Epidemiology of HPV and Cervical Cancer

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Brdo, Slovenia

15 October, 2014

International Agency for Research on Cancer
Lyon, France

Educational day of national cervical cancer screening programme ZORA

The epidemiology of HPV and cervical cancer

1. Natural history
   - Brief historical perspective, causality assessment
2. The IARC HPV Prevalence Surveys
   - HPV prevalence in the general population
   - HPV distribution in cancer and precursor lesions
3. Burden of HPV and cervical cancer
   - Population attributable fraction, current incidence rates
4. Time trends and impact of screening
   - Separating the effects of screening *versus* underlying risk factors
   - Quantifying the impact of screening in the Nordic countries

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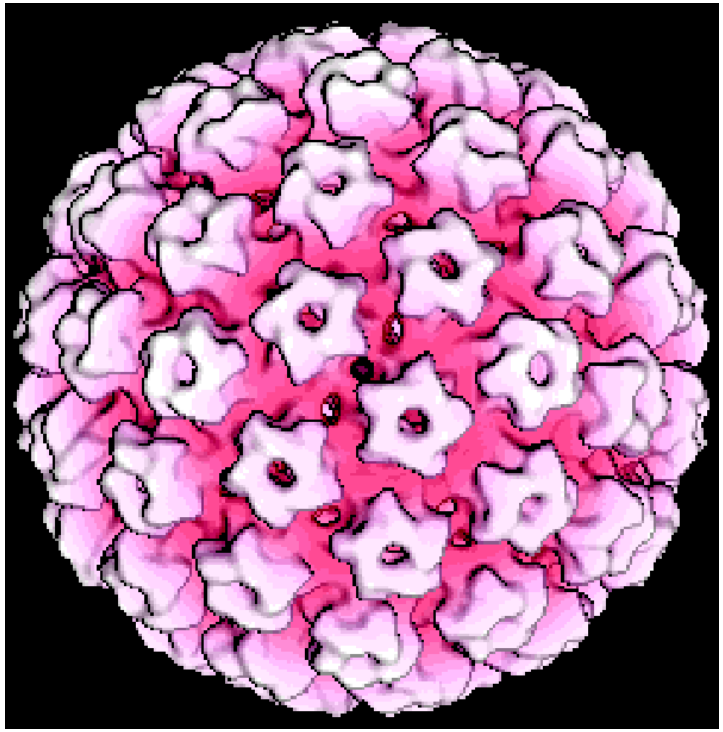
Human papillomavirus: a key discovery to improve the prevention of cervical cancer (vaccine + HPV test-based screening)



- **Sexually transmitted**
- **Non enveloped dsDNA virus, simple capsid of 2 proteins L1 and L2**
- **Common virus with >100 types identified**
- **Infects cutaneous and mucosal epithelia of women and men**

  - **13 high risk types causing cancer**

  16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59,68

  HPV 16,18 – most important

Current VLP-based vaccines have nearly >90% efficacy in preventing HPV16/18-related cervical infection and severe dysplasia in women who have not be previously infected.

HPV and cervical cancer, historical perspective

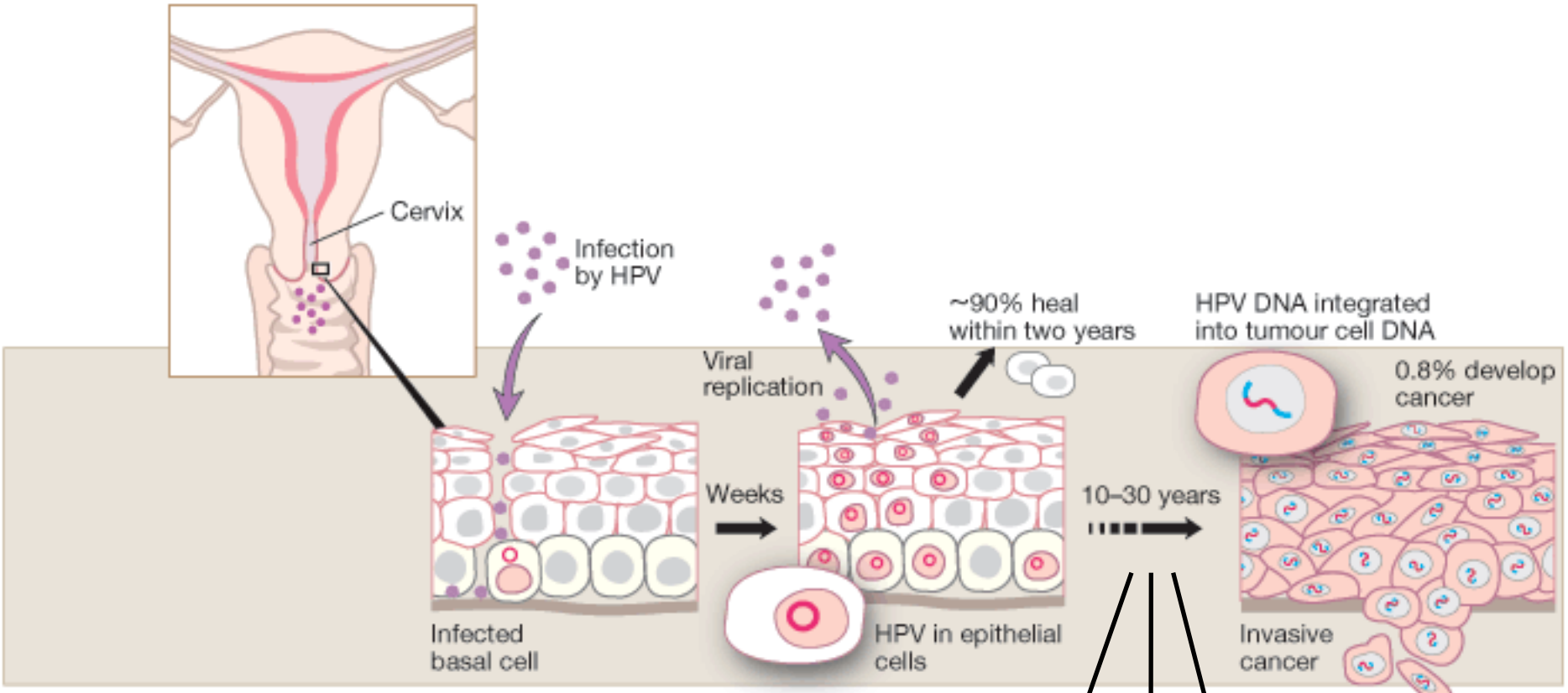
- One of the most important scientific discoveries of the past 30 years, comparable from the public health perspective to the discovery of the association between smoking and lung cancer
- Seminal work from Harald zur Hausen group, discovering that HPV16 can be detected in cervical cancer tissue
- Zur Hausen was awarded the Nobel Prize in Physiology or Medicine in 2008
- Enormous involvment of epidemiologists, molecular biologists, vaccinologists, and clinicians ended up with the development of prophylactic vaccine (could prevent about 70-80% of cervical cancer cases)

Causality criteria for the HPV and CC model

- ***Strength of the association***: one of the strongest associations ever observed in epidemiology (ORs ≈ 50-100);
- ***Consistency***: in several studies across different countries and populations;
- ***Specificity***: some degree of specificity for HPV types;
- ***Temporality***: established by several studies, follow-up etc. HPV precede cervical precursor lesions by a number of years;
- ***Biological gradient***: viral load is linked to higher risk of progression;
- ***Biological plausibility***: observations in humans, in vitro and animal experiment. Several studies on biological mechanisms of immunity, cellular growth, DNA repair, etc;
- ***Analogy***: analogous to other examples of animal PV and carcinomas.

HPV, the first ever identified "necessary cause" of human cancer

Natural History



CIN1 CIN2 CIN3

Pre-cancerous lesions

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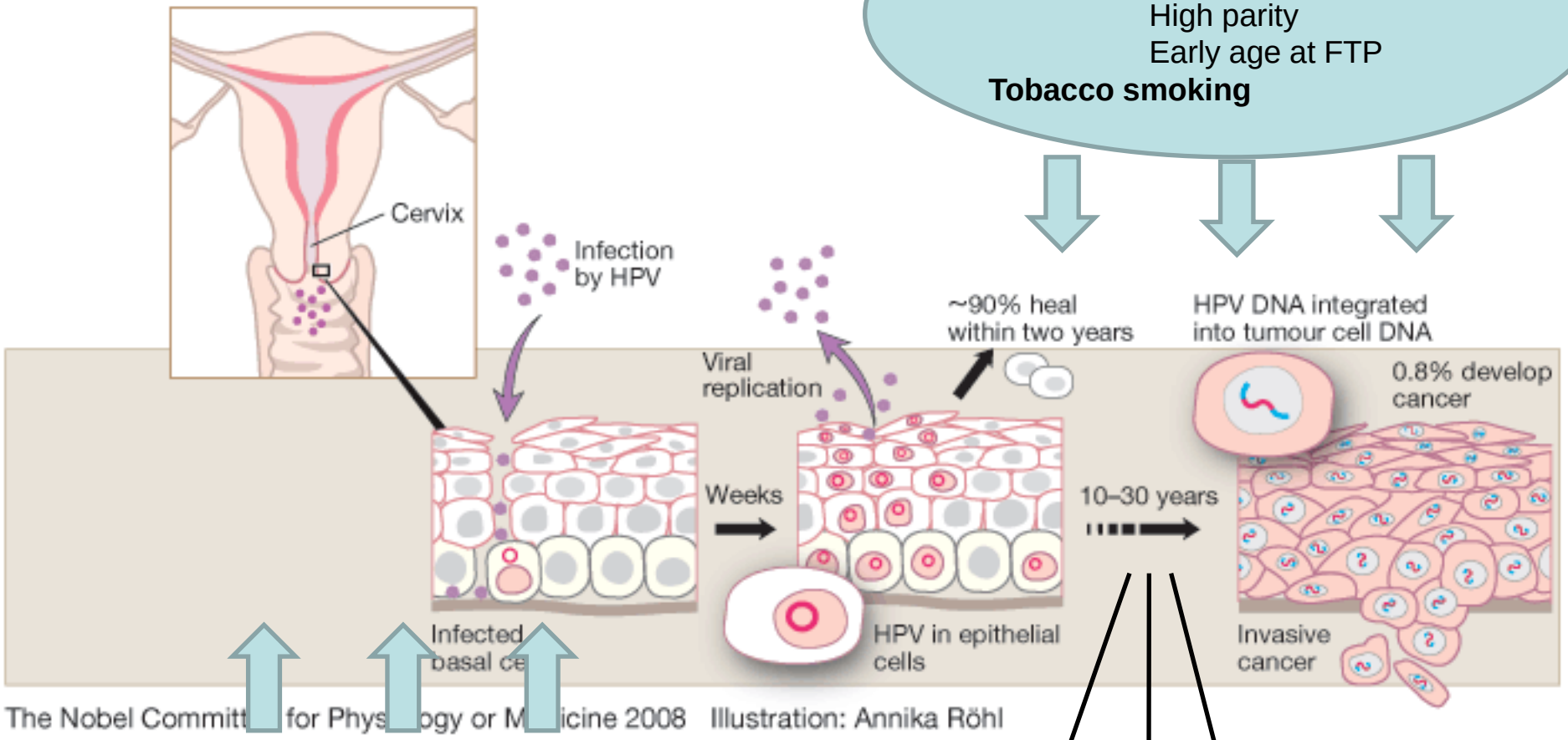
Natural History

Hormonal factors
Long-term OC use
High parity
Early age at FTP
Tobacco smoking



CIN1 CIN2 CIN3
Pre-cancerous lesions

HPV types and variants
Host factors
Genetic susceptibility
Immunological factors

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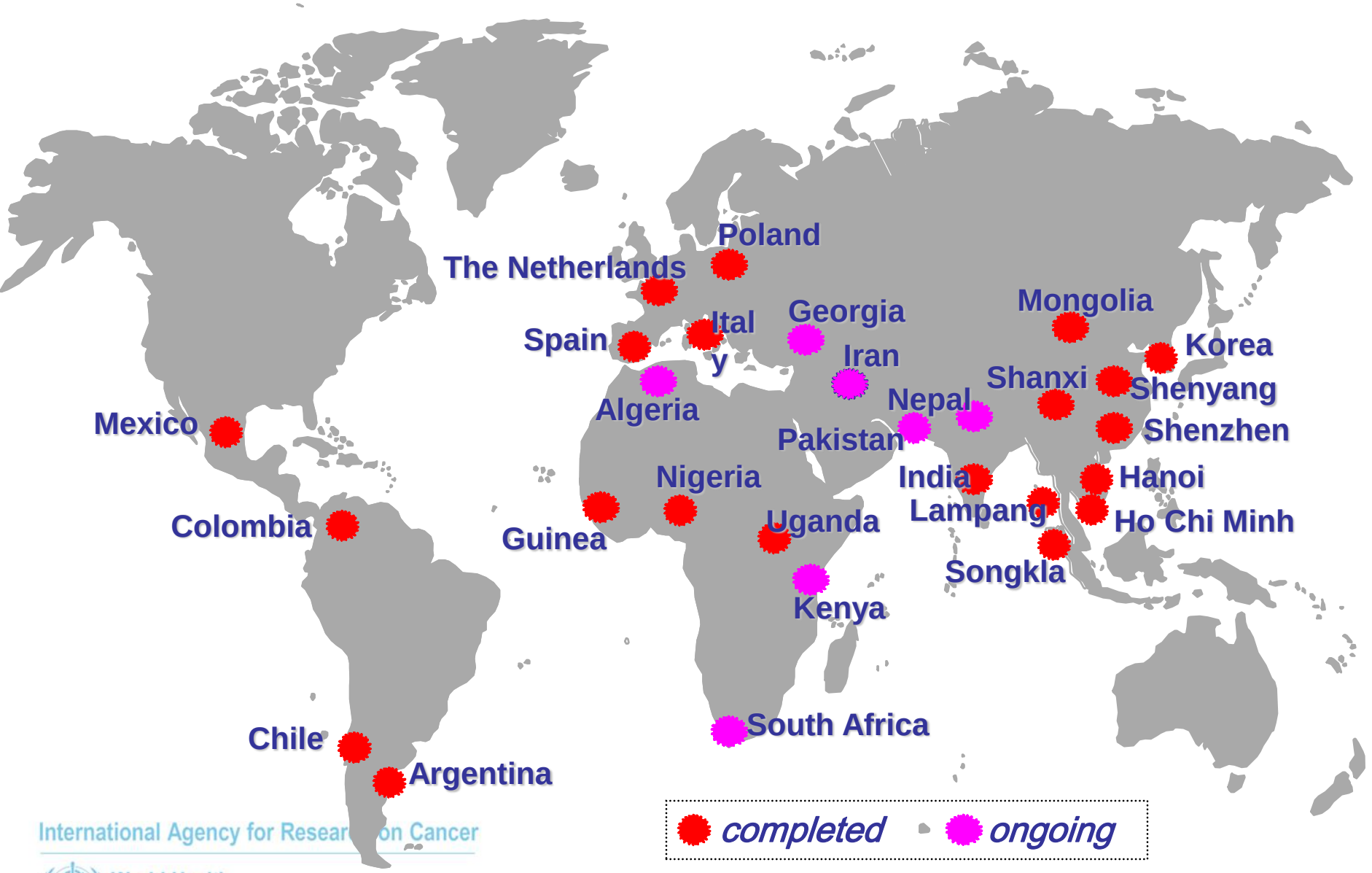
IARC Multi-centre HPV Prevalence Surveys

- The establishment of the viral aetiology of cervical cancer has raised the hopes for primary and secondary prevention through HPV vaccination and HPV DNA test-based screening, respectively.
- The planning of such interventions requires population-based epidemiological data on age and type-specific HPV prevalence in women with and without cancer.
- To this end, the International Agency for Research on Cancer (IARC) has carried out surveys in representative samples of women worldwide.[1]
- Priority has been given to countries where there is lack of previous HPV studies and even data on cervical cancer.

