- Lo screening per la prevenzione del cancro del collo dell'utero tra presente e futuro -
Convegno SIPMEL - Città di Castello 11 marzo 2017

Il cancro della cervice in Umbria e nel mondo

Fabrizio Stracci

Università di Perugia
Registro Tumori Umbro di Popolazione
GdL Siti Prevenzione Tumori/Screening

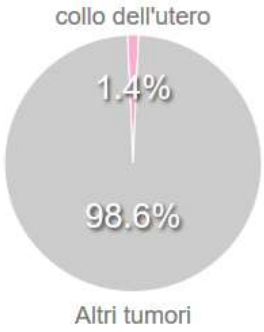
La classifica umbra e il trend

43 nuovi casi per anno nel periodo 2009-13

(1994-2013: 40 casi per anno) 17° tumore per frequenza

216 casi nel periodo 2009-2013

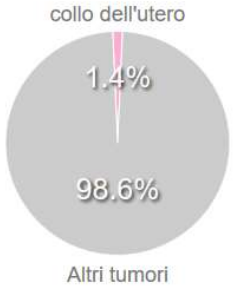
In media 43 casi per anno



Tasso standardizzato per 100,000 abitanti, popolazione Italia 2011:
8.87

804 casi nel periodo 1994-2013

In media 40 casi per anno



Tasso standardizzato per 100,000 abitanti, popolazione Italia 2011:
8.90

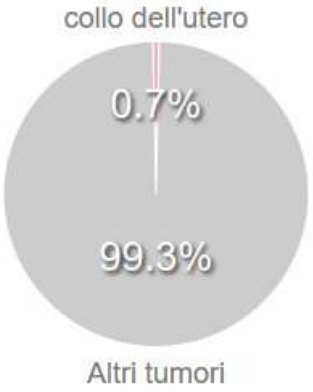
Primi cinque tumori più frequentemente diagnosticati in Umbria e proporzione sul totale dei tumori per sesso.

Periodo completo: 1994 - 2013 | Ultimi 10 anni: 2004 - 2013 | **Ultimi 5 anni: 2009 - 2013**

Rank	Maschi	Rank	Femmine	Rank	Tutta la popolazione
1	**Prostata** 687 casi per anno - 17.9%	1	**Mammella** 761 casi per anno - 23.9%	1	**Colon retto** 837 casi per anno - 11.9%
2	**Colon retto** 468 casi per anno - 12.2%	2	**Colon retto** 369 casi per anno - 11.6%	2	**Mammella** 769 casi per anno - 10.9%
3	**Bronchi e polmoni** 436 casi per anno - 11.4%	3	**Bronchi e polmoni** 171 casi per anno - 5.4%	3	**Prostata** 687 casi per anno - 9.8%
4	**Vie urinarie** 265 casi per anno - 6.9%	4	**Stomaco** 146 casi per anno - 4.6%	4	**Bronchi e polmoni** 608 casi per anno - 8.7%
5	**Stomaco** 185 casi per anno - 4.8%	5	**Corpo dell'utero** 137 casi per anno - 4.3%	5	**Vie urinarie** 334 casi per anno - 4.8%
		17	**Collo dell'utero** 43 casi per anno - 1.4%	22	**Collo dell'utero** 43 casi per anno - 0.6%

183 casi nel periodo 1994-2014

In media 9 casi per anno



Tasso standardizzato per 100,000 abitanti, popolazione Italia 2011:
1.78

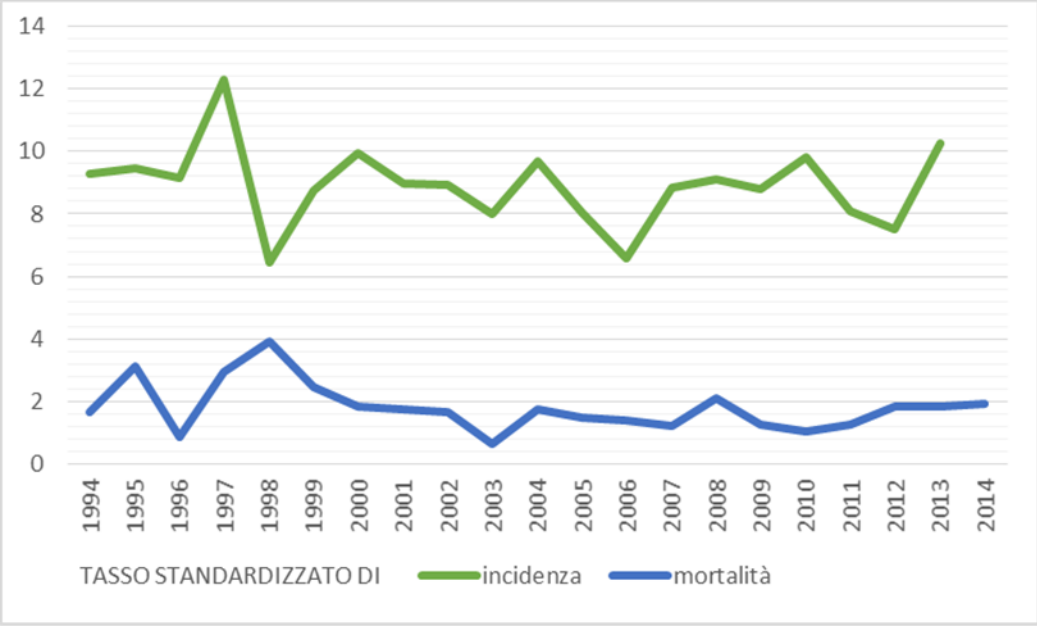
9 decessi per anno nel periodo 2010-14
24° tra le cause di morte oncologiche

