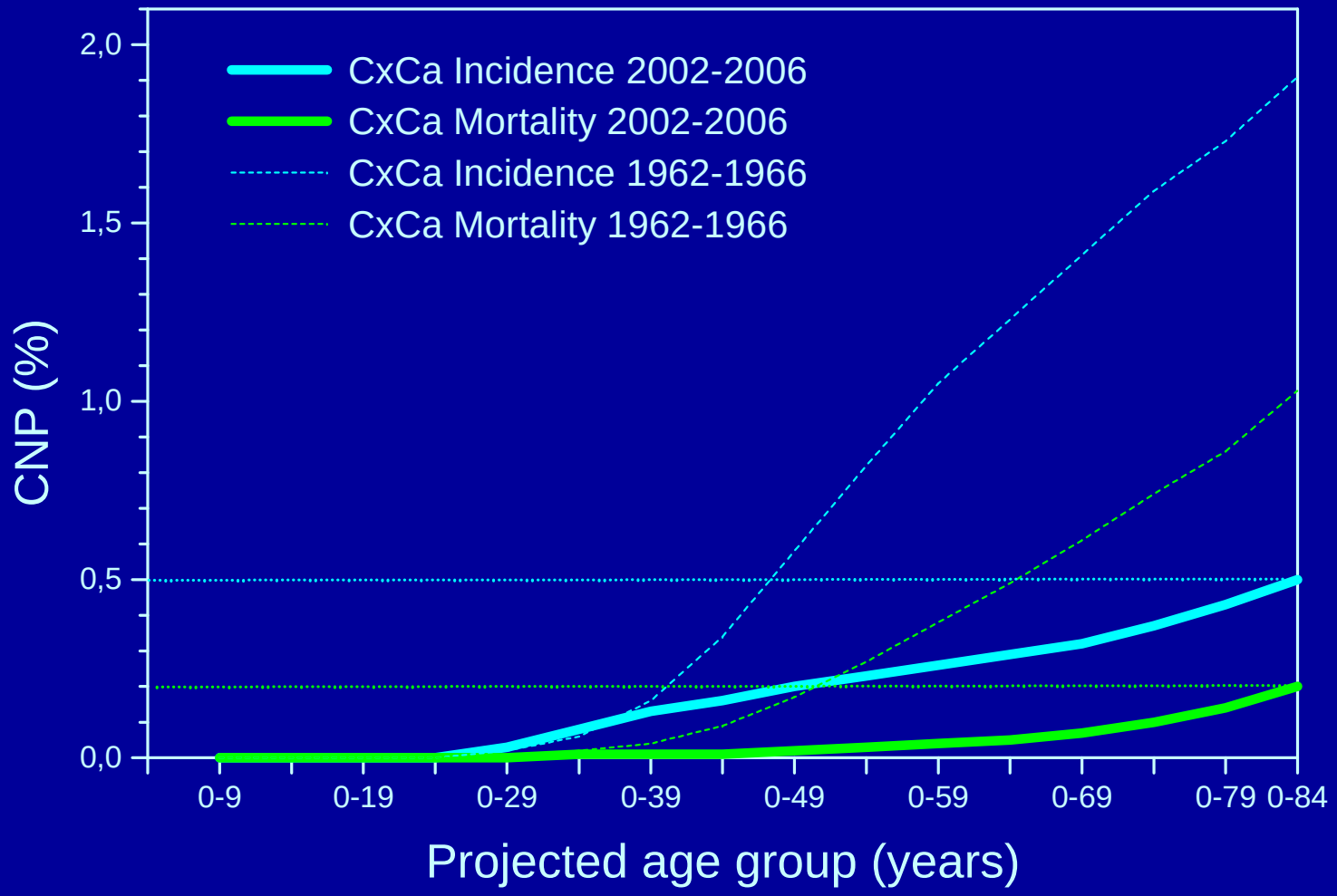


Fig 2 | Odds ratio for developing invasive cervical cancer stage IA or worse (in the next five year interval) in those screened in a given (three year) age band compared with those not screened in that age band (or in two previous years). Odds

Sasieni & Cuzick, BMJ 2009

Cumulative net probability of cervix carcinoma in Finland, 1962-1966 vs. 2002-2006, in % among women by age (Finnish Cancer Registry, 2008)