[1] supported by Bill and Melinda Gates Foundation

IARC Multi-centre HPV Prevalence Surveys



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IARC Multi-centric HPV Prevalence Survey

- Population-based samples of approx. 1000 women
- 100 women per 5-year age group (15-19 to 65+)
- Standard HPV testing by GP5+/6+ PCR for 36 types
- Standard questionnaire on several characteristics

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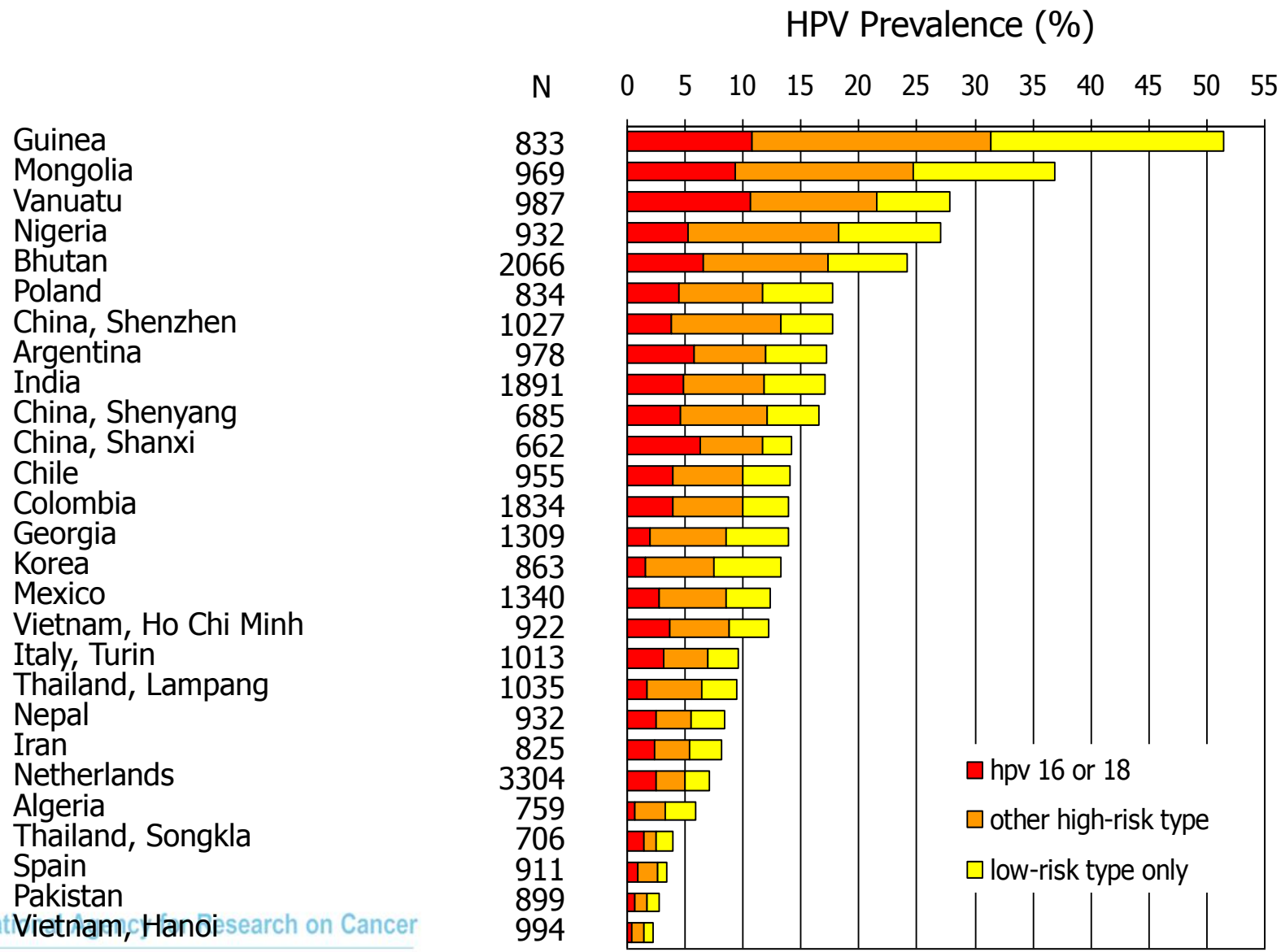
IARC HPV Surveys, sexually active women, 15-59 yrs (1995-2013)



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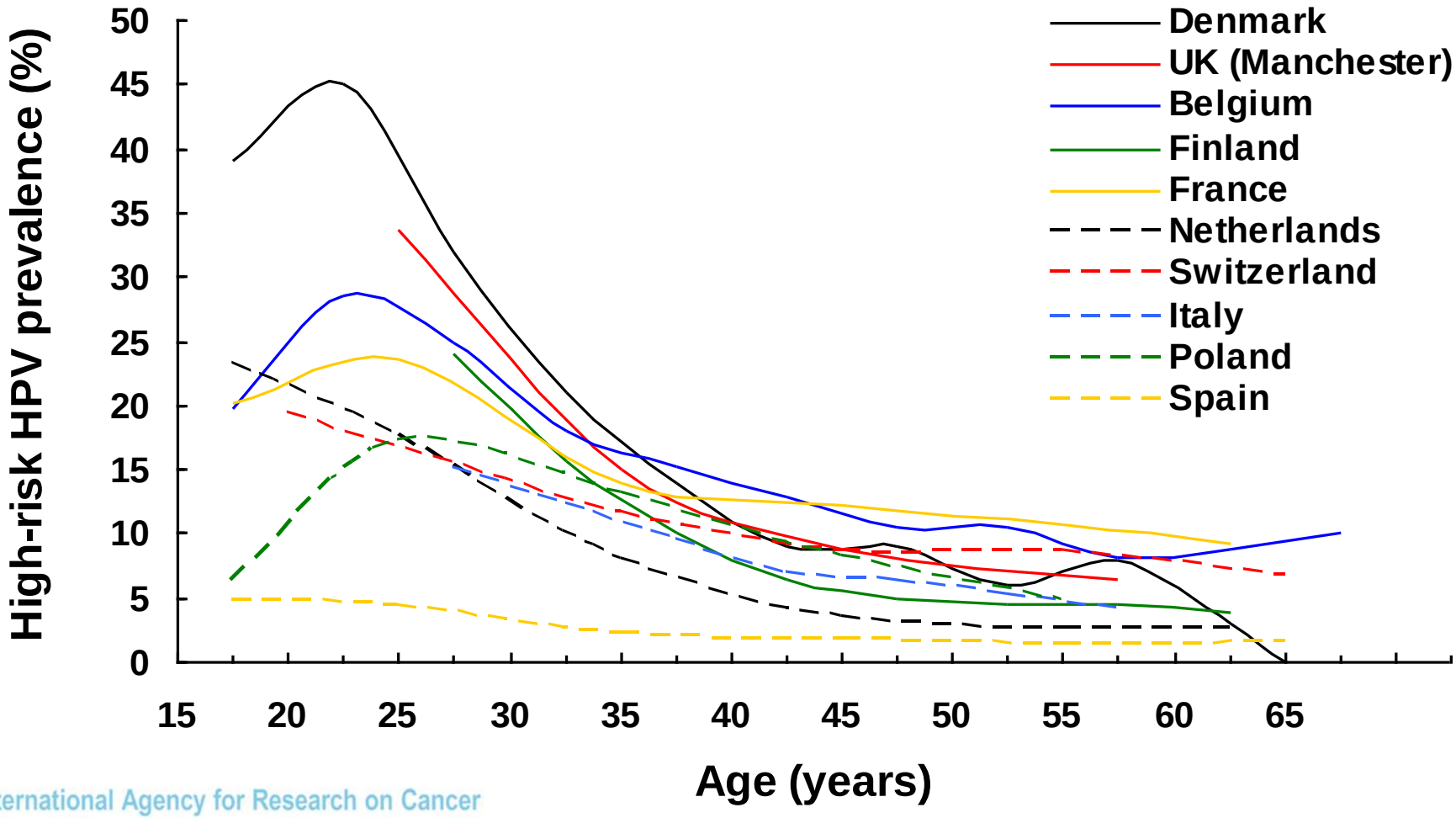
Age-specific high-risk HPV prevalence in 9 European Union countries and Switzerland (mainly HC2 and GP5+/GP6+)



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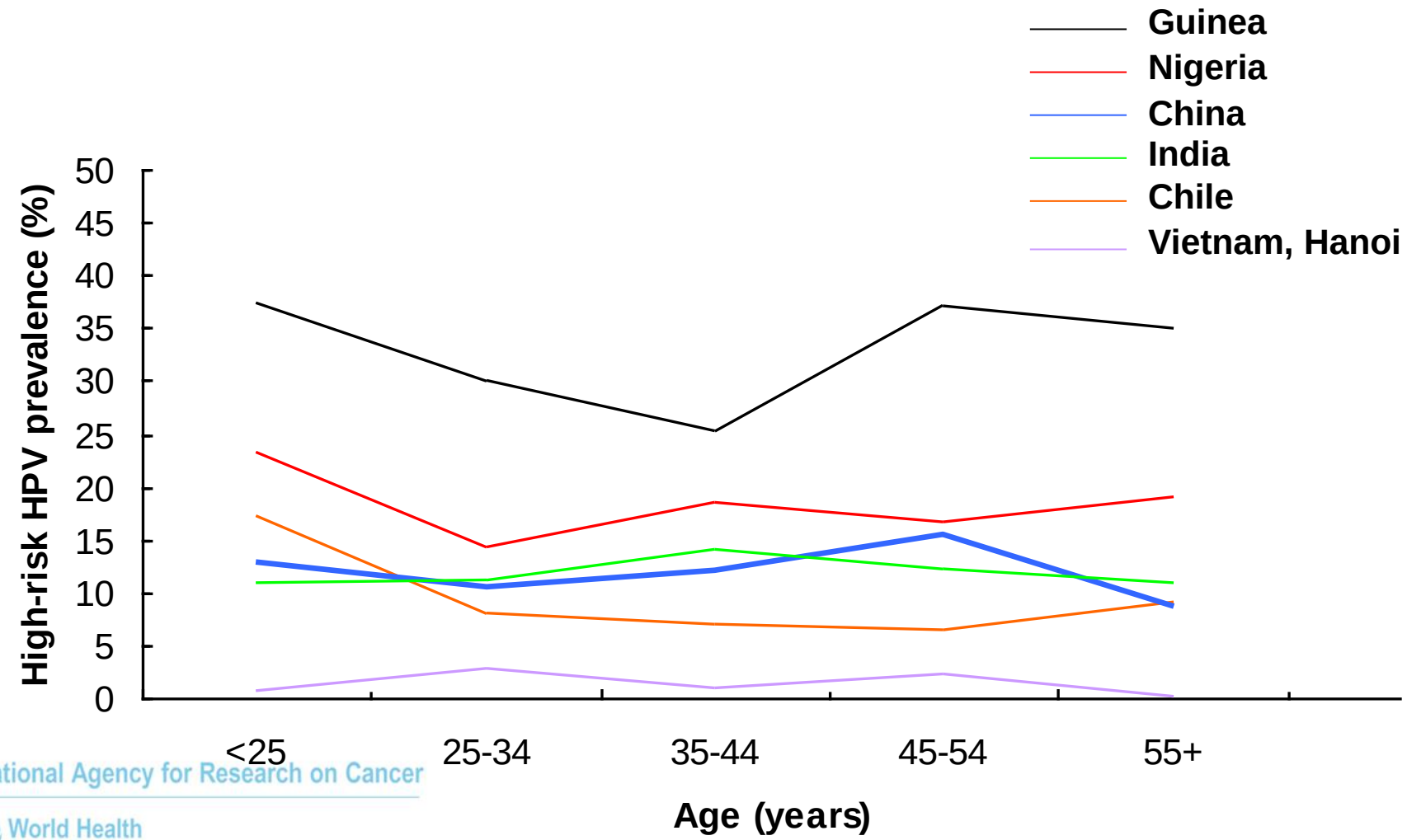
Age-specific prevalence of high-risk HPV types in selected areas. IARC HPV prevalence Surveys (GP5+/GP6+)



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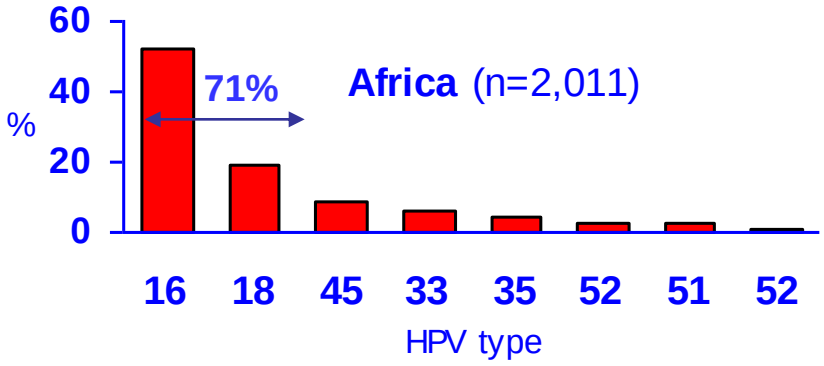
Summary findings of the IARC HPV prevalence Surveys

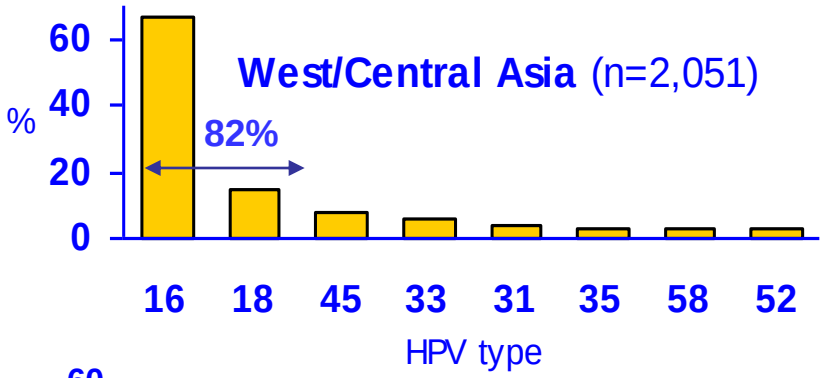
- The very heavy burden of HPV infection in certain areas, i.e., Guinea, Nigeria, Mongolia, and Pacific Islands, calls for urgent effective interventions.

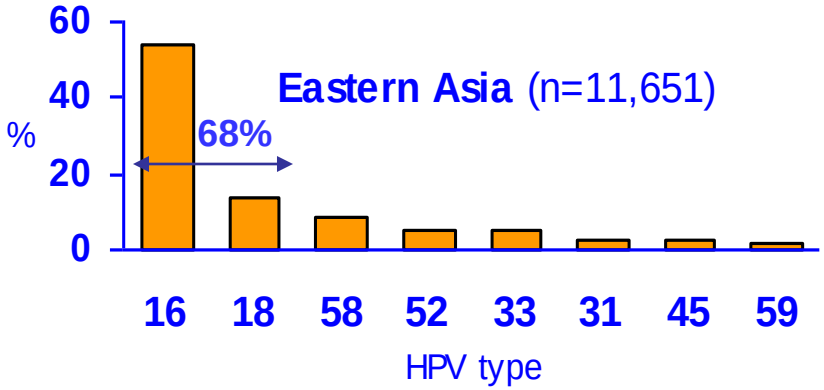
- “Western” age-specific curve of HPV prevalence should not be taken as the “natural history of HPV infection”.

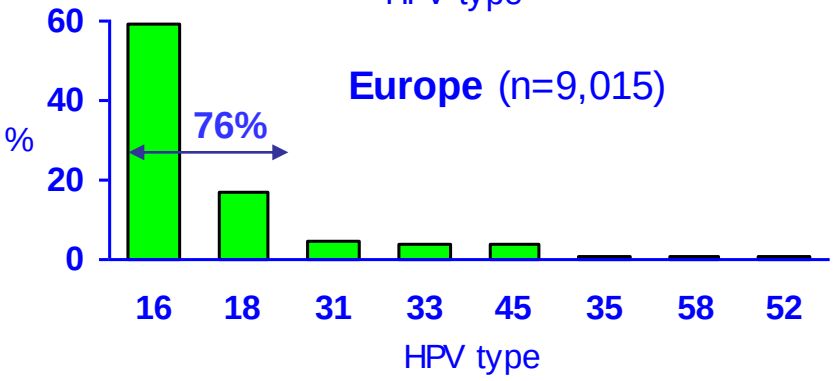
- Vaccination and screening are priorities in countries where HPV is very common, even if no good cervical cancer data exist.

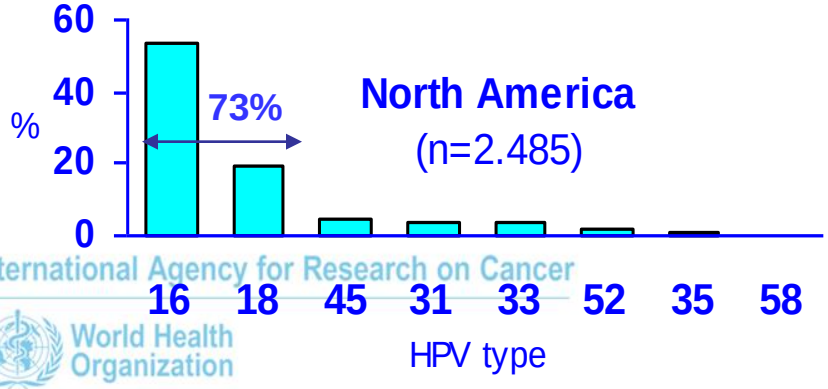
8 most common HPV types in 30,743 cases of invasive cervical cancer by region

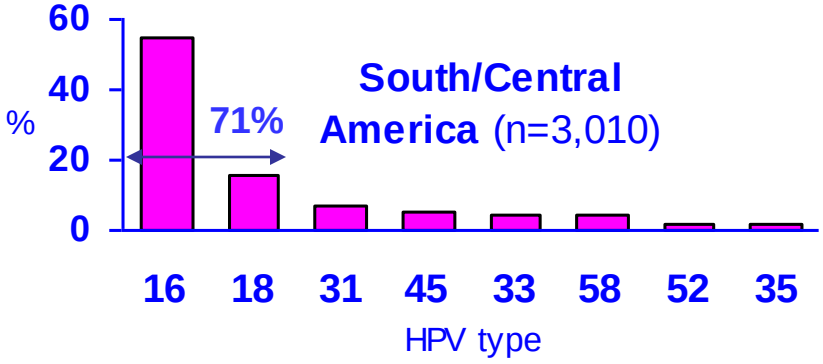












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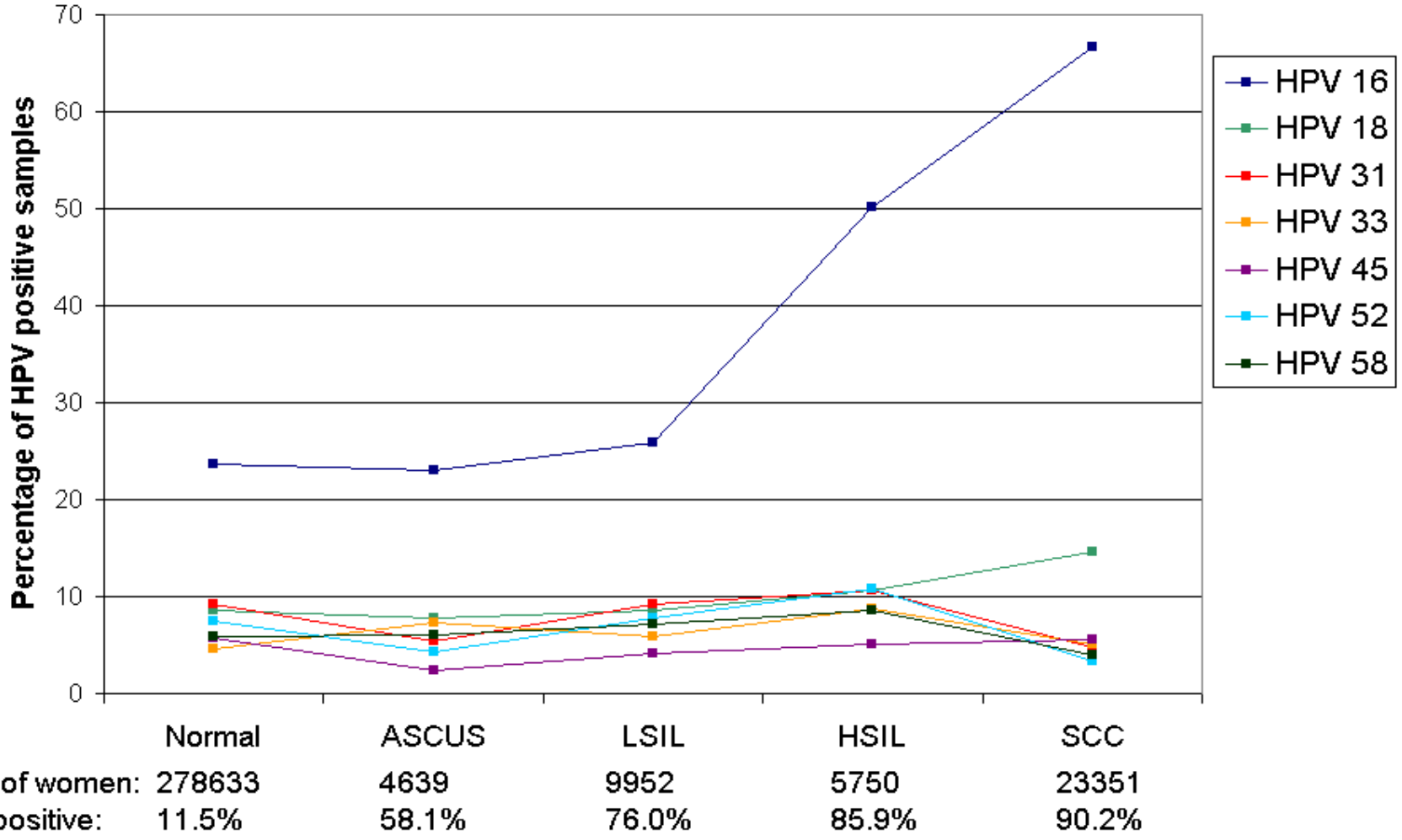
IARC meta-analyses of HPV-type distribution:

among HPV-positive samples of increasing severity



	Normal	ASCUS	LSIL	HSIL	SCC
Number of women:	278633	4639	9952	5750	23351
% HPV positive:	11.5%	58.1%	76.0%	85.9%	90.2%

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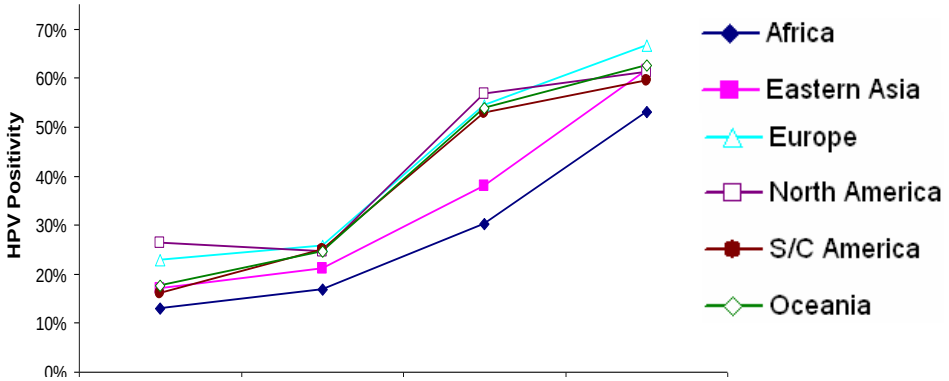
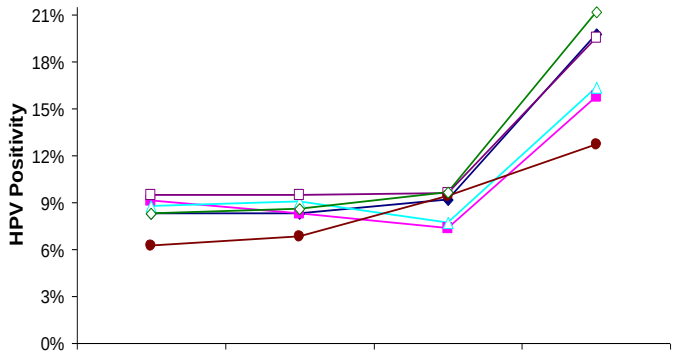
HPV types 16, 18, 45 and 58: by region



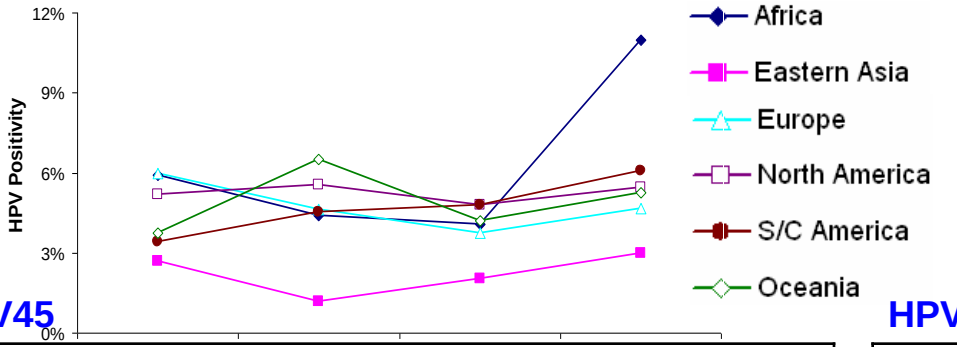


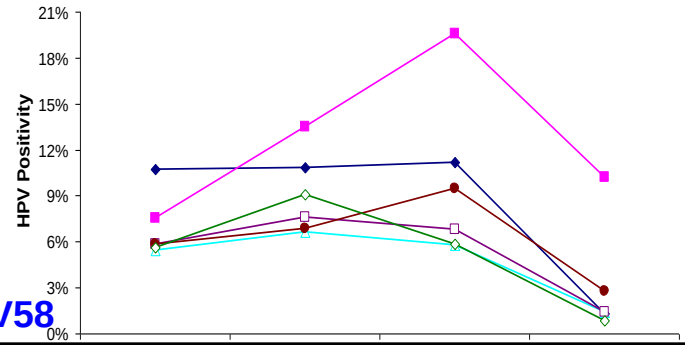
HPV16

	Normal	Low-grade	High-grade	ICC	ICC: Normal ratio
Africa	13.1 ± 3.3	16.8 ± 5.5	30.3 ± 5.2	53.1 ± 4.4	4.07
Eastern Asia	17.0 ± 10.9	21.1 ± 5.7	37.9 ± 7.1	61.7 ± 5.9	3.64
W/C Asia	29.5 ± 14.7	30.8 ± 14.4	68.4 ± 16.4	73.0 ± 4.6	2.48
Europe	22.8 ± 3.4	25.9 ± 3.1	54.4 ± 5.6	66.7 ± 2.0	2.92
North America	26.3 ± 16.2	24.7 ± 4.3	56.8 ± 3.1	61.2 ± 3.2	2.33
S/C America	16.1 ± 7.8	25.1 ± 9.1	52.8 ± 8.1	59.5 ± 2.8	3.69
Oceania	17.6 ± 2.7	24.7 ± 9.2	53.9 ± 3.5	62.6 ± 5.4	3.55

HPV18

	Normal	Low-grade	High-grade	ICC	ICC: Normal ratio
Africa	8.3 ± 1.9	8.3 ± 1.7	9.2 ± 2.8	19.8 ± 4.1	2.39
Eastern Asia	9.1 ± 1.3	8.3 ± 1.9	7.4 ± 1.9	15.8 ± 2.6	1.73
W/C Asia	6.3 ± 2.3	6.8 ± 2.7	6.3 ± 5.0	15.1 ± 3.7	2.39
Europe	8.8 ± 1.2	9.1 ± 1.5	7.7 ± 1.1	16.4 ± 4.6	1.87
North America	9.5 ± 6.6	9.5 ± 1.4	9.6 ± 2.7	19.6 ± 4.3	2.06
S/C America	6.2 ± 3.4	6.8 ± 4.4	9.4 ± 3.5	12.7 ± 4.5	2.04
Oceania	8.3 ± 2.0	8.6 ± 5.1	9.6 ± 1.7	21.2 ± 4.2	2.56





HPV45

Africa	5.9 ± 2.0	4.4 ± 3.8	4.1 ± 3.1	11.0 ± 2.2	1.85
Eastern Asia	2.7 ± 0.8	1.2 ± 0.5	2.0 ± 1.0	3.0 ± 1.3	1.12
W/C Asia	6.3 ± 6.9	2.1 ± 3.0	7.1 ± 4.2	5.7 ± 2.7	0.90
Europe	6.0 ± 1.3	4.6 ± 1.2	3.7 ± 1.0	4.7 ± 0.7	0.78
North America	5.2 ± 0.8	5.6 ± 1.2	4.8 ± 1.7	5.5 ± 1.9	1.05
S/C America	3.4 ± 1.6	4.5 ± 1.7	4.8 ± 3.0	6.1 ± 0.9	1.79
Oceania	3.7 ± 1.4	6.5 ± 1.7	4.2 ± 1.5	5.3 ± 2.1	1.41

HPV58

Africa	10.7 ± 5.1	10.8 ± 5.6	11.2 ± 4.4	1.3 ± 0.6	0.12
Eastern Asia	7.5 ± 2.2	13.5 ± 3.6	19.6 ± 1.8	10.2 ± 3.9	1.36
W/C Asia	3.4 ± 3.4	6.3 ± 2.0	10.7 ± 9.9	2.8 ± 1.9	0.83
Europe	5.5 ± 1.3	6.7 ± 1.6	5.8 ± 0.9	1.4 ± 0.3	0.26
North America	5.9 ± 1.1	7.6 ± 1.5	6.8 ± 1.5	1.4 ± 1.1	0.24
S/C America	5.9 ± 1.8	6.8 ± 3.9	9.5 ± 2.4	2.8 ± 1.0	0.47
Oceania	5.6 ± 1.6	9.1 ± 4.7	5.8 ± 2.3	0.8 ± 0.7	0.15

Organization

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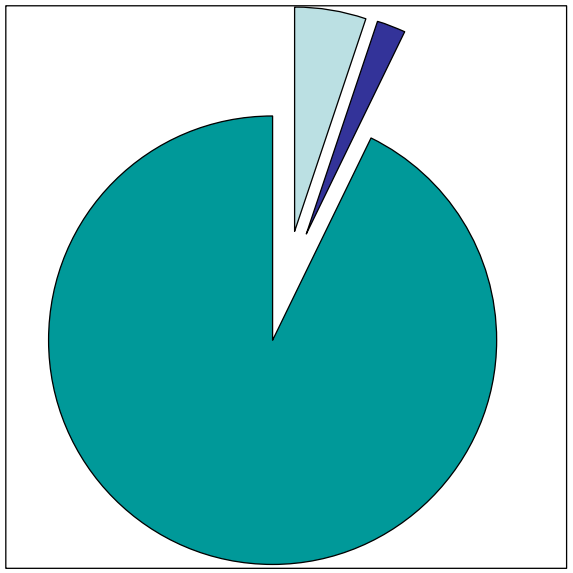
Cancer incidence 2008 attributable to infection and HPV-associated in both sexes (de Martel et al, Lancet Oncol 2012)

More developed regions



5.6 million new cancer cases
2.1% attributable to HPV
(i.e. 120,000 cancer cases)
5.3% attributable to other infections

Less developed regions

7.1 million new cancer cases
6.9% attributable to HPV
(i.e. 490,000 cancer cases)
16% attributable to other infections

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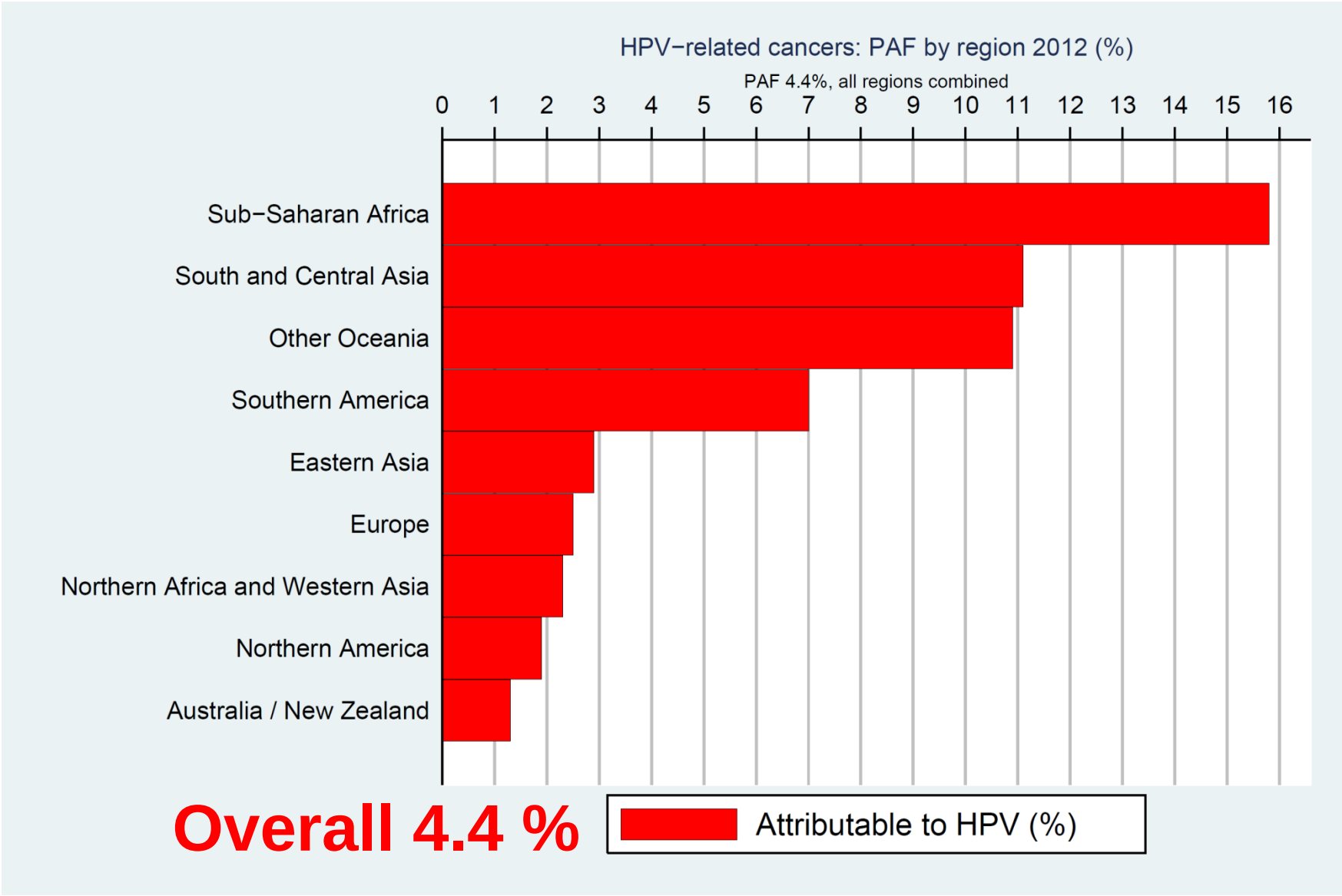
HPV-associated cancer burden 2012