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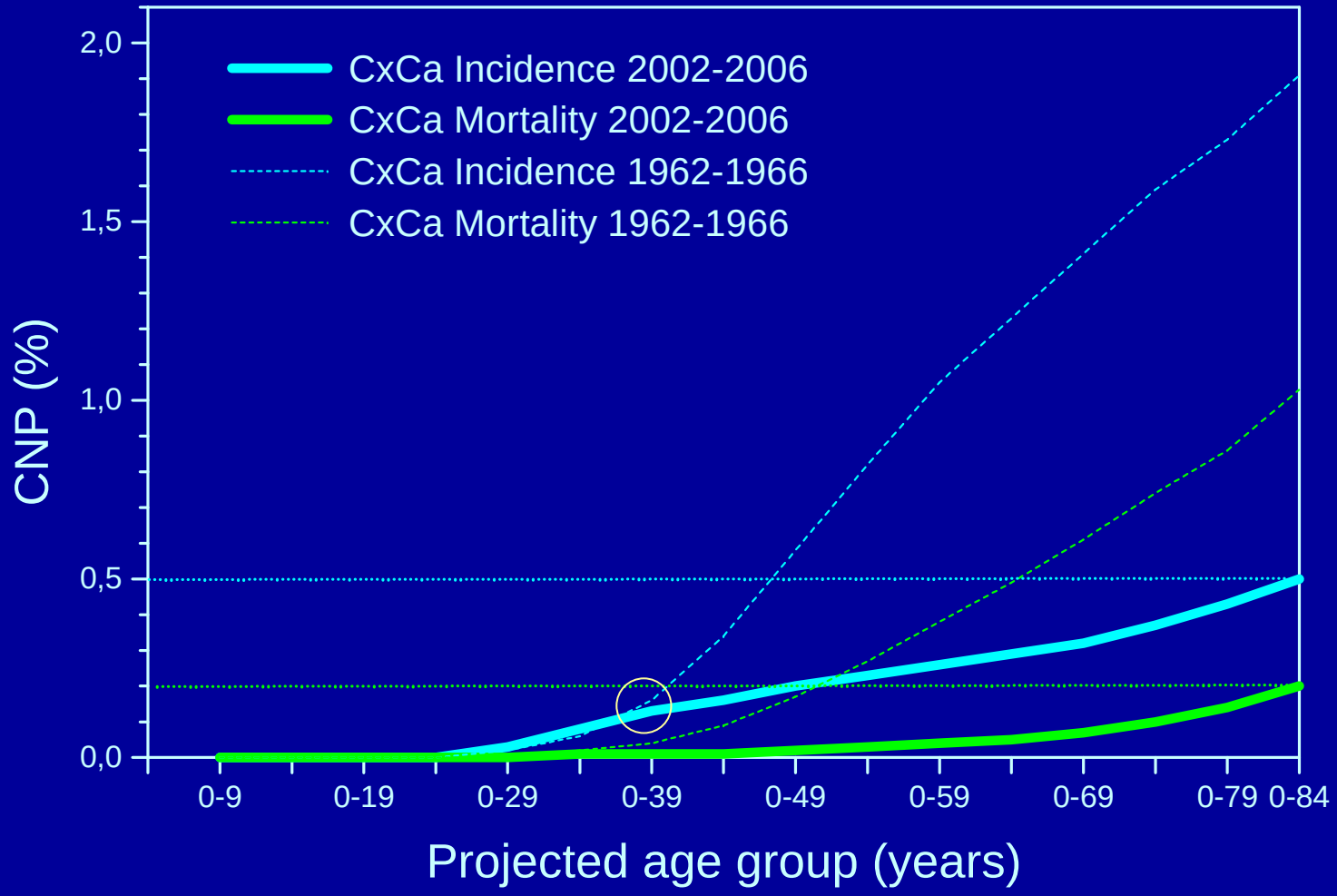


Natural history of CIN and cervical cancer

- Length of pre-cancer phase on average 10-12 years
- Progression rates of CIN to invasive cancer (Oortmassen & Habbema, 1991)
  - 16% in lesions in age 18-34 years
  - 60% in lesions in age 35-64 years
- Among 13 – 22 –years old girls and women up to 90 % of pre-cancer lesions regress naturally even in rather short-term follow-up (Moscicki et al.)

PURPOSE OF POPULATION-BASED CERVICAL CANCER SCREENING

- Prevent mortality from invasive cervical cancer, also incidence can be prevented effectively
- Improve quality of life
  - Less invasive treatment if cancer treated early, or a precancer treated
    - Essential to develop QA of the whole diagnostic and clinical chains of the programme
  - Diagnosis of cancer or precancer at earlier age bring adverse aspects to the quality of life

Organized, Population-based Screening Recommended by the EU Council (12/ 2003)

- **Provide population-based cancer screening only in organised programmes:**
  - Evidence-based & cost-effective screening policy with an appropriate balance between benefit and harm
  - Appropriate QA at all levels, with systematic monitoring and outcome evaluation
  - Proper information among population and health-care professionals
  - Not start a new programme before the efficacy evaluation has provided adequate evidence

Quality Primate of Cancer Screening - 1

- Screening is applied to predominantly healthy populations
- The needs and concerns of healthy clients (population) differ significantly from those of symptomatic patients
- Because the vast majority of participants in cancer screening are not affected by the target disease, only a few will have a health benefit from screening
- All participants are exposed to the risks of screening
- The risks, even if only slight, may collectively shift the balance between harm and benefit into an inappropriate range

Contents of the Guidelines, Cx/EU

Epidemiological Guidelines

Methods for screening and diagnosis

Cytopathology laboratory guidelines

Histopathology

Managament of abnormal cytology

Key performance indicators

Annexes and appendices

European screening policy

With cytology-based screening, programme should start in the age range 20 -30, but **preferably not before age 25 or 30 years**

It is recommended to continue screening at 3- to 5-year intervals **until the age of 60 or 65**

- Stopping screening in older women is probably appropriate among women who have had three or more consecutive previous (recent) normal cytology results
- Special attention should be paid to the problem of older women who have never attended screening as they exhibit increased risk for cervical cancer

Opportunistic screening should be discouraged

Evidence on optimal starting and stopping ages and on intervals need to be acquired within programmes