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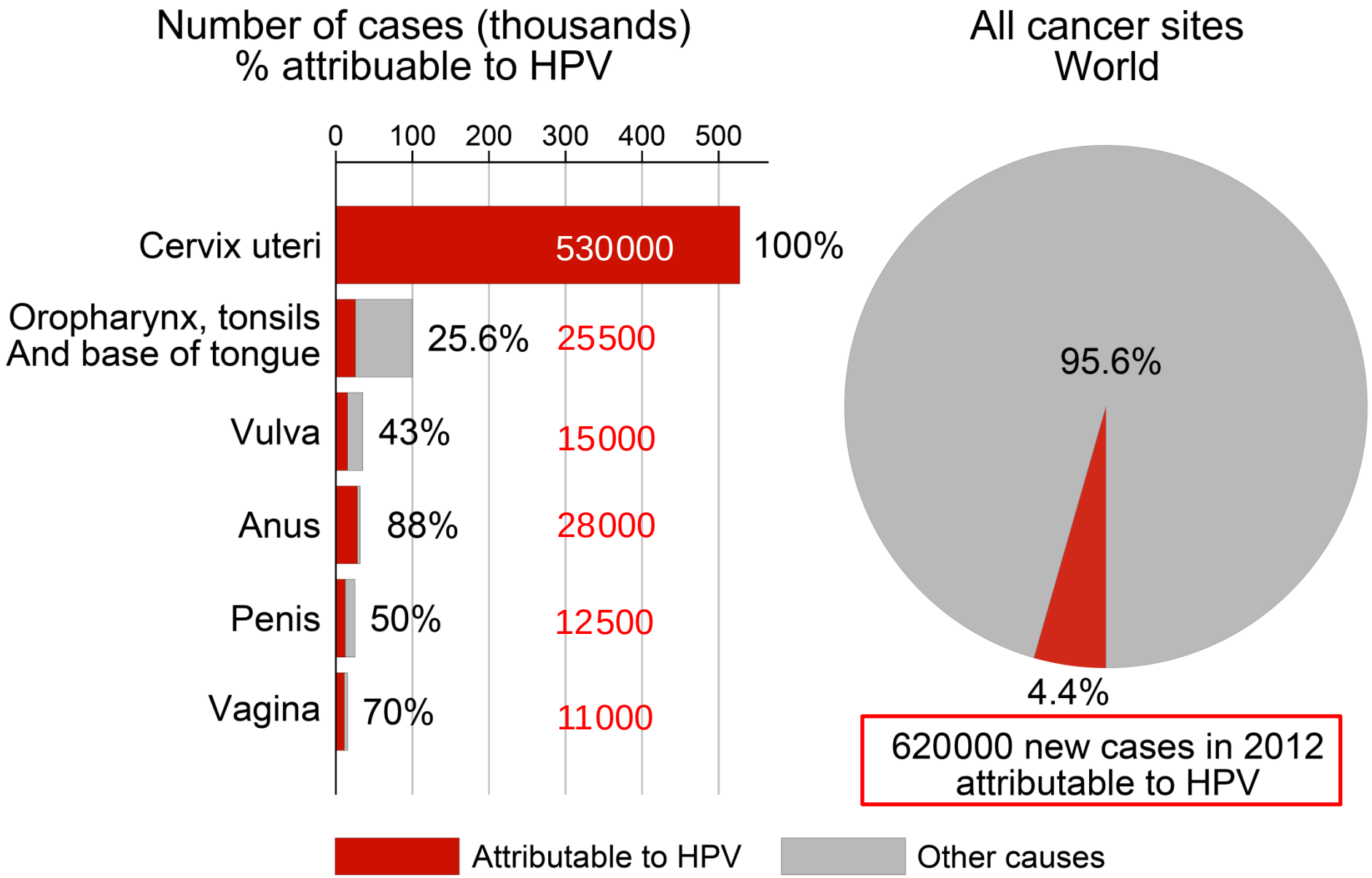
Work in progress: preliminary estimates (personal correspondence, M Plummer)

HPV-associated cancer burden 2012



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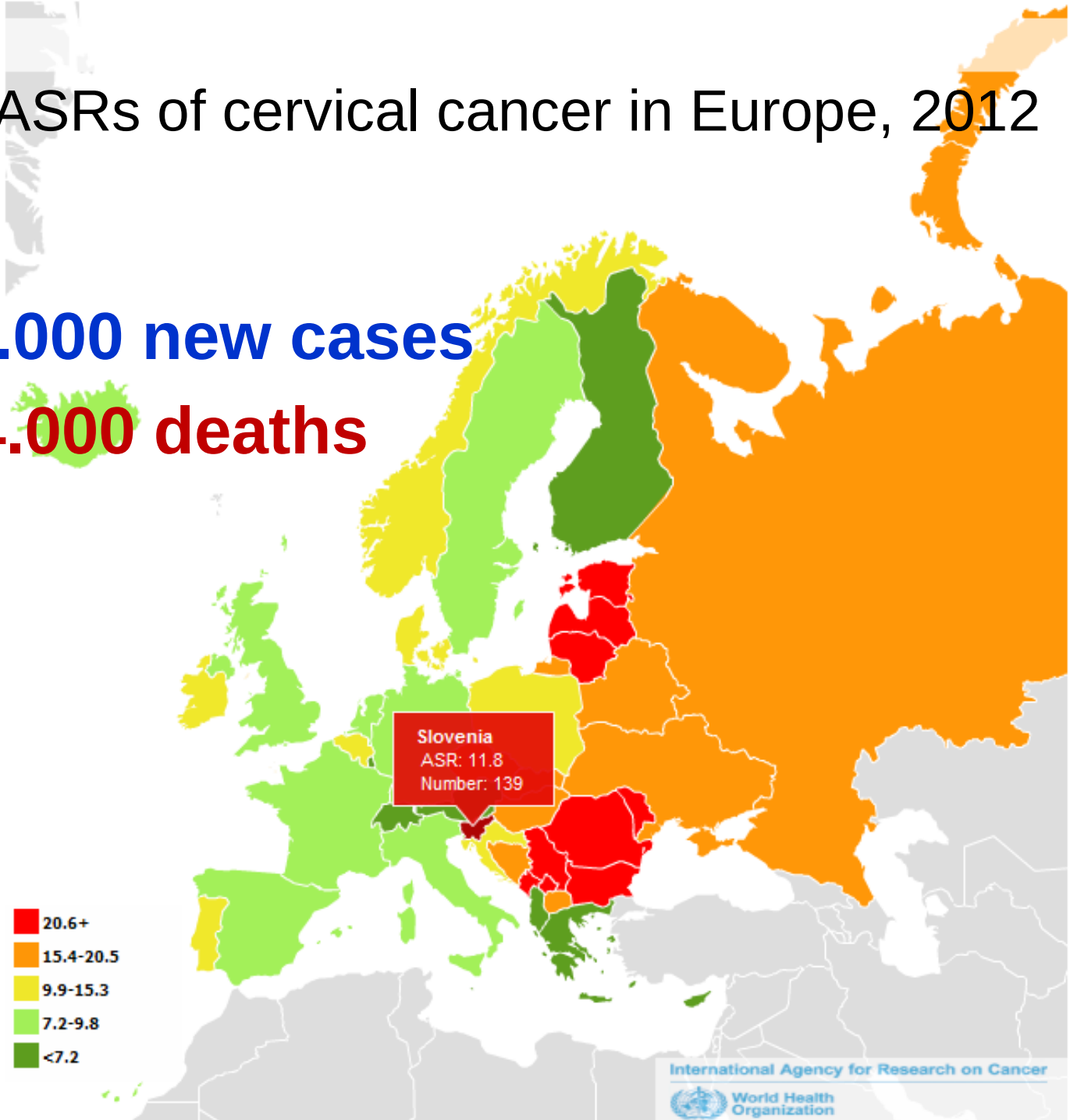
ASRs of cervical cancer in Europe, 2012

58.000 new cases

24.000 deaths



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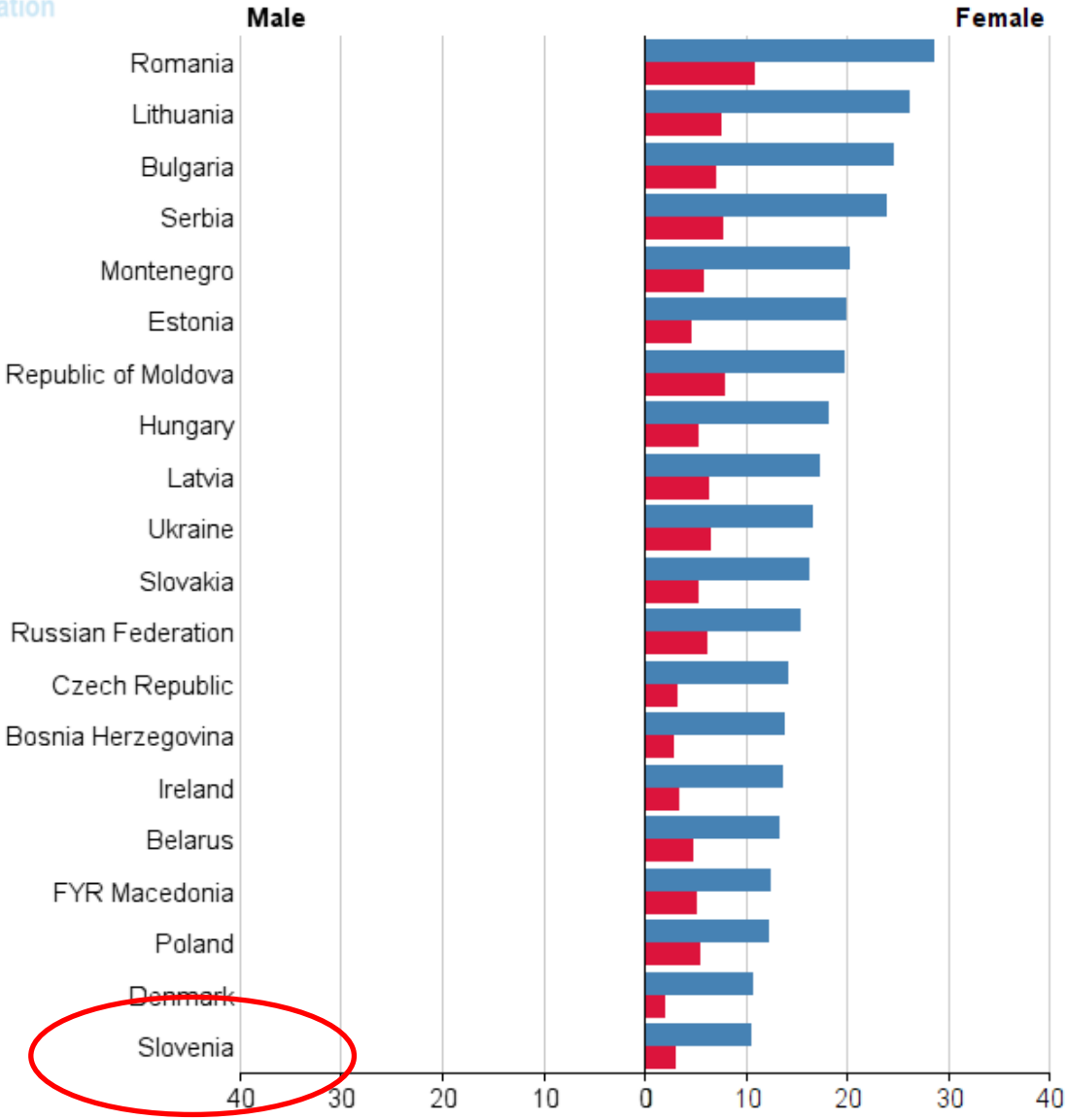
Cervix uteri
ASR (W) per 100,000, all ages



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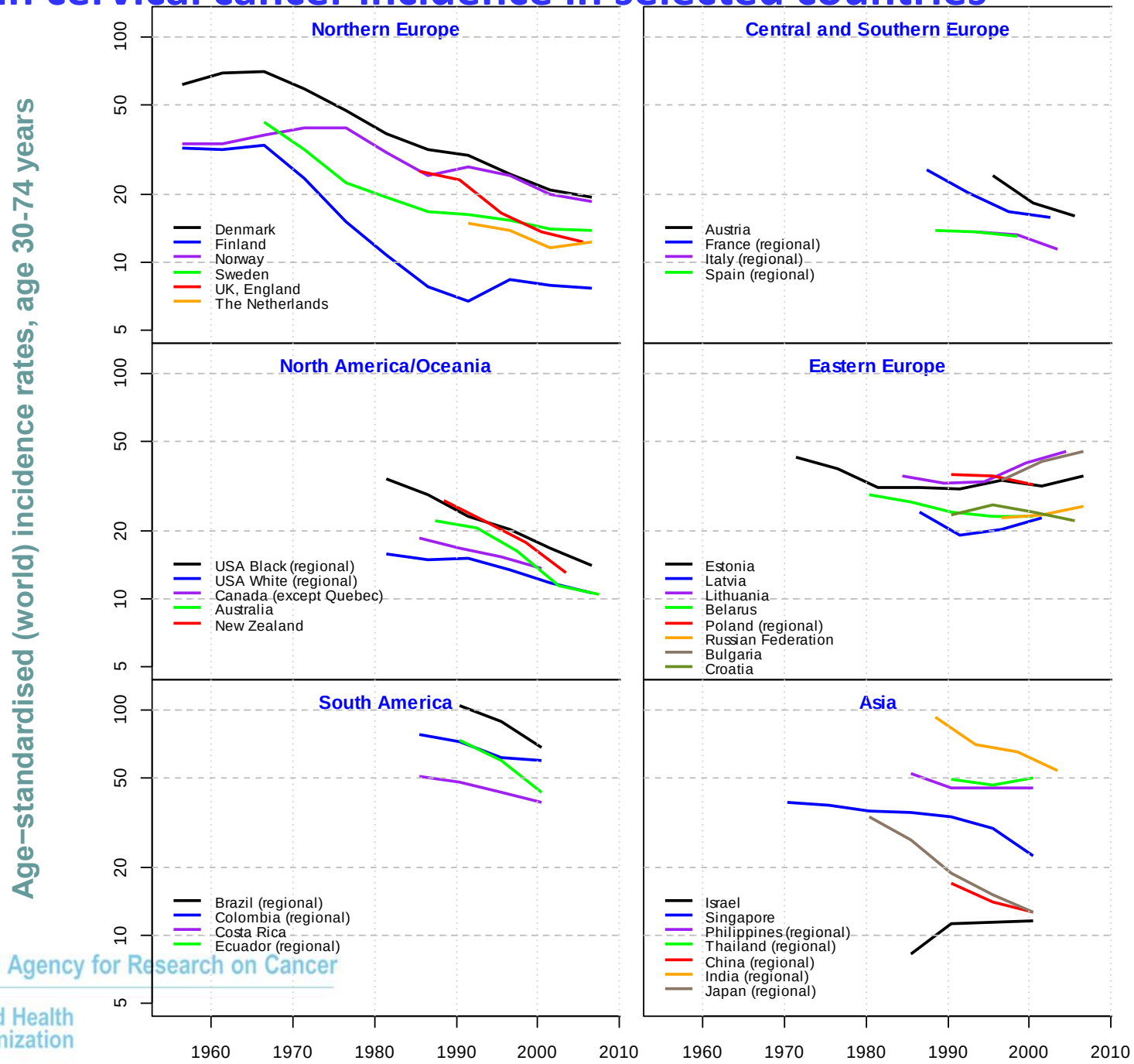
GLOBOCAN 2012 (IARC) (13.10.2014)

Trends in cervical cancer incidence in selected countries



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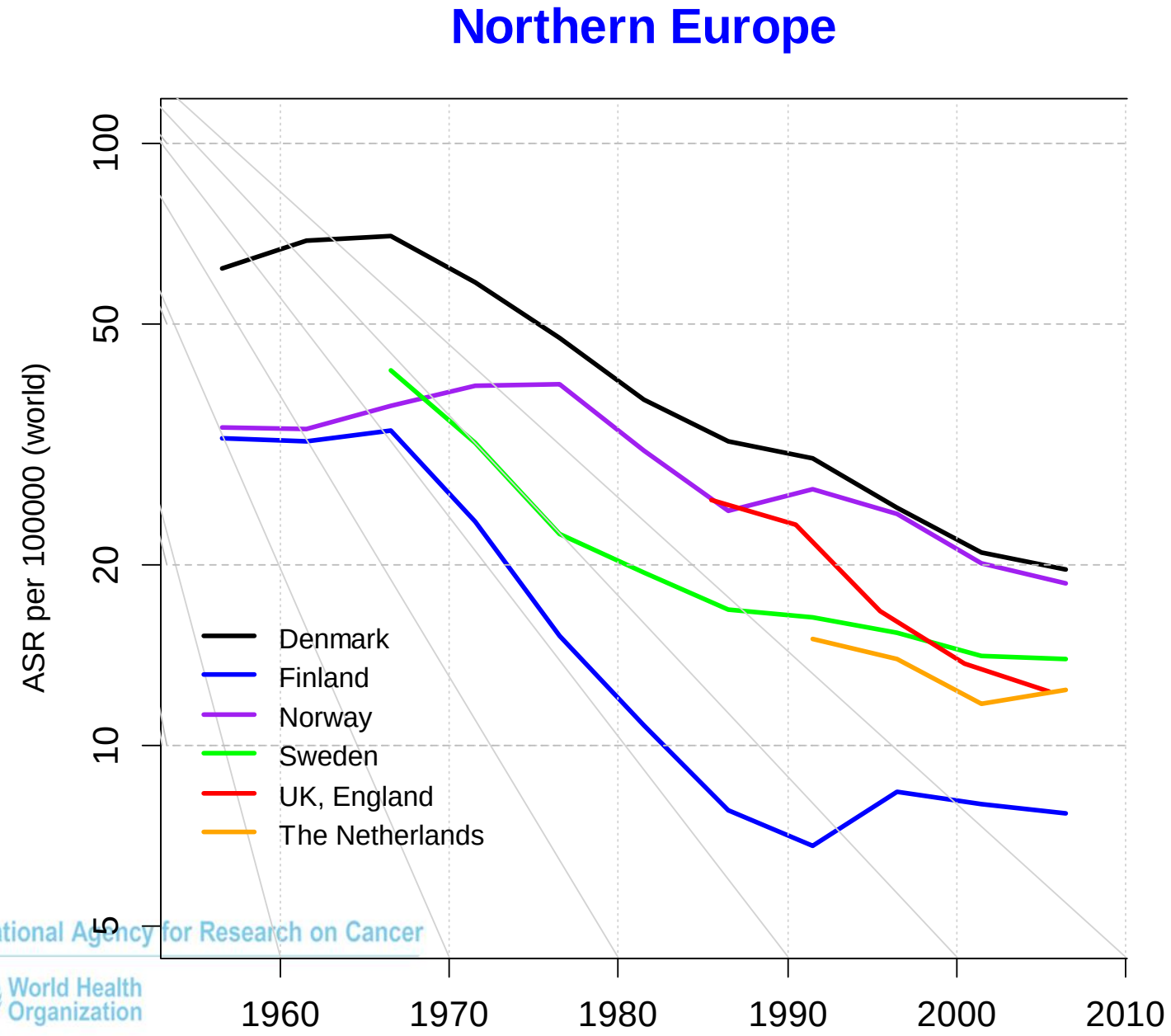
Age−standardised incidence rates of cervical cancer



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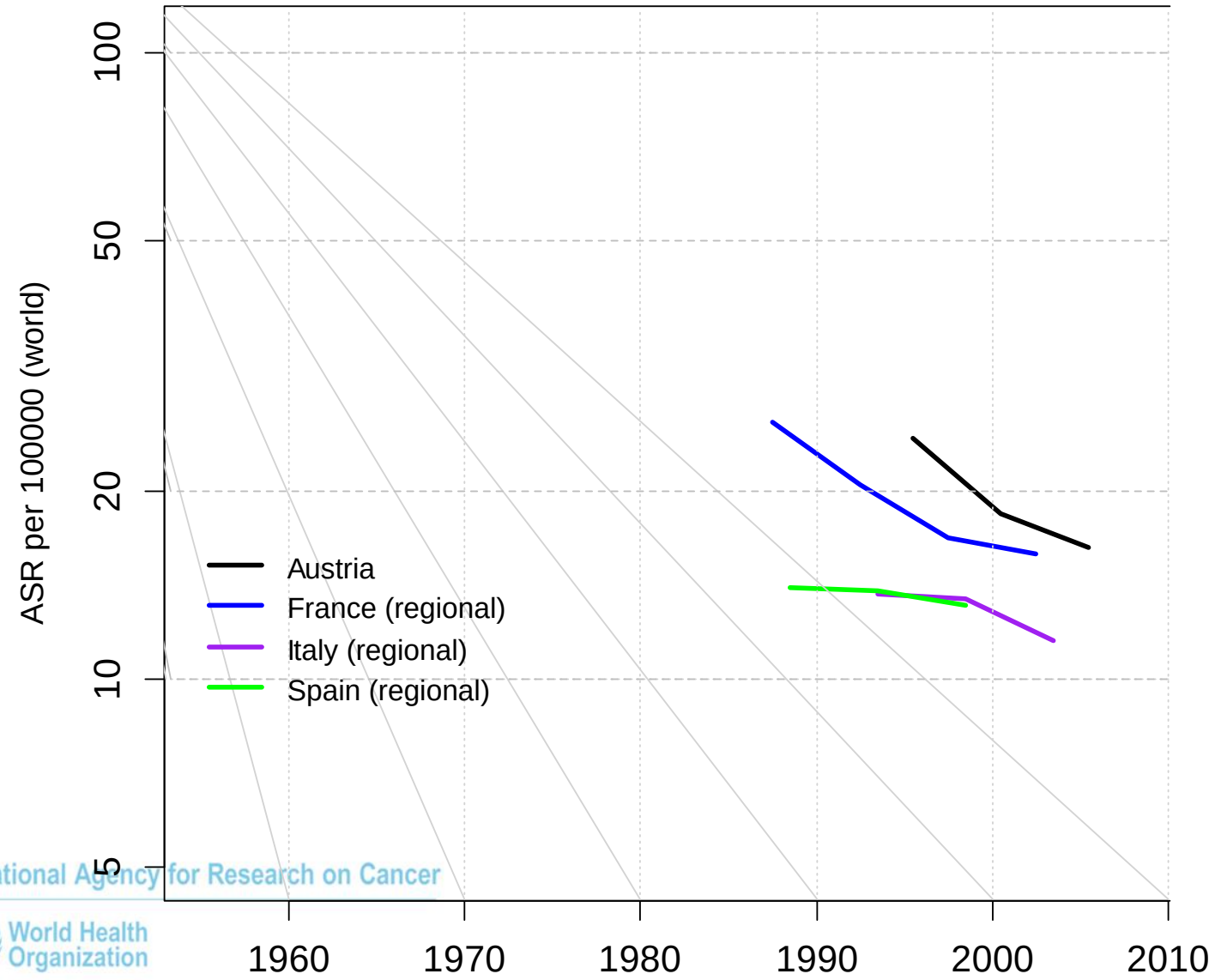
Age−standardised incidence rates of cervical cancer

Western and Southern Europe



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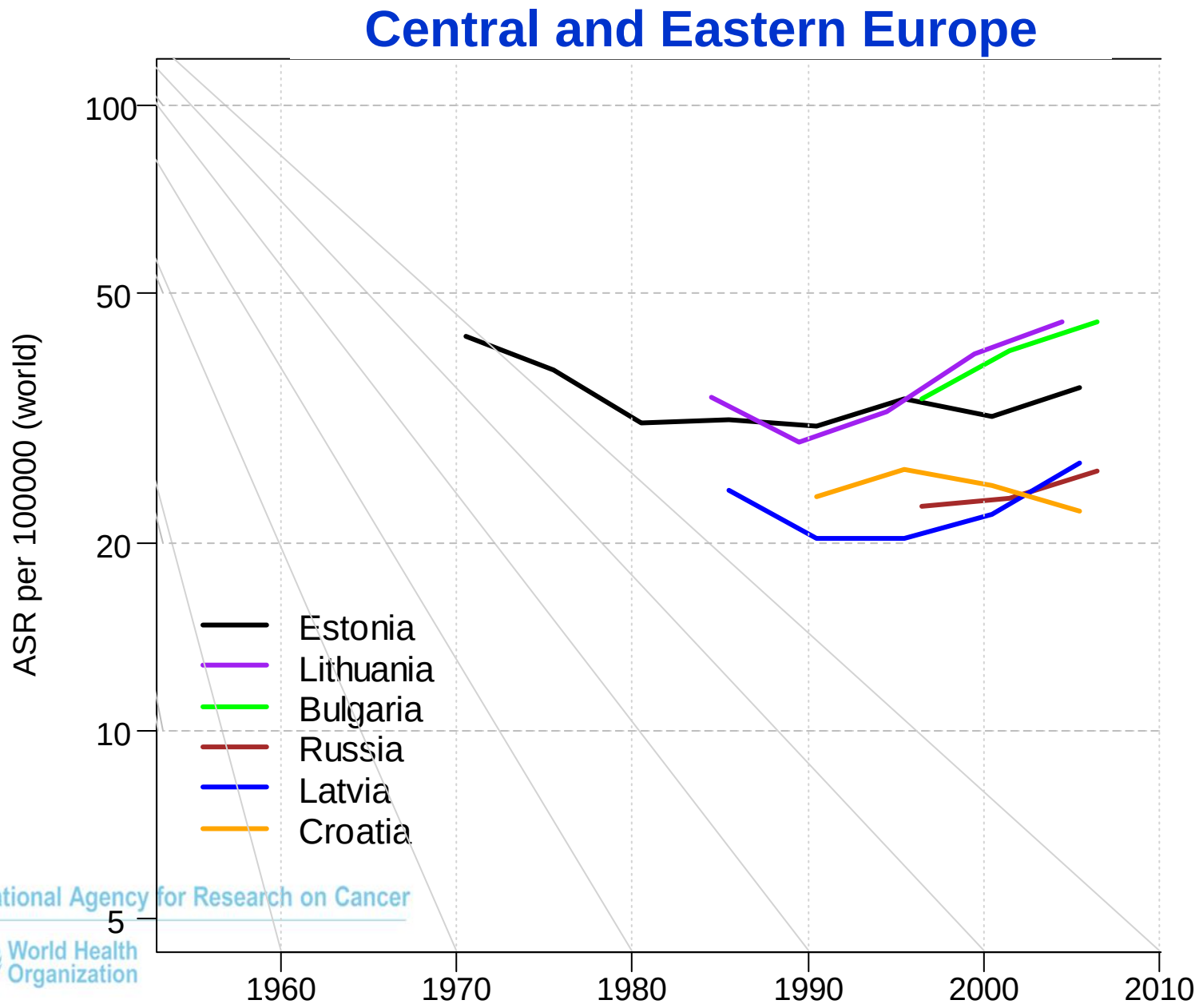
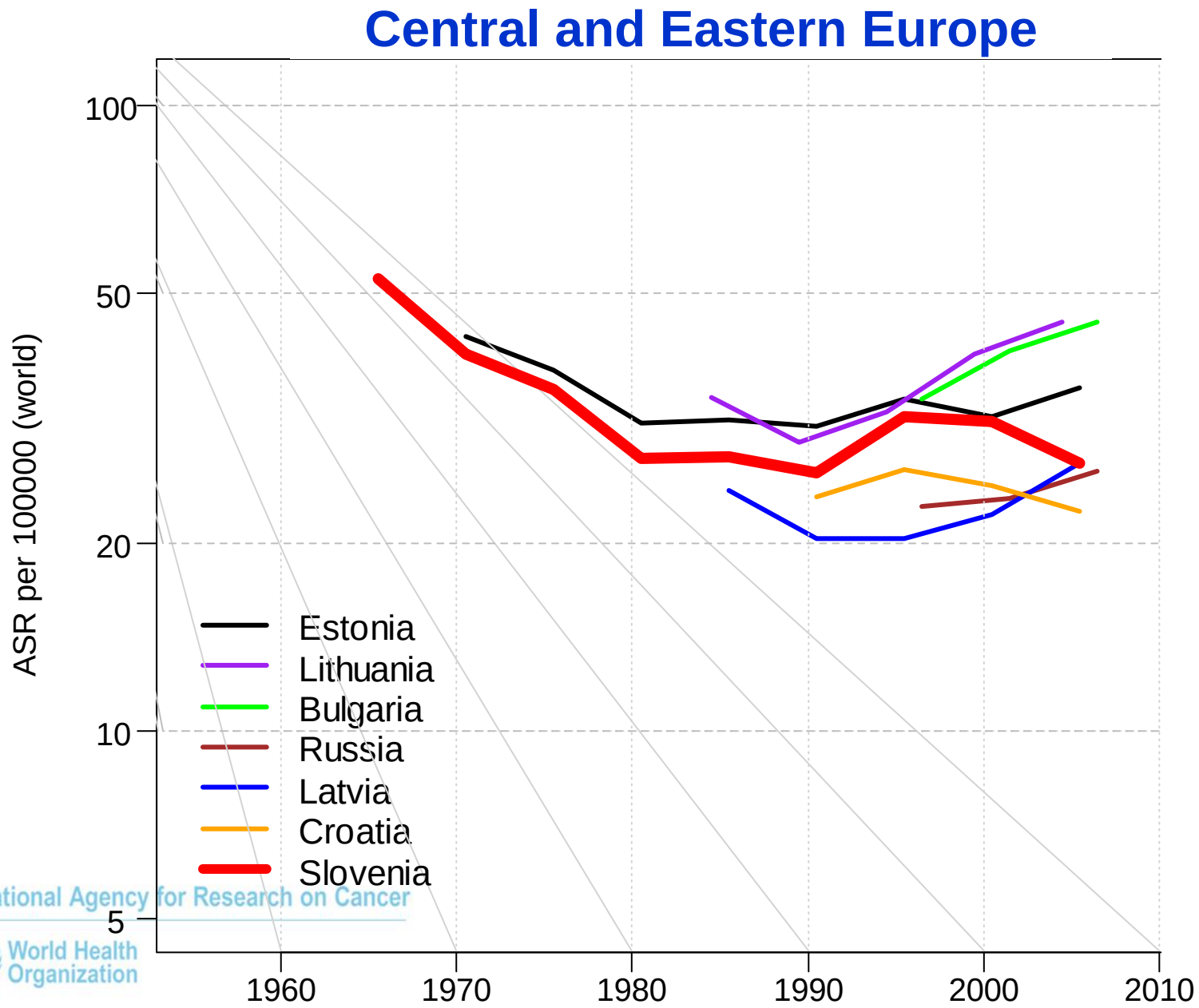
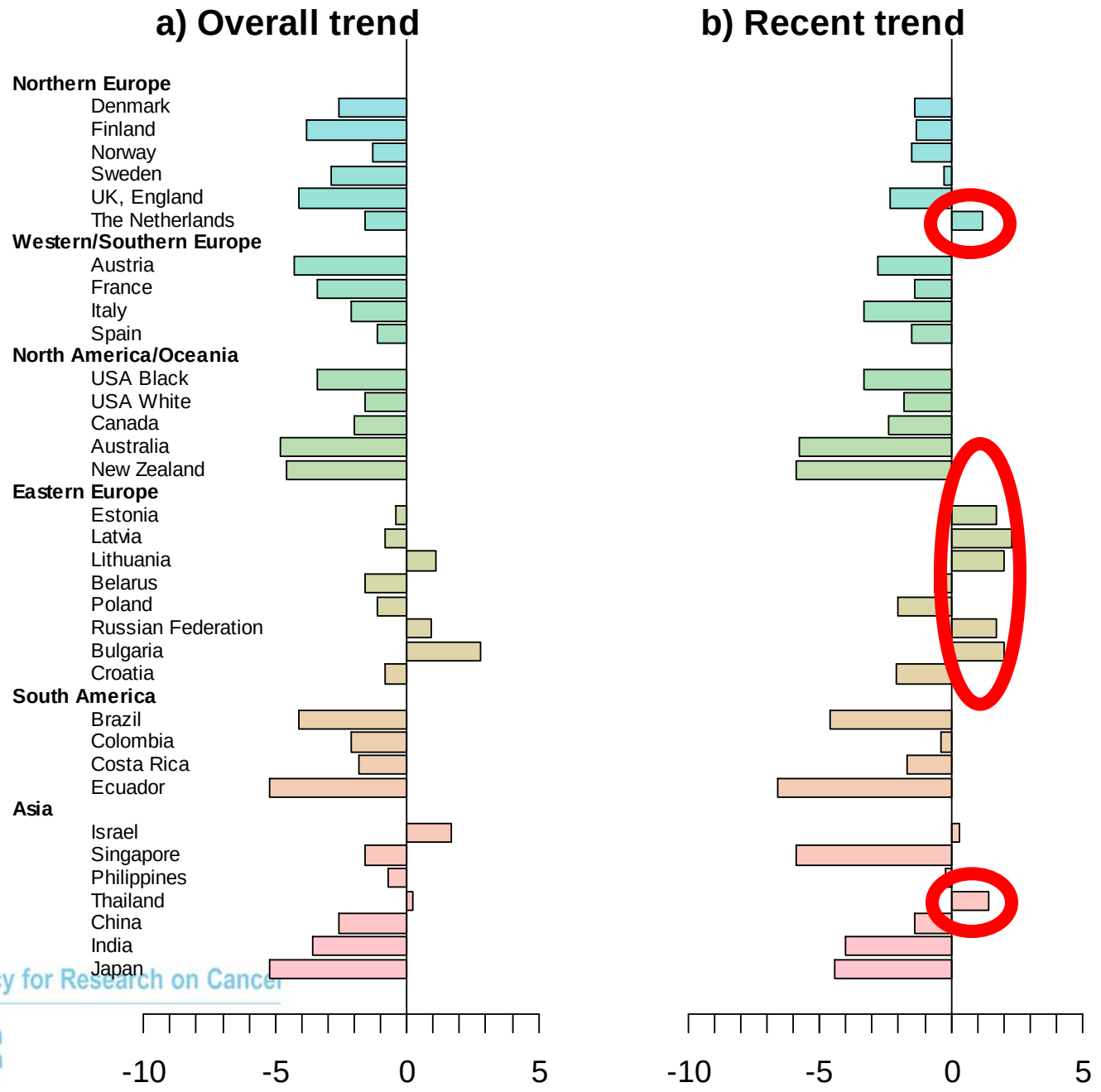
Age−standardised incidence rates of cervical cancer



Age−standardised incidence rates of cervical cancer



Annual percentage change



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- Cervical cancer trends, worldwide

European Journal of Cancer (2013) **49**, 3262–3273

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journal homepage: www.ejcancer.com

Worldwide trends in cervical cancer incidence: Impact of screening against changes in disease risk factors

Salvatore Vaccarella *, Joannie Lortet-Tieulent, Martyn Plummer, Silvia Franceschi, Freddie Bray

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Screening *versus* underlying risk factors

- **Screening** should deflect trends downward across *targeted age groups*, and should become apparent as **Period effect**, in populations where it has been introduced;

- **Changing exposure to etiologic factors** in successive generations of women (i.e., modifications in the population prevalence of persistent infection with oncogenic HPV) should be visible as **Cohort effect**.