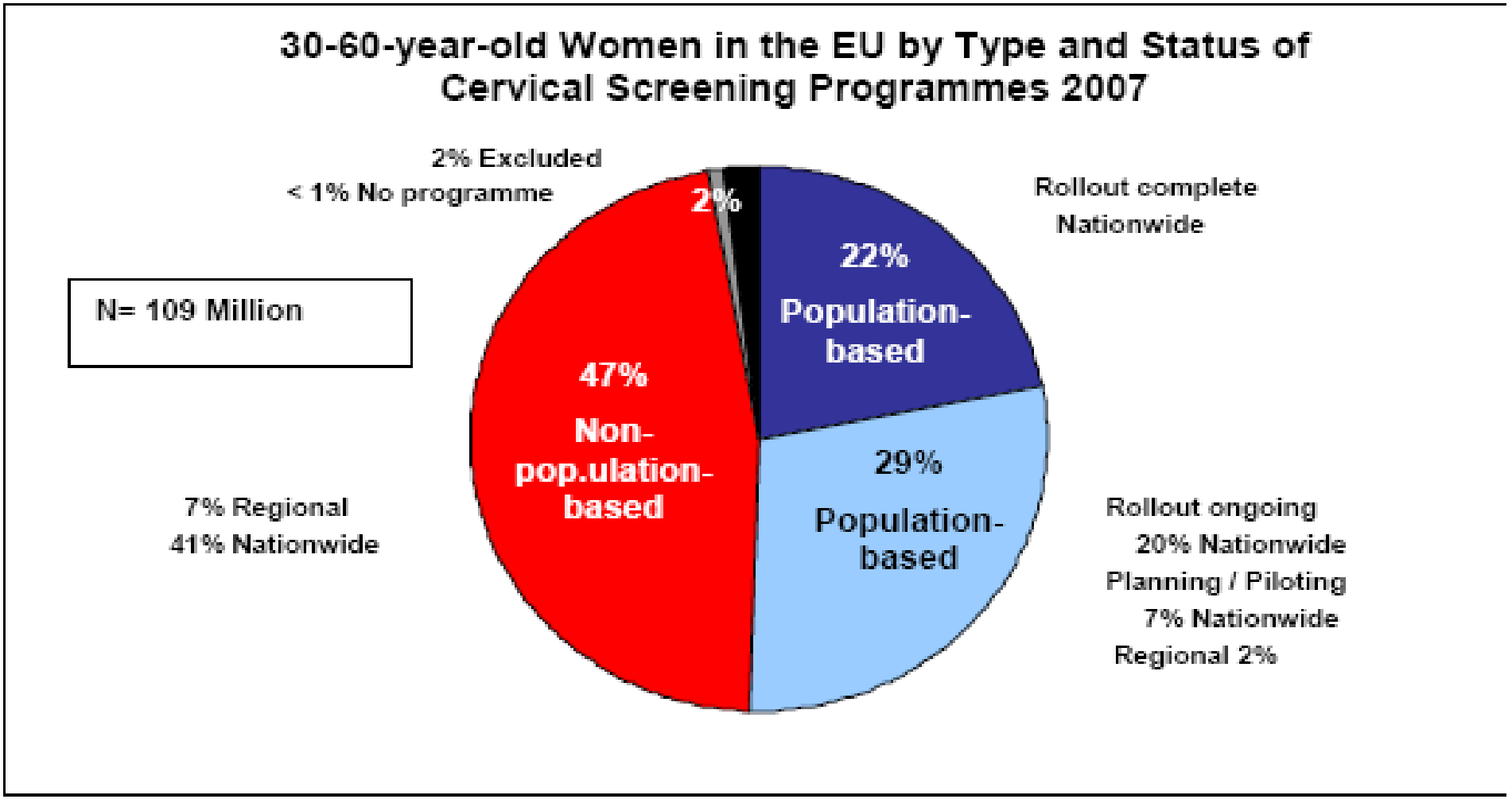


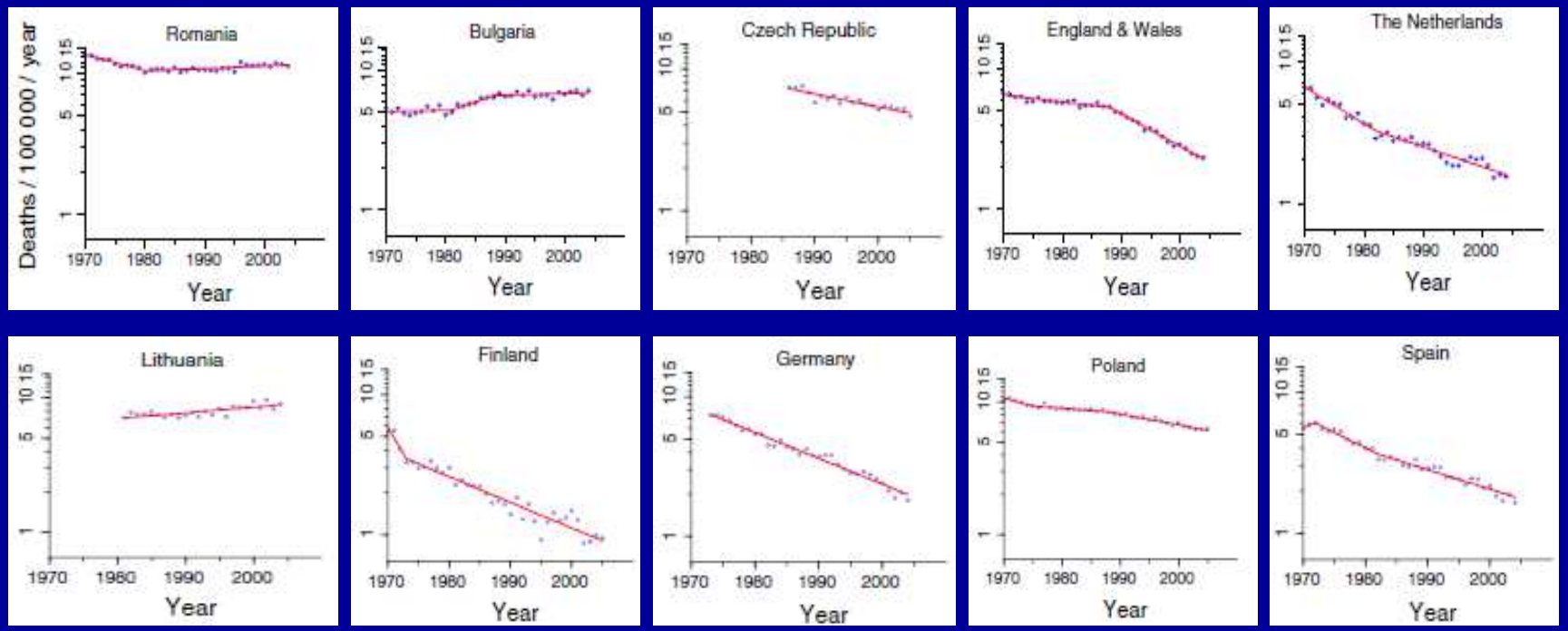
Figure 4 c. Proportion of 30-60-year-old women in the European Union targeted for cervical cancer scree in 2007, by programme type and country implementation status, and women excluded due to age or lac regional programmes in countries with regional implementation status (proportions of 30-60-year-old wome the EU population in %). For definitions of programme type and status see the text (section 2.3).