?Can we distinguish these effects?

Age-period-cohort (APC) models

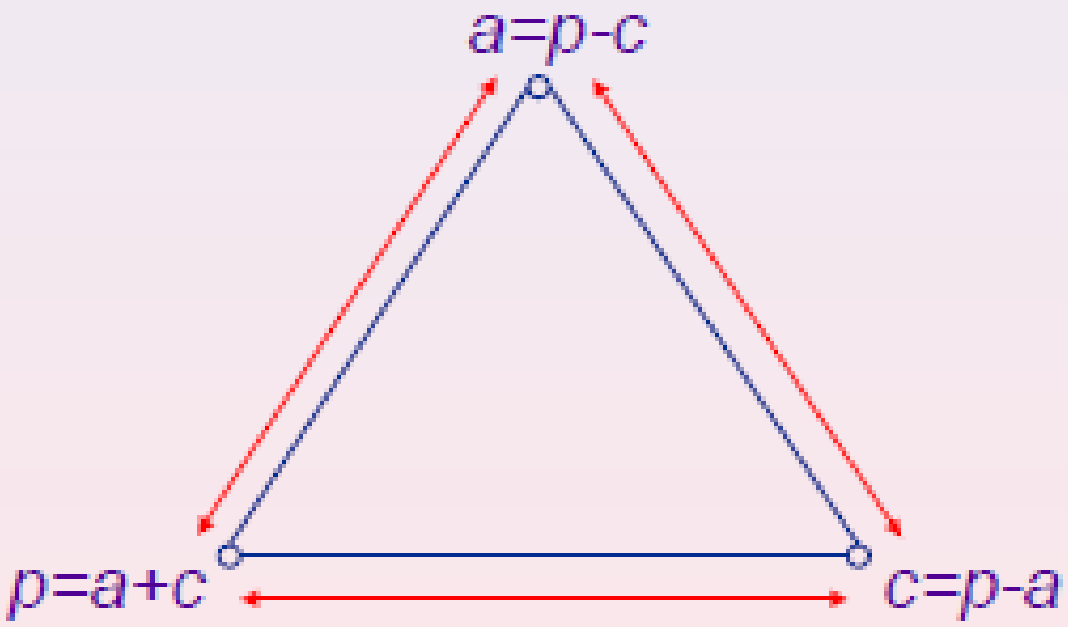
- Utilise a log-linear model to describe incidence rates λ(a,p) with the effects for ***age***, ***period*** and ***cohort***:

$$\text{Log}[\lambda(a,p)] = A + P + C$$

with A, P, and C referring to the effects of age, period and cohort

- However….

Knowledge of two of age, period and cohort leads to knowledge of the third and *non-identifiability*.



- The model is *not-identifiable*

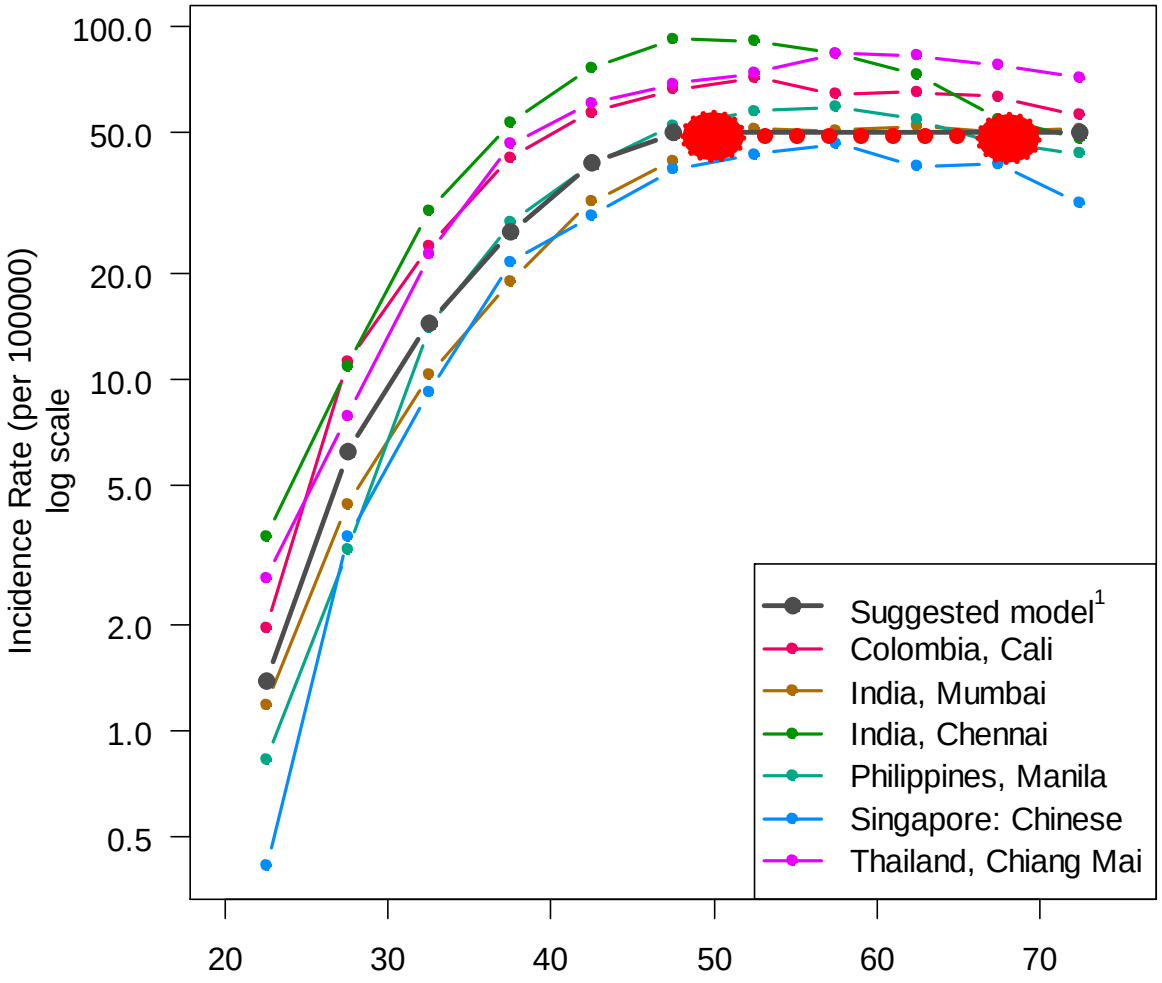
Age-period-cohort (APC) models
Identifiability problem

Possible solution

to use external information to add a constraint to one of the 3 variables, in order to extract identifiable answers for each of the parameters

(Vaccarella et al, 2014, BJC)
(Vaccarella et al, 2013, EJC)
(Bray et al, 2005, CEBP)

Relationship between age and incidence of CC



Constraint: **same risk at ages 45-49 and 65-69 years**

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(Plummer et al, 2011, IJC)

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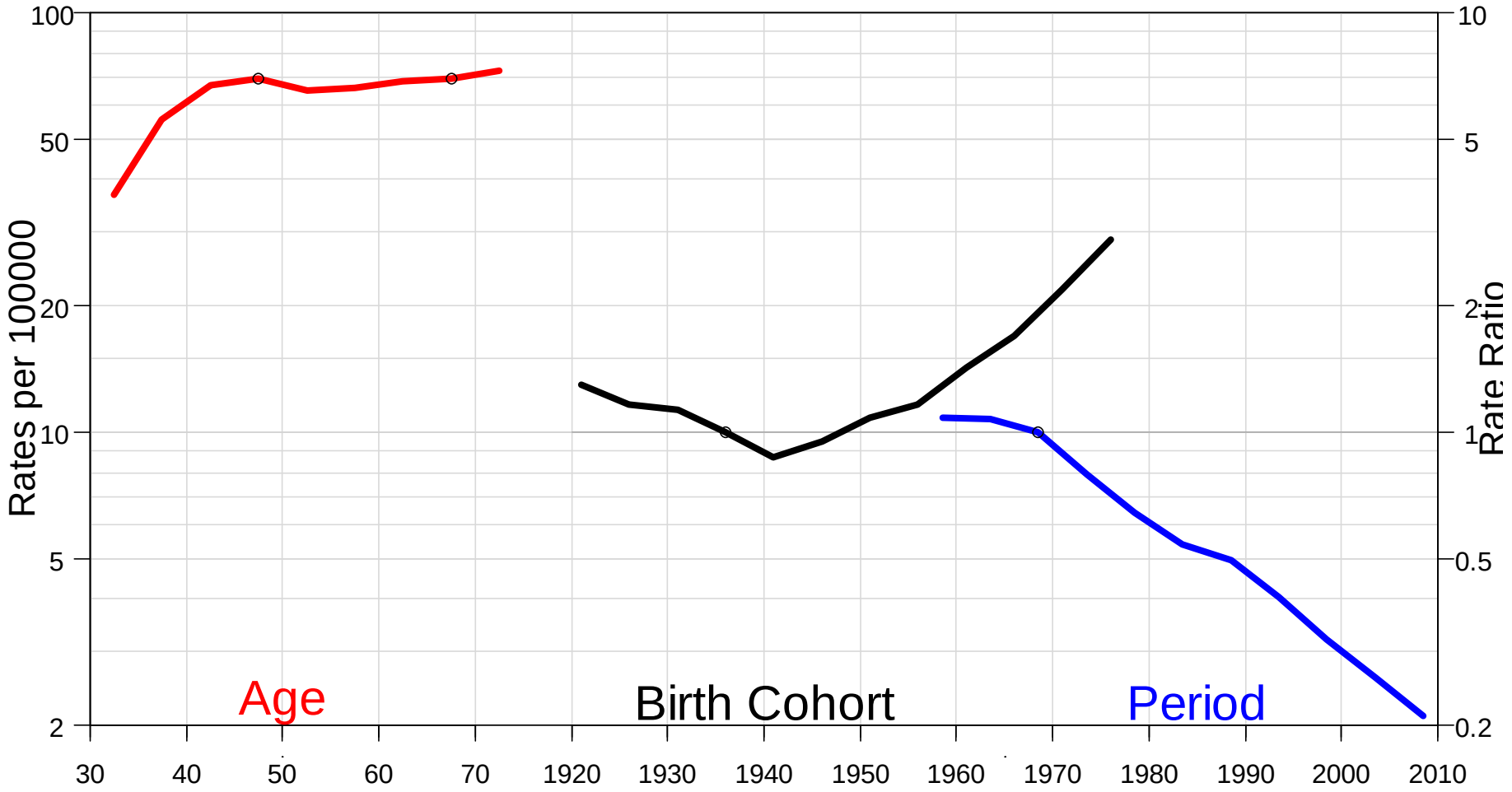
Age-period-cohort analysis

Results

Denmark



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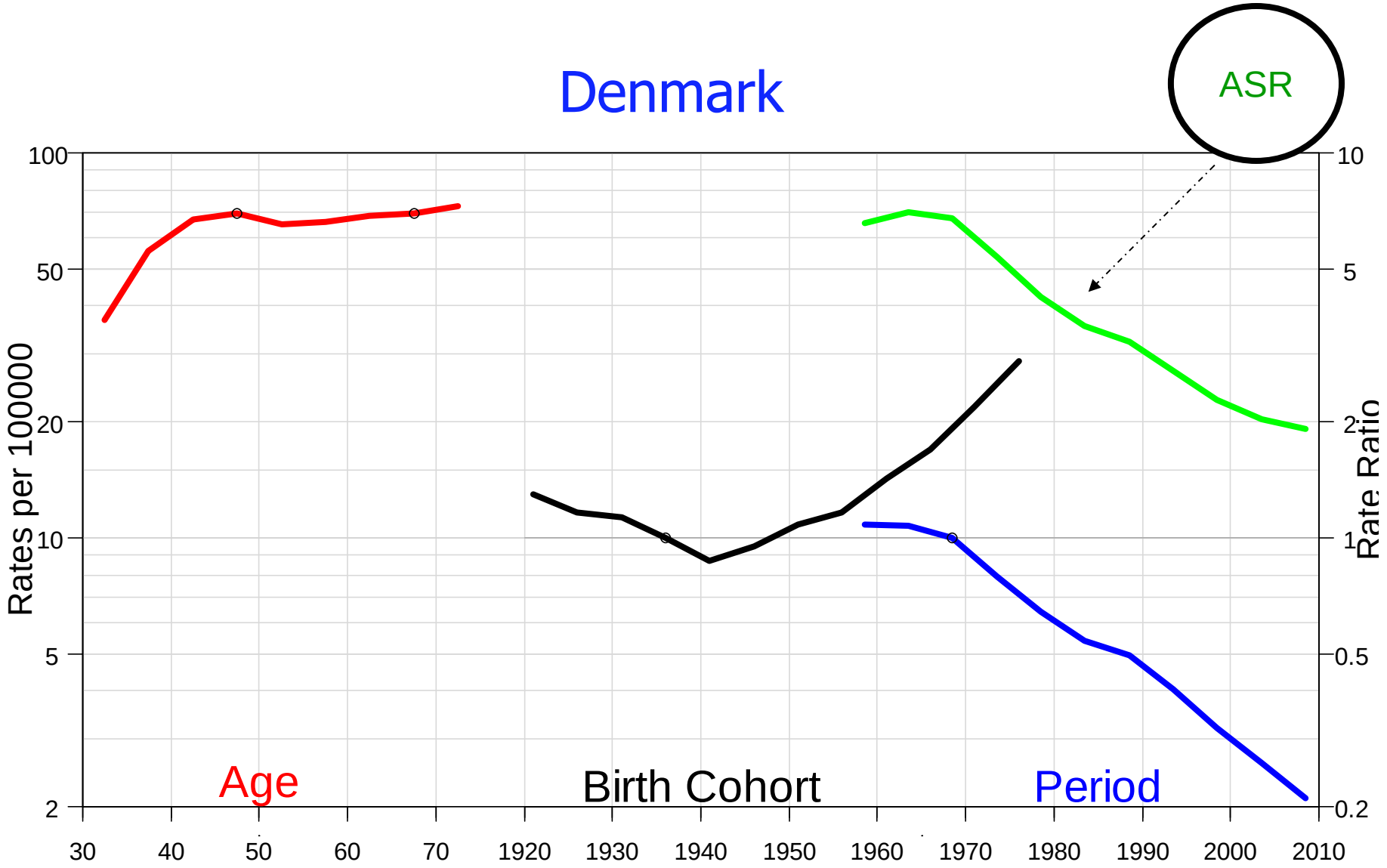
rate-scale for age-effects

relative risk scale for period and cohort effects



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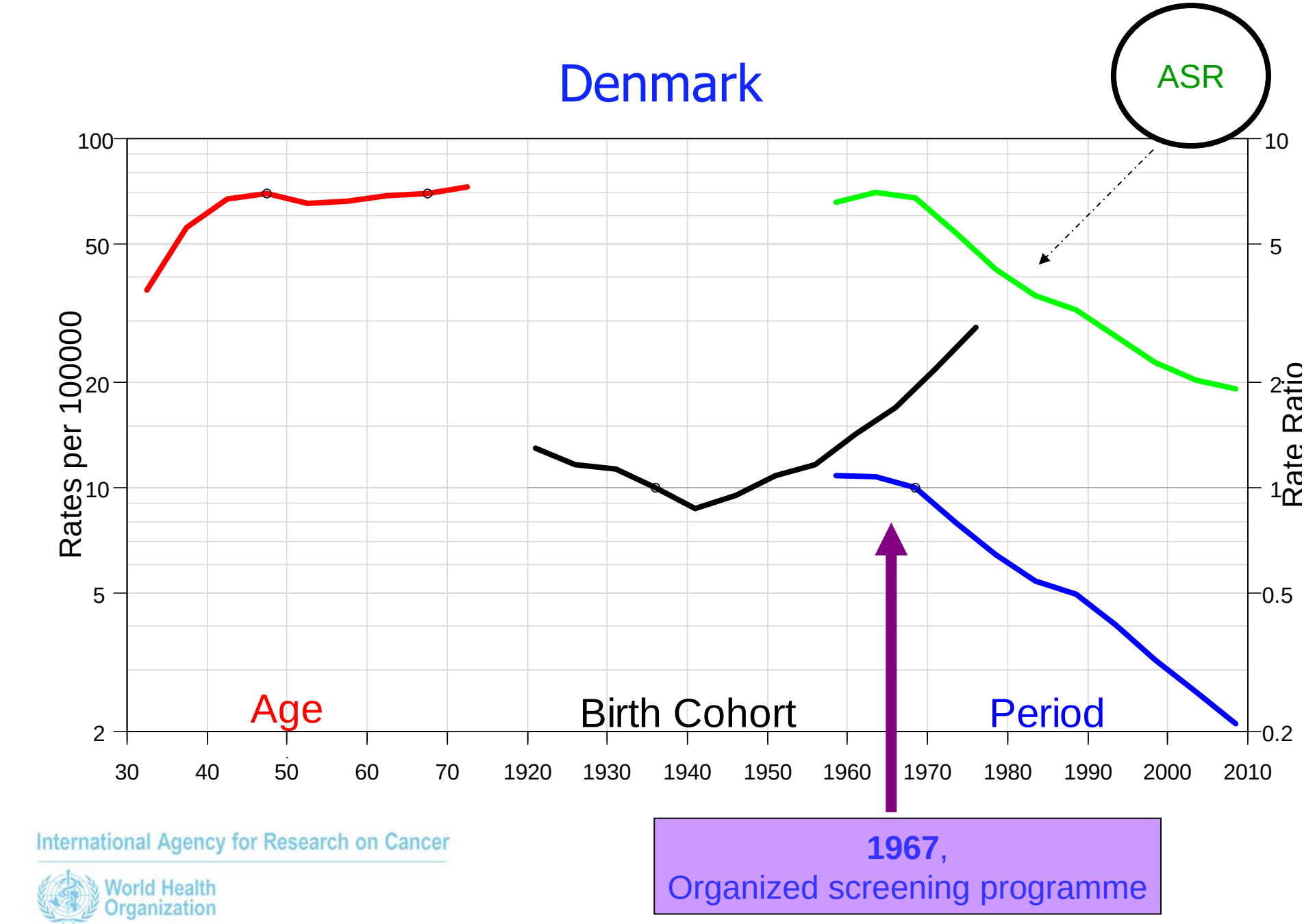
rate-scale for age-effects and ASR