Source: European Commission (DG SANCO, 2007); IARC (ECN and EUNICE projects, 2007)

Examples of screening policy for cervical cancer in EU countries (Anttila et al. EJC 2009)

	Target age	Screening interval (years)	Smears per woman lifetime	Population-based	Non-population based
Czech Republic	25-69	1	45	No	Yes
Finland	(25)30-60(65)	5	7 (9)	Yes	Yes
Germany	20+	1	50+	No	Yes
Lithuania	30-60	3	11	No	Yes
Netherlands	30-60	5	7	Yes	No
Slovenia	20-64	3	15	Yes	Yes
Spain	(18)30(35)-(50)59(65)	3 or 5	5-15	Regional	Regional
Sweden	23-60	3 or 5	12	Yes	Yes
UK (England)	(20)25-(60)64	3 or 5	10-16	Yes	No

Estimated/re-allocated age-adjusted mortality trends from cervical cancer in some EU member states (Arbyn et al., 2009)



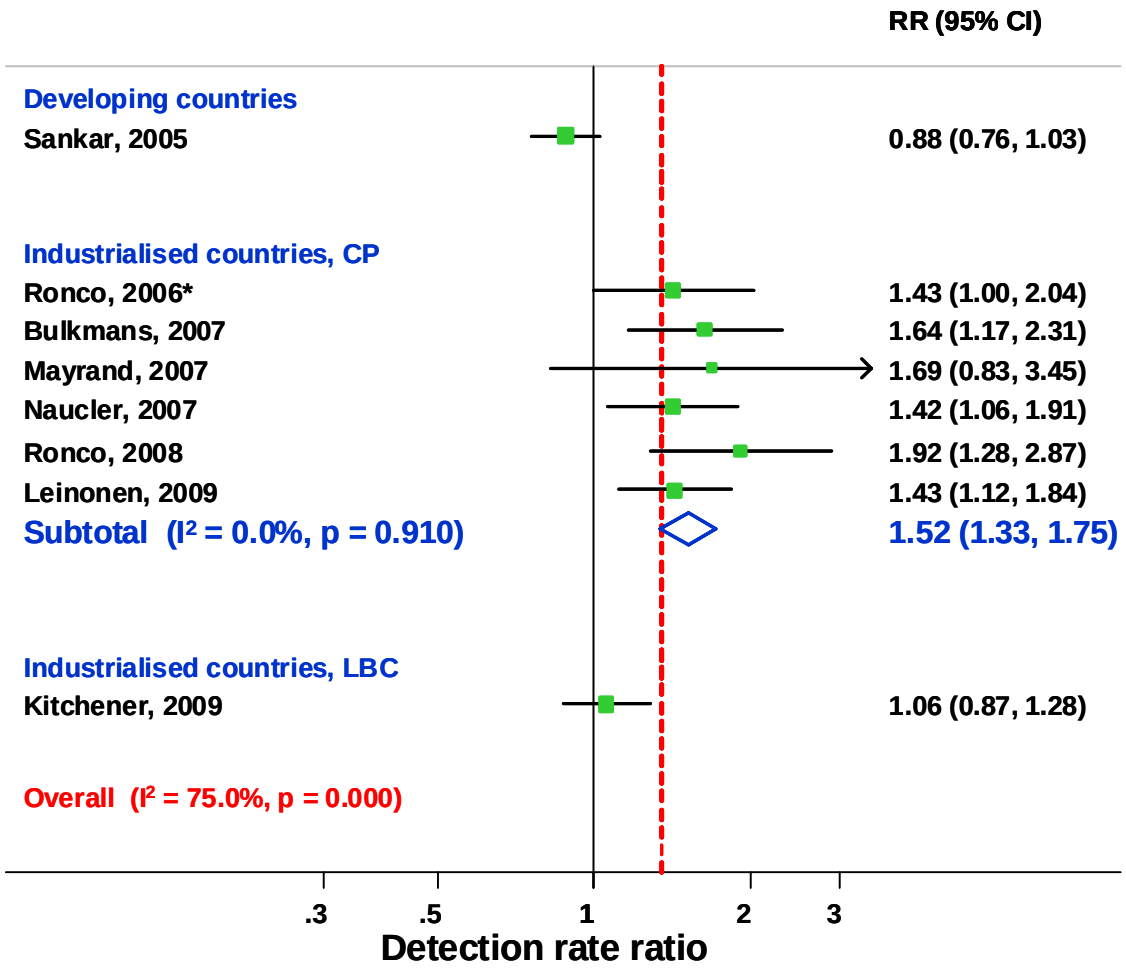
EUROPEAN JOURNAL OF CANCER 45 (2009) 2640–2648

Where can a screening programme fail in its effectiveness?

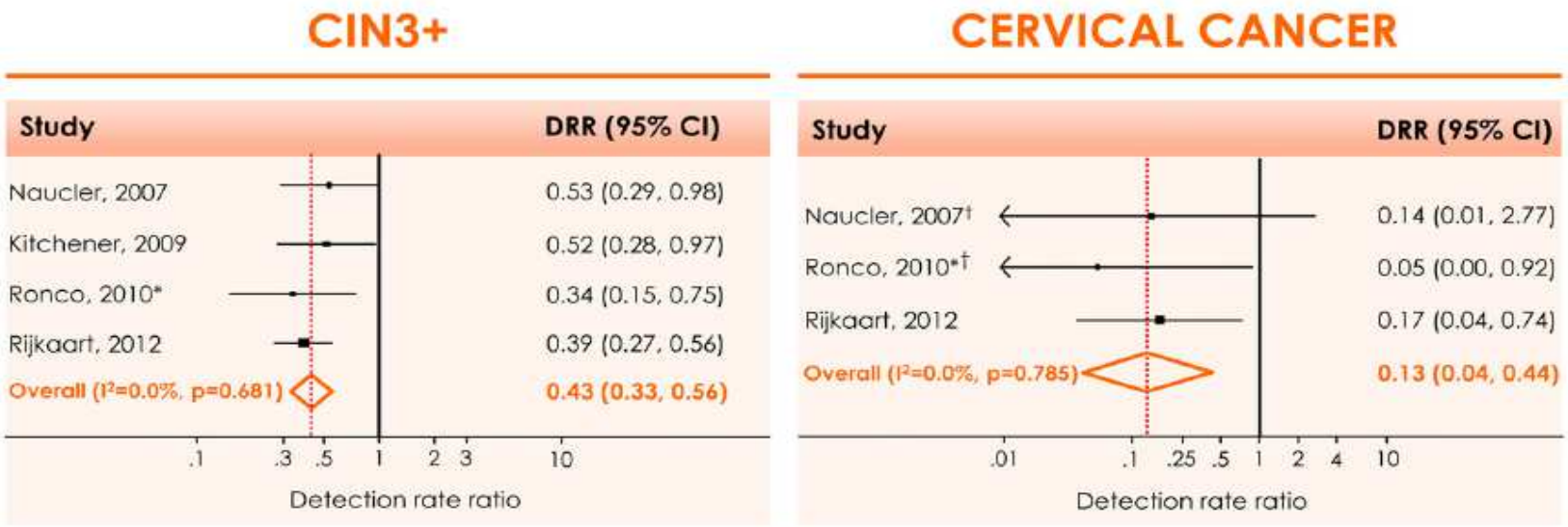
- Women remain unscreened or underscreened – even though a large proportion of the population may be screened frequently
  - Good information among the population and medical personnel is a key to achieve acceptance to optimal policy
- Sampling or diagnostic error in screening test
  - More common in Europe than usually thought
- Sampling or diagnostic error in triage or confirmation
- Management error; e.g. drop-out prior to management or in the management follow-up, or inappropriate management procedure
- Optimal treatment of cancer - not yet available throughout the Europe

All these programme components need systematic quality assurance, and should be monitored and evaluated continuously as defined in the European QA Guidelines. Errors and drawbacks must be corrected

New methods in cervical cancer control



Detection of CIN2+ in eight randomised trials identified by hrHPV testing versus cytology. * restricted to women older than 35 years.
Source: M.Arbyn EUROGIN 2009



* restricted to women of 35 years or older.
† continuity correction (+.5 in each cell because of zero cancer cases among HPV-negative women).

Fig. 7. Meta-analysis of the main outcomes from randomised trials comparing HPV- and cytology-based cervical cancer screening. Relative detection rate of CIN3+ (left panel) and cervical cancer (right panel), observed in the second screening round among women who were HPV-negative versus cytology-negative at enrolment. See web table liststudies.xls-screening for publication information. CI: Confidence interval; CIN: Cervical intraepithelial neoplasia; DRR: Detection rate ratio; I^2: the percentage of total variation across studies due to heterogeneity; p: test for inter-study heterogeneity.

Please cite this article in press as: Arbyn M, et al. Evidence Regarding Human Papillomavirus Testing in Secondary Prevention of Cervical Cancer. Vaccine (2012), http://dx.doi.org/10.1016/j.vaccine.2012.06.095

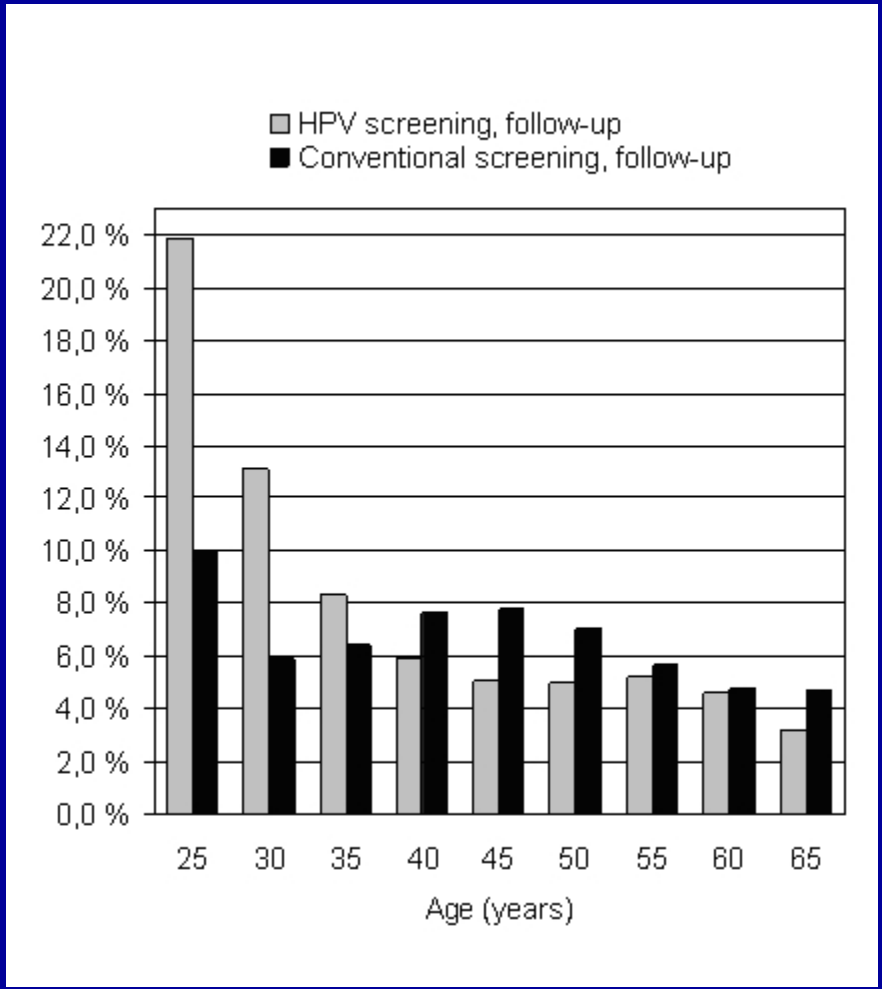
Frequency of recommendations for intensified screening at recruitment