relative risk scale for period and cohort effects



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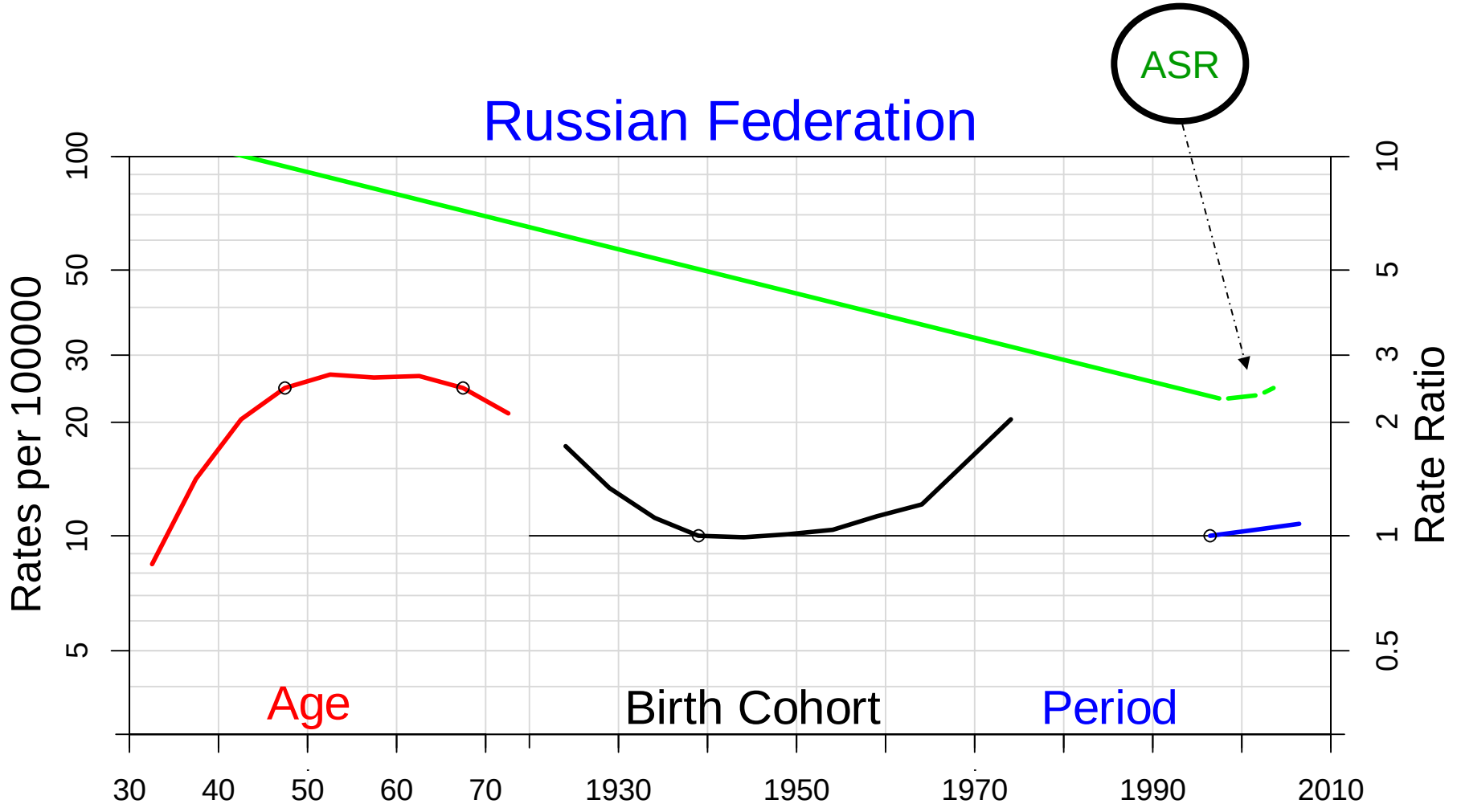
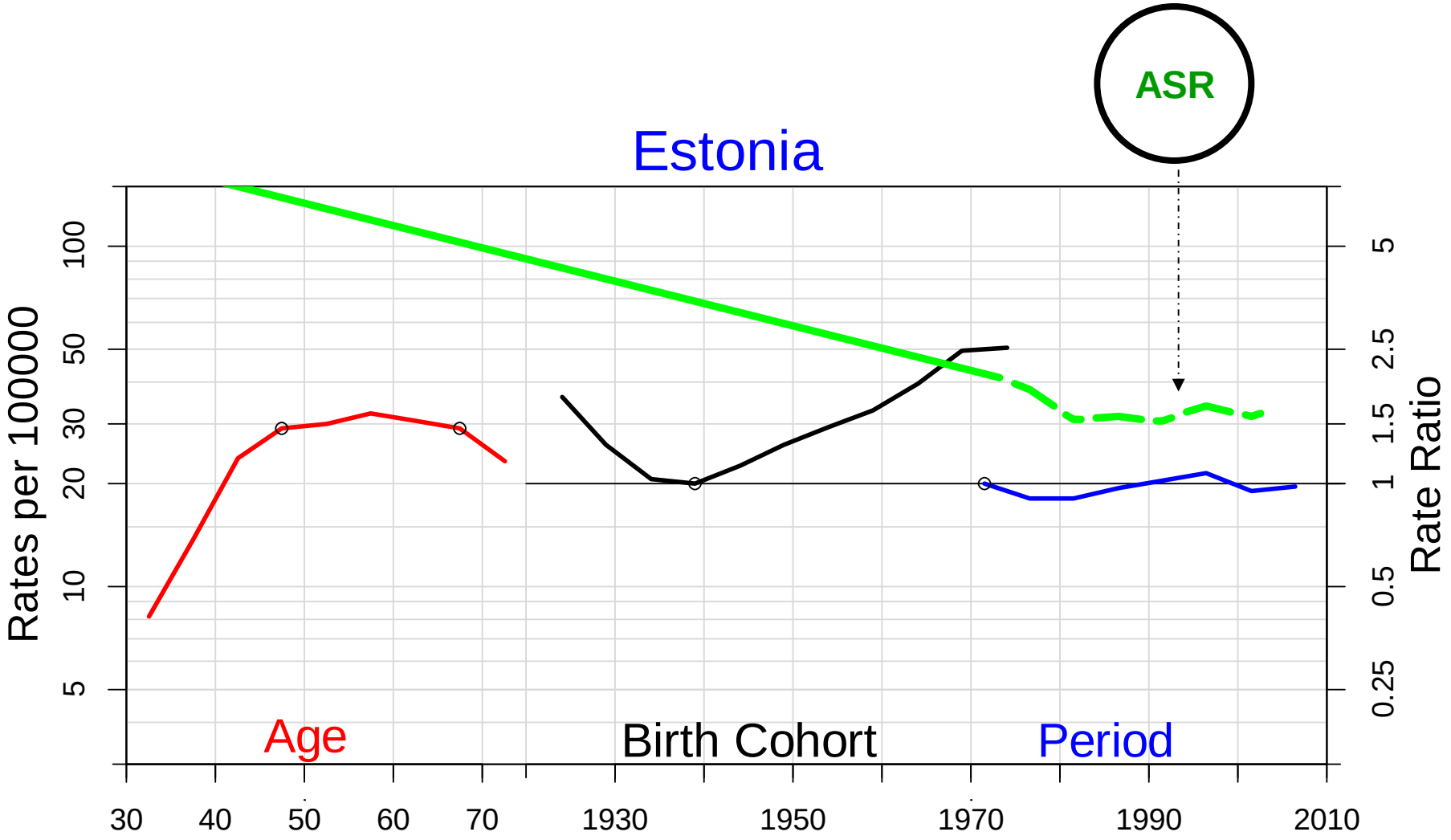
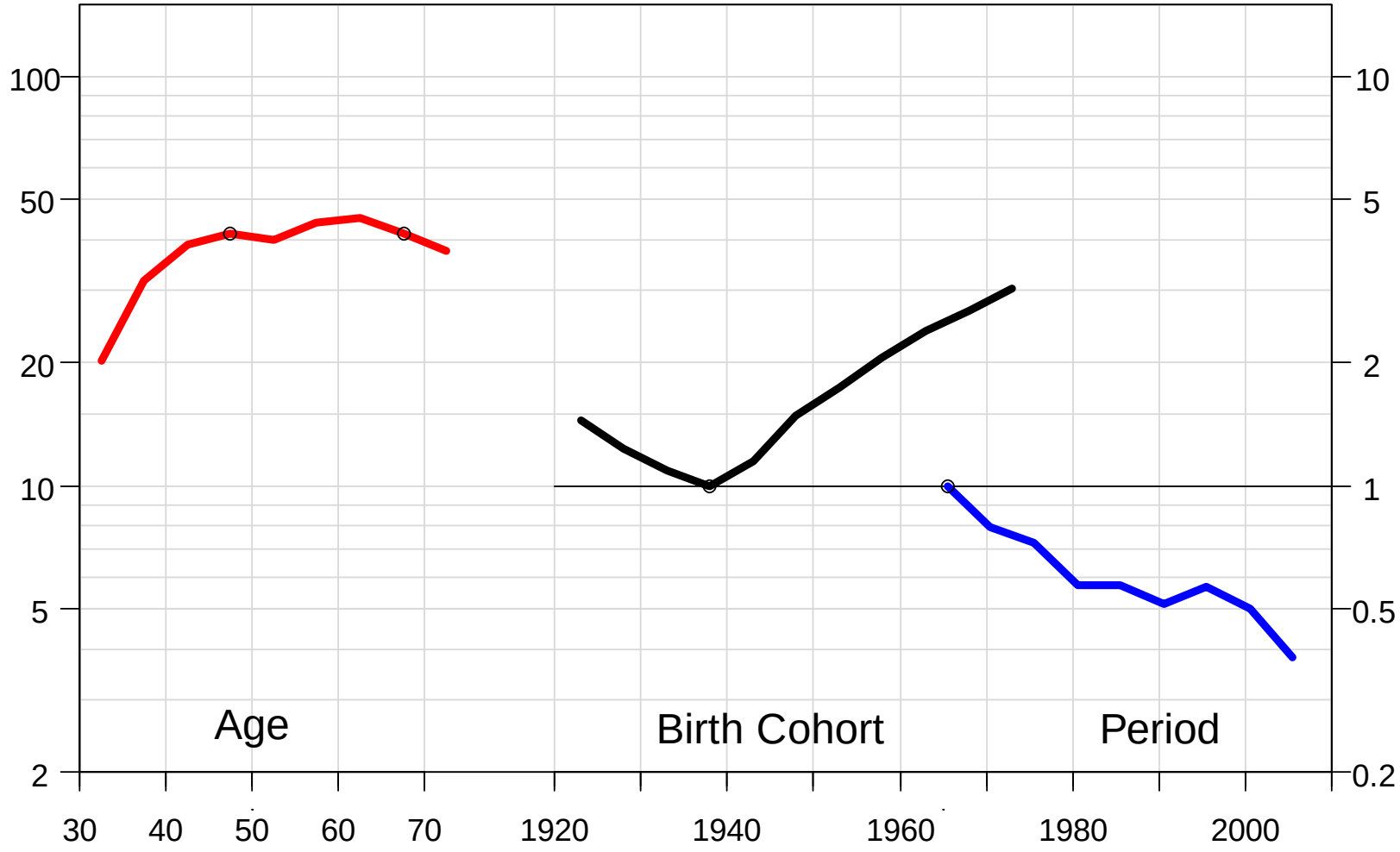


rate-scale for age-effects and ASR
relative risk scale for period and cohort effects


ASR
Estonia
Rates per 100000
100
50
30
20
10
5
Rate Ratio
5
2.5
1.5
1
0.5
0.25
Age
Birth Cohort
Period
30
40
50
60
70
1930
1950
1970
1990
2010

Slovenia



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Quantify the cervical cancer epidemic that has been prevented by screening

- In 4 Nordic countries
- With over 50 years of cancer incidence data
- Counterfactual scenario

BJC

British Journal of Cancer (2014), 1–5 | doi: 10.1038/bjc.2014.362

Keywords: screening; cervical cancer; incidence; age-period-cohort models

50 years of screening in the Nordic countries: quantifying the effects on cervical cancer incidence

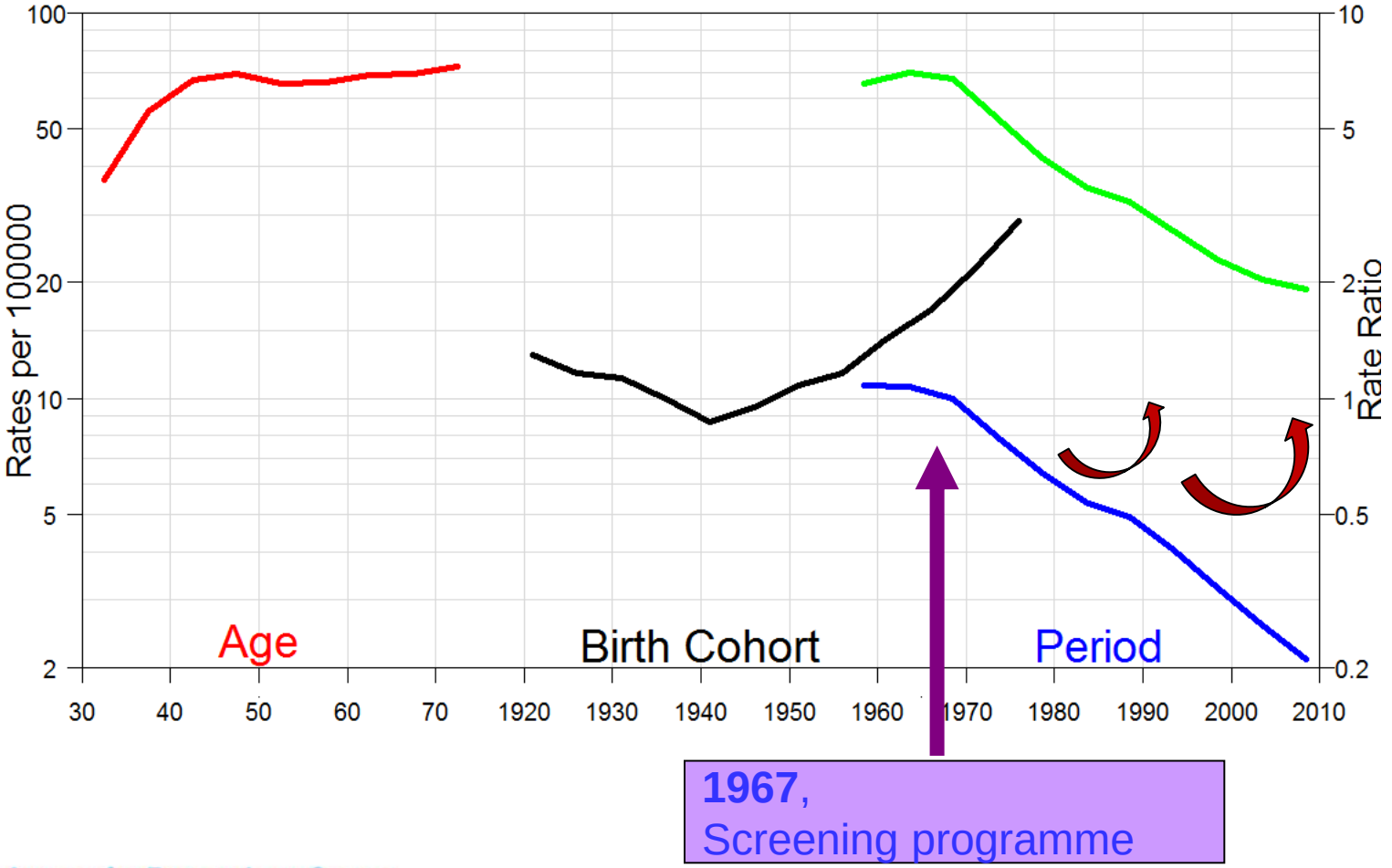
S Vaccarella*[,1], S Franceschi[1], G Engholm[2], S Lönnberg[3], S Khan[4] and F Bray[1]