- 2581 recommendations in the HPV arm, 2340 in the conventional arm during 2003-2005
- 9% more recommendations

  in the HPV arm overall

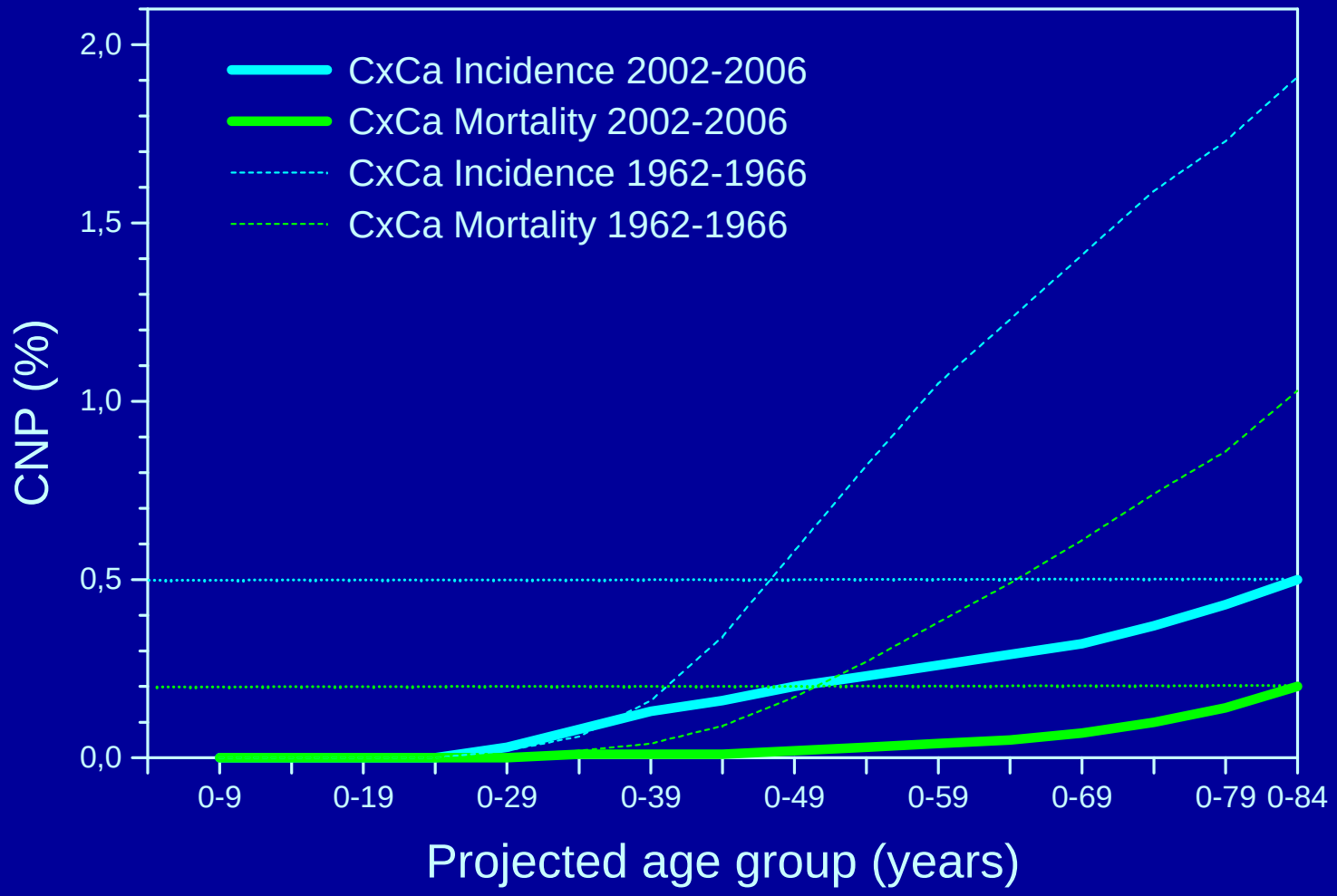
  (95% CI 3-15%)
- From age 40 onwards, rate was constantly lower in HPV arm
- The rate was modified by age in both arms (p-value for age,

  and for the interaction term 'age x arm' < 0.001)



Leinonen et al. JNCI 2009

Cumulative net probability of cervix carcinoma in Finland, 1962-1966 vs. 2002-2006, in % among women by age (Finnish Cancer Registry, 2008)



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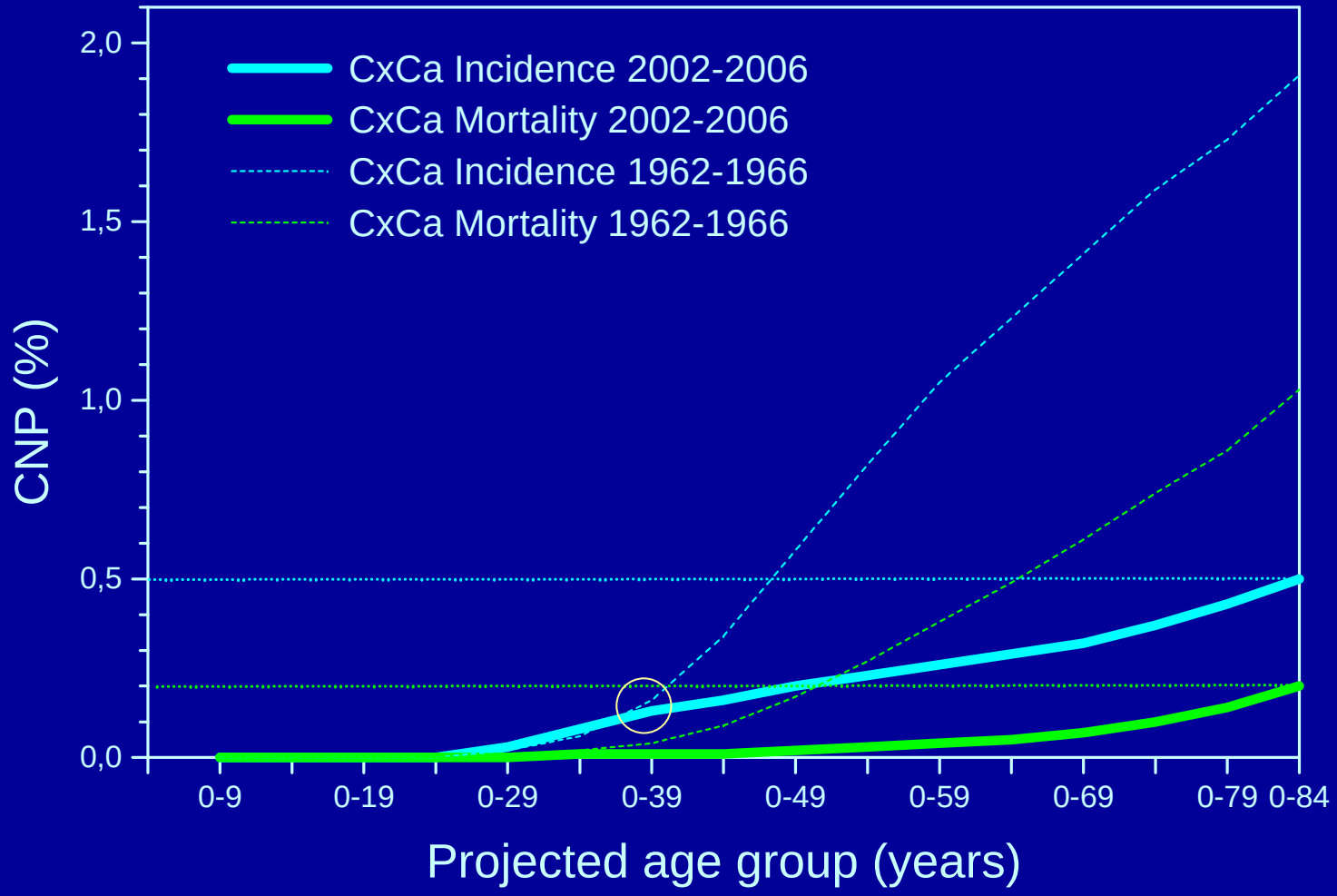