[1]International Agency for Research on Cancer, 150 cours Albert Thomas, 69372 Lyon cedex 08, France; [2]Department of Documentation & Quality, Danish Cancer Society, Strandboulevarden 49, 2100 Copenhagen, Denmark; [3]Cancer Registry of Norway, P.O. box 5313 Majorstuen, Oslo N-0304, Norway and [4]Swedish Cancer Registry, National Board of Health and Welfare, S-106 30 Stockholm, Sweden

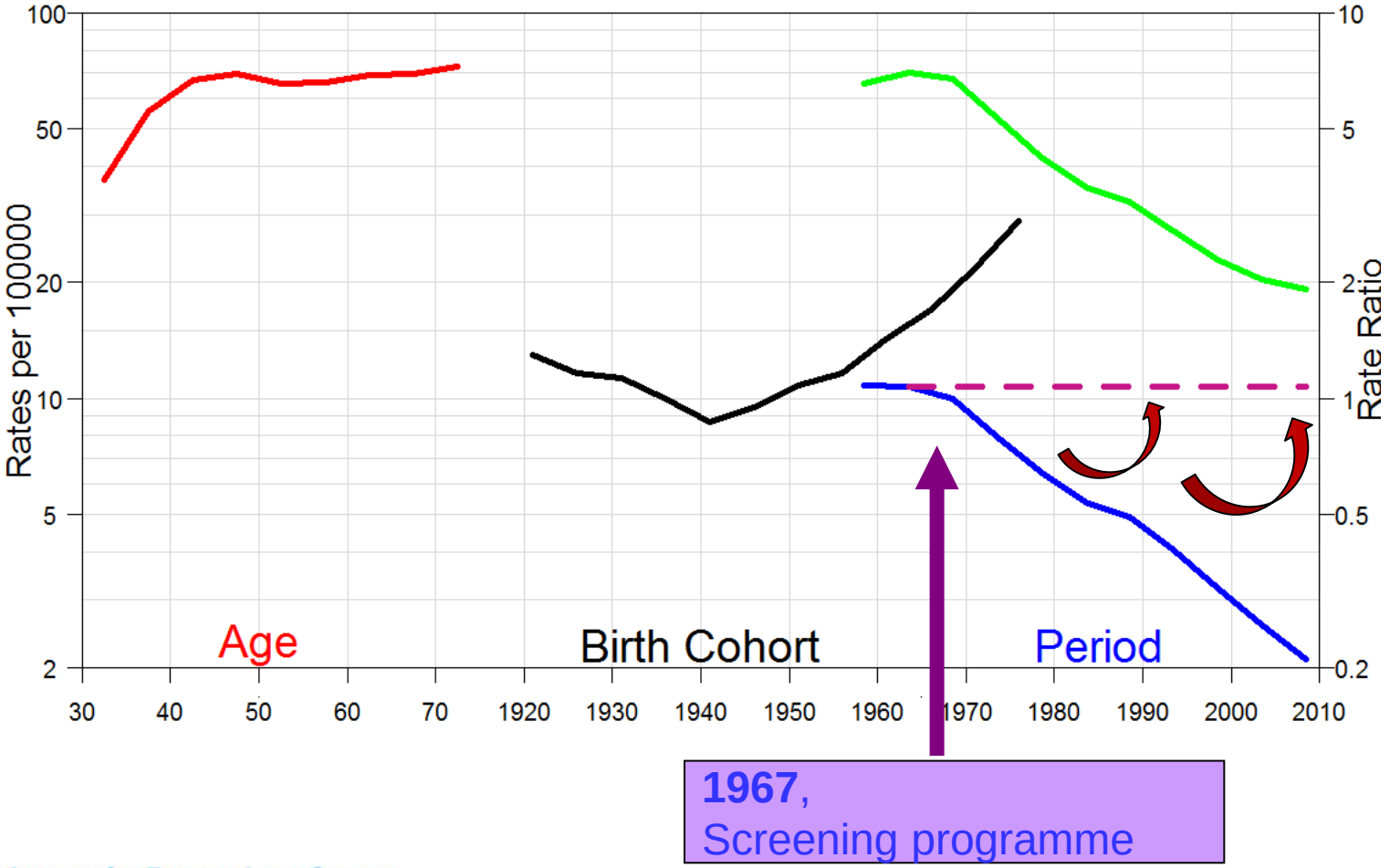
Projections of ASRs in a no-screening scenario

Assumption: declines in period effects are due to screening

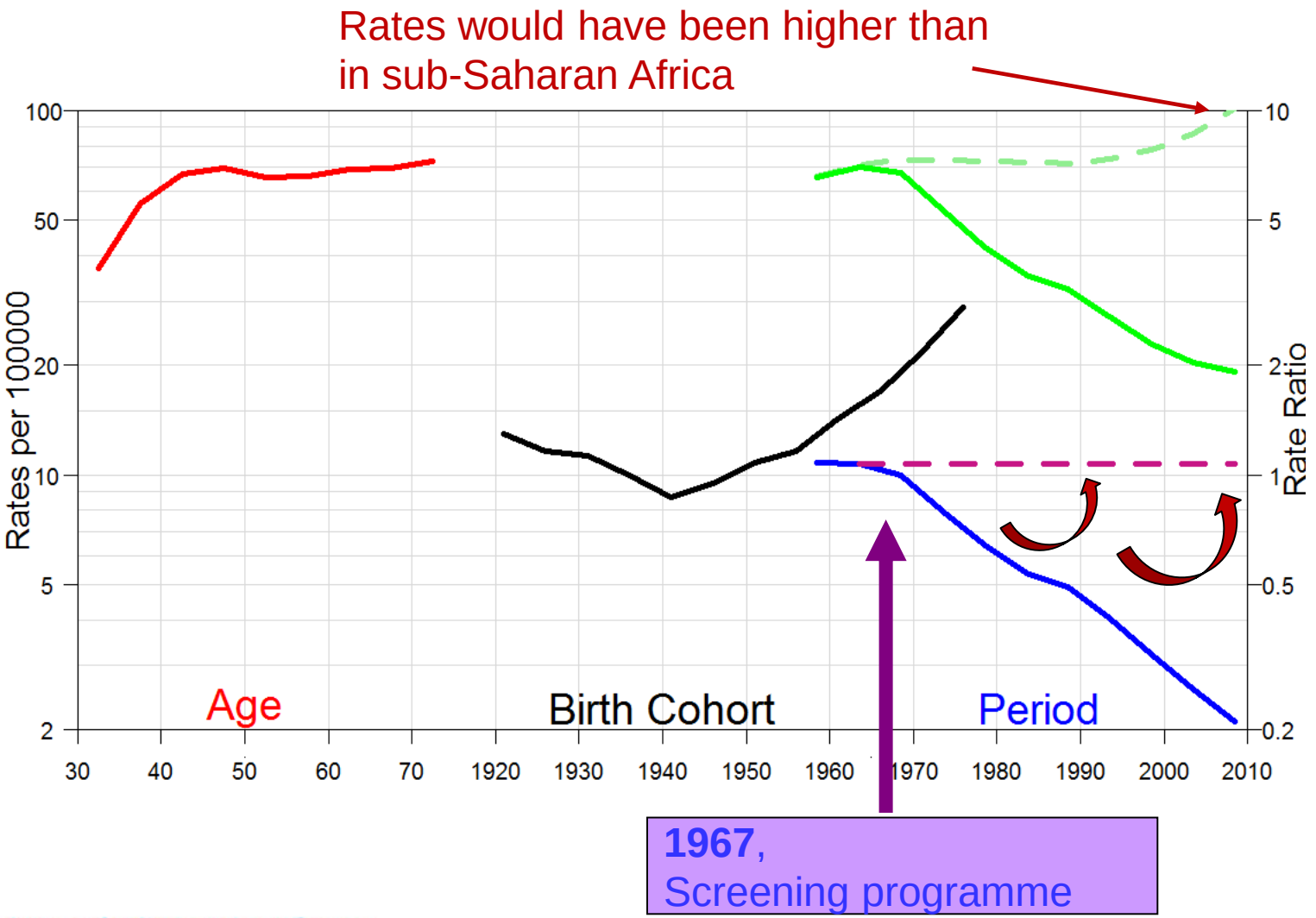
Cervical cancer cases prevented by screening in Denmark, 1956-2010:



Cervical cancer cases prevented by screening in Denmark, 1956-2010:



Cervical cancer cases prevented by screening in Denmark, 1956-2010:



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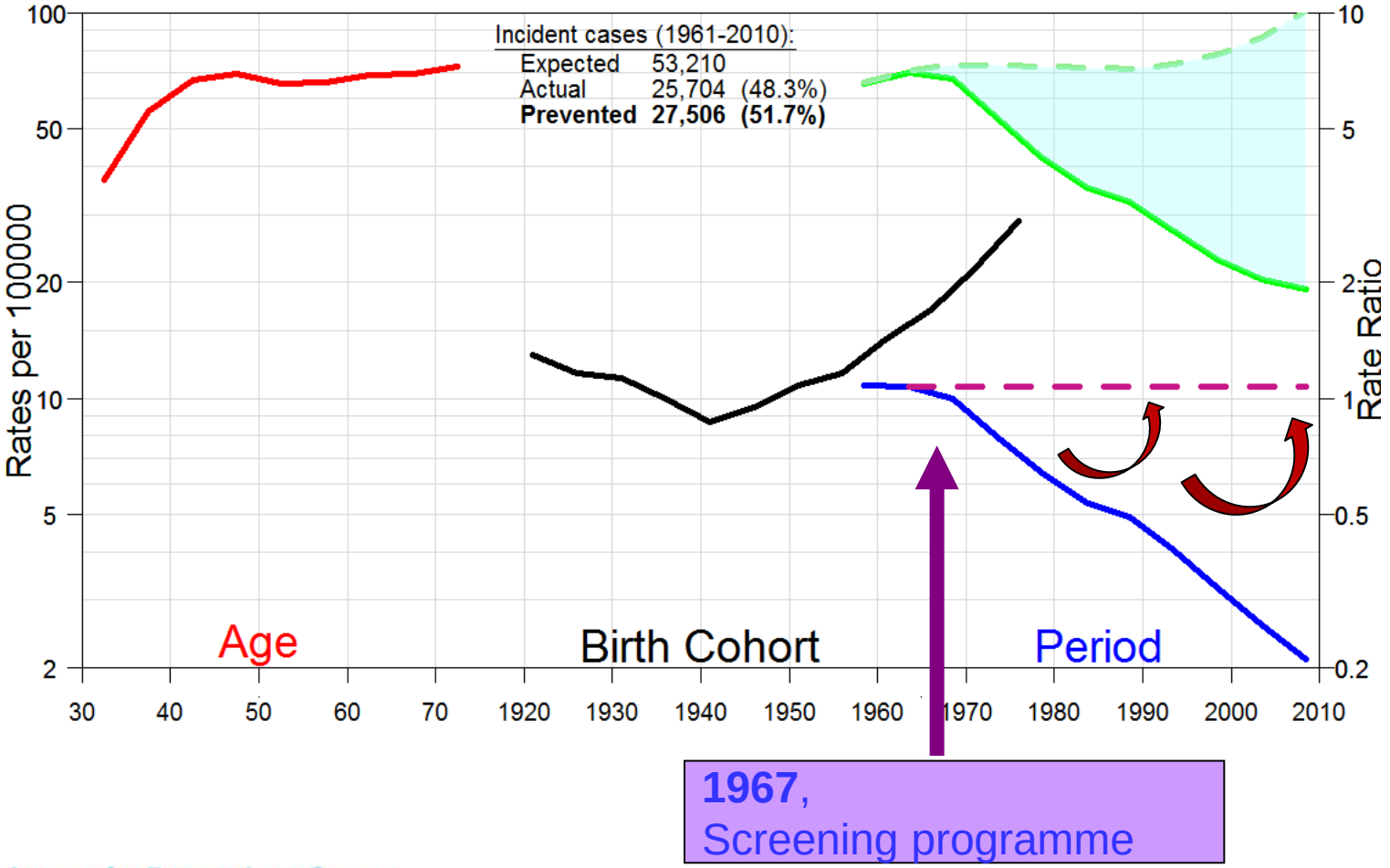
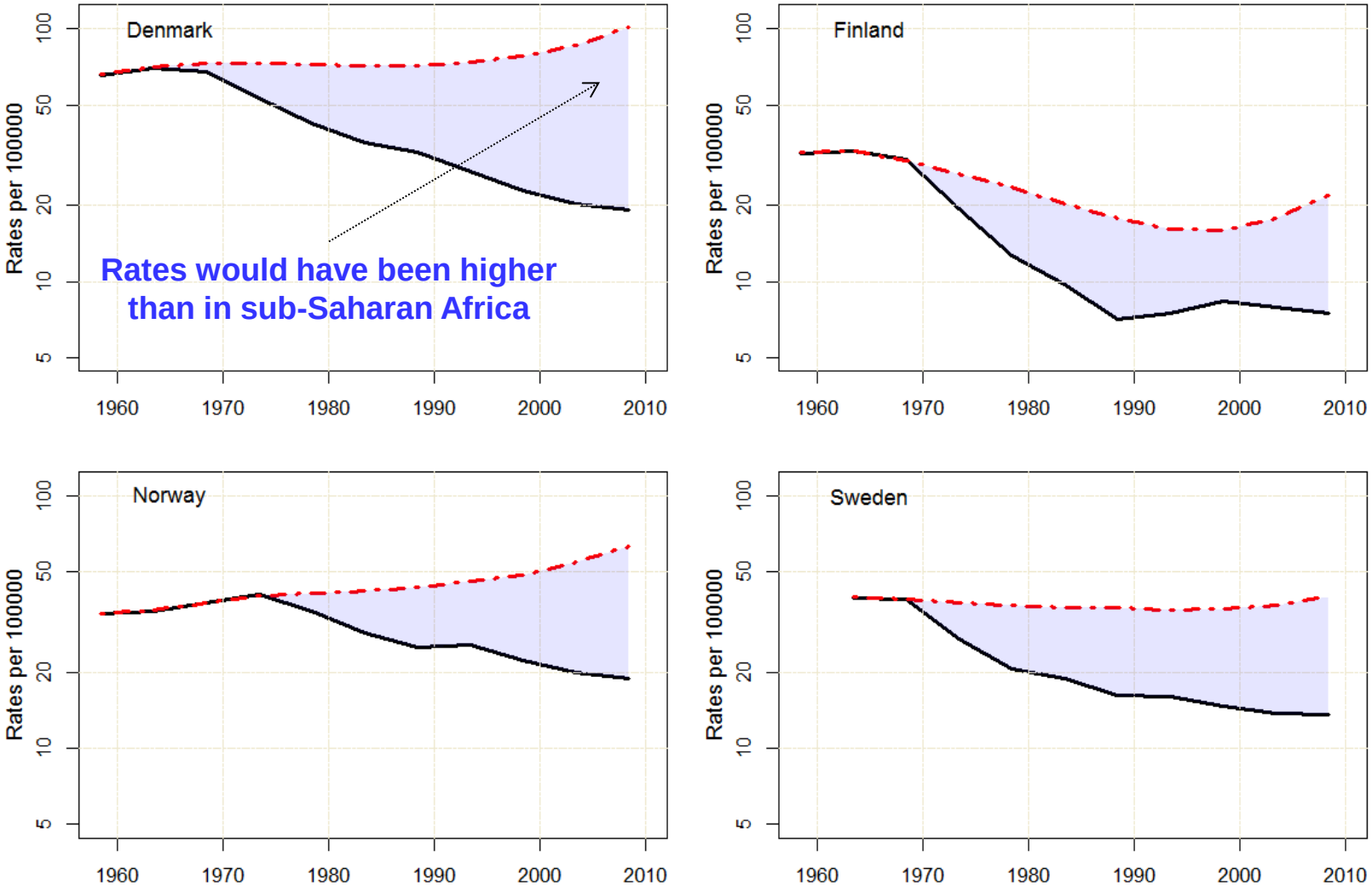
Cervical cancer cases prevented by screening in Denmark, 1956-2010:



Nearly 50% of cervical cancer cases might have been prevented by screening in the Nordic Countries, 1956-2010

(no screening→ increase due to changes in sexual habits)



According to a counterfactual scenario based on ad hoc refined age-period-cohort model (Vaccarella et al)

Five decades of cervical cancer screening:

Observed and projected number of incident cases and ASRs, age 30-74

Country	Cumulative number of incident cases, 1961-2010						ASR (per 100,000)	
	Observed	Projected		Prevented by screening			Observed	Projected
				Cumulative		Average per year, 2006-10	2006-10	
	N	N	95% CI	N	%	N		
Denmark	25,704	53,210	48,038-58,806	**27,506**	*51.7*	1,239	19.2	**102.0**
Finland	9,410	15,133	12,814-18,136	**5,723**	*37.8*	202	7.5	**21.8**
Norway	15,146	24,603	21,555-28,393	**9,457**	*38.4*	552	19.0	**62.8**
Sweden	24,556	42,777	38,018-48,312	**18,221**	*42.6*	647	13.6	**40.0**

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CONCLUSIONS

- Without screening, current rates in the Nordic countries would have been **3-to-5 times higher** that those observed, i.e., comparable to rates in low-income countries

- Screening programs might have prevented over **60,000 cases** of cervical cancer in the Nordic countries, i.e., **nearly half** of the cases expected in a no-screening scenario

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- Cancer Surveillance Section, IARC
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