CIN3+ cumulative incidence after screening visit (Dillner ym., BMJ 2008)

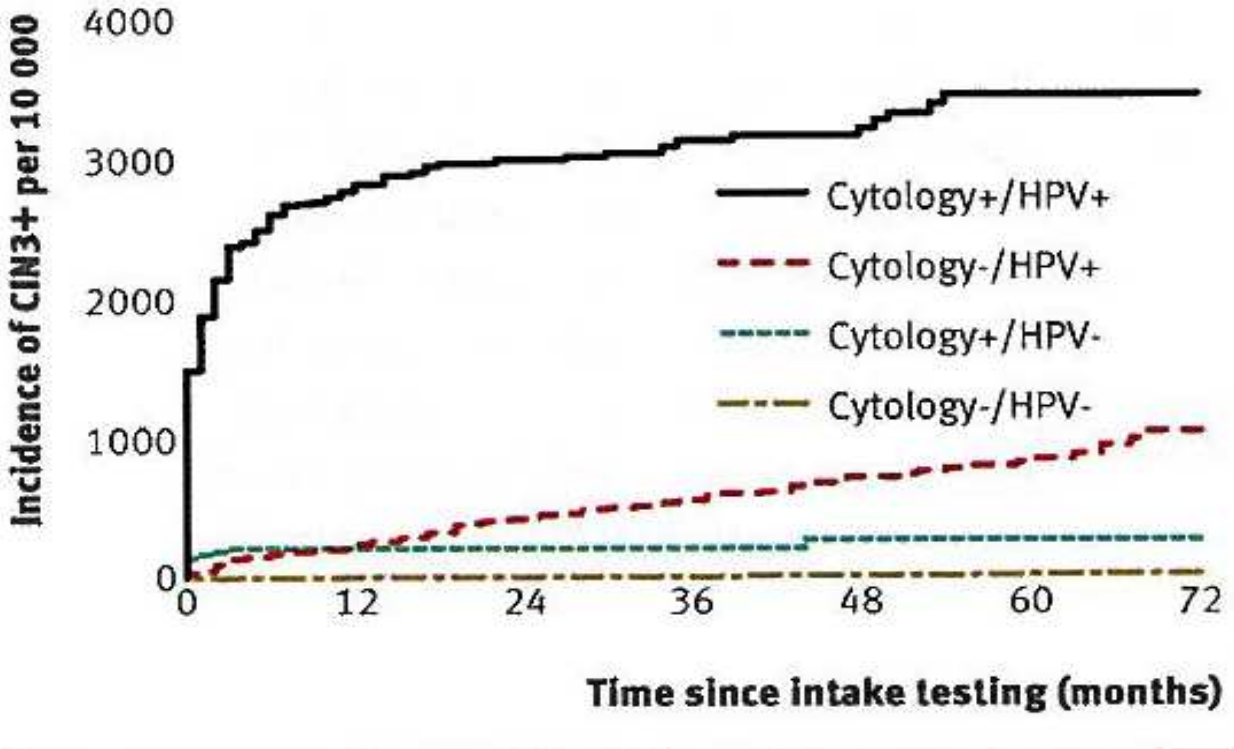

Fig 1 | Kaplan-Meier plots of cumulative incidence rate for CIN3+ for women according to baseline test results in the first 72 months of follow-up in all seven countries

Conclusions, HPV screening

Organised screening modality in a key for HPV screening, organisation even more important for HPV test than for conventional methods

- Under-screened need to be identified
- Invitation with scheduled intervals and age-groups
  - **Do not start HPV testing before age 35 (30 can be sometimes considered)**
- Screening test negatives: back to normal schedule with a long interval
  - **At least 5-6 years is safe; interval possibly up to 10 years (CIN3+ data)**
- Quality-controlled management of screen positives
  - **Avoid double-testing; triage of hrHPV positives can be done by diagnostic cytology**
- Systematic registration, monitoring and outcome evaluation
- Appropriate information integrated, based on evaluation

Planning and piloting according to these principles in organised programmes recommended in the EU guidelines (2008, 2nd Edition)

Guideline supplements on primary HPV testing and implementation of population-based HPV-vaccination programmes under preparation

Considerations to move towards organised CxCa screening in Europe

- Improve adherence to population-based work models
  - Education, training, attitudes among medical professionals
  - **Planning and piloting** invitational & information systems to demonstrate good participation in women, high quality or the service, as well as acceptance to avoid overuse of services
  - Legal frameworks enabling QA and organised screening
  - **Other regions** that those leading the developments by the pilot programmes can have the current policy and switch to the new policy as soon as it has been demonstrated to work well enough

Considerations to move towards organised CxCa screening in Europe (2)

- Reducing ineffective use of services related to adverse aspects and costs
  - Target appropriate age range -- not start at too early age
  - To reduce lifetime tests provided for healthy women
  - Include all tests and treatments in the evaluation systems
- Introduce new methods in organised programmes rather than in opportunistic services

Examples of barriers to organised screening among medical professionals and practitioners

- ”Culture” of opportunistic services; role of medical practitioners in private ambulatories does not include systematic screening ’chain’ Arbyn et al. 2009; Viberga et al. 2010
- Key professionals may need extensive re-training after using non-standard methods over decades Viberga et al. 2010 or if properly trained staff is lacking Nicula et al. 2009
- Insufficient communication and interaction with decision-making Todorova et al. 2006; Nicula et al. 2009;
  - Insufficient knowledge regarding **natural history** and **effectiveness** of screening programmes
  - Insufficient organisational models & financing

Actual steps what to do, with estimated duration of the phase

To reach a population-based national programme

- Careful **planning and feasibility** phase, based on the national consensus [**1- 3 years**]
- **Pilot phase**: randomised or non-randomised settings, depends whether performance only or also outcome evaluation is included [**3 to 10 years**]

  New modifications may be needed
- **Nationwide rollout** [**5-10 years**]

The above indicates the quickest possible alterations. It may take 15-20 years until the **full** population-based impact will be there

Mathematical cost-effectiveness simulation of simultaneous control strategies for HPV-induced disease burden in Finland

H.Salo, S.Vänskä, P.Nieminen & WORKGROUP, THL June 2011

Screening policy scenario	CIN1 cases	CIN2 cases	CIN3 AIS cases	CxCa cases	QALY loss	Cost million euro	Δ cost million euro	ICE euro /QALY gain
Organised throughout 30 to 60 (5y)	260	417	885	187	1507	14.4	baseline	baseline
Organised throughout 25 to 60 (5y)	367	552	959	157	1367?	15.8	+1.4	10,000?
Organised throughout 30 to 70 (5y)	278	445	946	155	1294	16.2	+1.8	8,451
Organised throughout Cytology: 25-34 (5y) HPV: 35 to 65 (5y) +HPV Exit test at 70	459	675	1035	98	985?	17.9	+3.5	6,705?
Current organised and non-organised	621	775	901	137	1375	34.0	+19.6	148,485

Consequences for HPV vaccination

- Effectiveness of vaccination variable, depend on coverage by vaccinated age groups, screening intensity, and developments in screening methods
- Vaccination alone, without simultaneous changes to improve overall cost-effectiveness screening services, would not be enough to reduce the costs by opportunistic pap smear testing, and CIN and *mild* cytological abnormalities in the young female population
- Instead of incremental cost-effectiveness on vaccination, guidance should be based on overall cost-effectiveness taking all prevention strategies simultaneously into account

Table 1. Current status of HPV immunisation programmes in EU/EEA countries (data adapted from the VENICE 2 Report, WP 3, Dec 2010 and from the official national immunisation programmes)

	Introduction	Target age group	Coverage (three doses, %)	Financing	Delivery infrastructure
Austria [5]	2006	9-15 (female and male)	n/a	Fully covered by patient	Private sector (100%)
Belgium [6]	2007	10-13	n/a	75% supported by national health authorities	Private sector (100%)
Bulgaria [7]	No*	-	-	-	-
Cyprus [8]	No	-	-	-	-
Czech Republic [9]	No*	-	-	-	-
Denmark [10]	2008	12	79 (2011)§	Fully covered by national health authorities	PH (100%)
Estonia [11]	No	-	-	-	-
Finland [12]	No	-	-	-	-
France [13]	2007	14	24 (2008)	65% supported by national health authorities	PH (5%), Private sector (95%)
Germany [14]	2007	12-17	n/a	Fully covered by national health authorities	PH (5%), Private sector (95%)
Greece [15]	2008	13-18	n/a	Fully covered by national health authorities	PH (30%), Private sector (70%)
Hungary [16]	No	-	-	-	-
Iceland [17]	2011	12	n/a	Fully covered by national health authorities	SHS (100%)
Ireland [18]	2008	~12-13**	n/a	Fully covered by national health authorities	SHS (100%)
Italy [19]	2007–2008 (a)	11-18	56 (2009)	Fully covered by national health authorities	PH (100%)
Latvia [20]	2009	12	n/a	Fully covered by national health authorities	PH (95%), SHS (4%), Private sector (1%)
Lithuania [21]	No	-	-	-	-
Luxembourg [22]	2008	12	17 (2009)	Fully covered by national health authorities	Private sector (100%)
Malta [23]	No	-	-	-	-
Netherlands [24]	2009	12-13	58 (2011)§	Fully covered by national health authorities	PH (100%)
Norway [25]	2008	12-13	63 (2011)§	Fully covered by national health authorities	SHS (100%)
Poland [26]	No	-	-	-	-
Portugal [27]	2007	13	84 (2011)§	Fully covered by national health authorities	PH (100%)
Romania [28]	2008	12	n/a	Fully covered by national health authorities	PH (5%), SHS (95%)
Slovakia [29]	No	-	-	-	-
Slovenia [30]	2009	11-12	55 (2011)§	Fully covered by national health authorities	SHS (100%)
Spain [31]	2007	11-14	64 (2011)§	Fully covered by national health authorities	PH (50%), SHS (50%)
Sweden [32]	2008	10-12	n/a	Fully covered by national health authorities	SHS (100%)
UK [33]	2007	12-13	80 (2009)	Fully covered by national health authorities	PH (6%), SHS (94%)

ECDC 2012

Challenges

- Organised population-based screening programmes for cervical cancer are not yet in place throughout Europe, planning and piloting them are in a priority
- Due to increasing burden of CIN treatments and to high prevalence of HPV infections, *primary HPV screening* should be introduced only in organised population-based programmes
- No follow-up data on impact of *HPV vaccination* programme on cervical and other HPV related cancer burden exists, it is important to start to consider the potential synergies of the primary and secondary prevention strategies for cervical cancer

Thank you for your attention