Prime cinque cause di morte per tumore più frequenti e proporzione sul totale dei decessi oncologici per sesso.

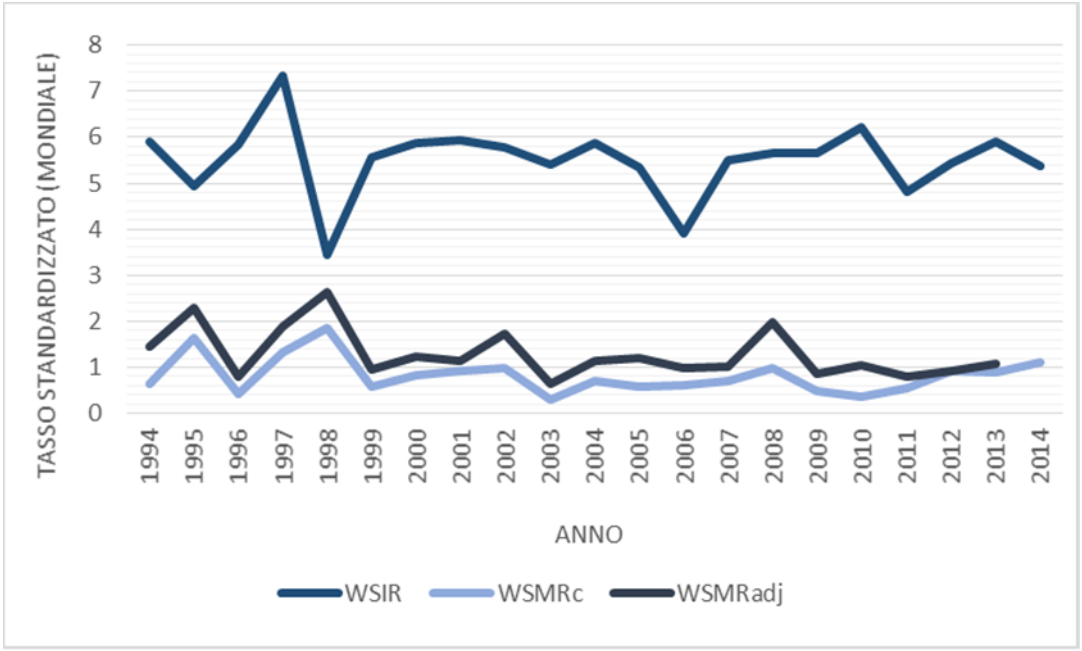
Periodo completo: 1994 - 2014 | Ultimi 10 anni: 2005 - 2014 | Ultimi 5 anni: 2010 - 2014

Rank	Maschi	Rank	Femmine	Rank	Tutta la popolazione
1	**Bronchi e polmoni** 362 casi per anno - 20.6%	1	**Mammella** 175 casi per anno - 12.9%	1	**Bronchi e polmoni** 500 casi per anno - 16.0%
2	**Colon retto** 186 casi per anno - 10.6%	2	**Colon retto** 149 casi per anno - 10.9%	2	**Colon retto** 335 casi per anno - 10.7%
3	**Prostata** 135 casi per anno - 7.7%	3	**Bronchi e polmoni** 138 casi per anno - 10.1%	3	**Stomaco** 223 casi per anno - 7.1%
4	**Stomaco** 129 casi per anno - 7.3%	4	**Pancreas** 98 casi per anno - 7.2%	4	**Pancreas** 182 casi per anno - 5.8%
5	**Vie urinarie** 88 casi per anno - 5.0%	5	**Stomaco** 94 casi per anno - 6.9%	5	**Mammella** 178 casi per anno - 5.7%
		24	**Collo dell'utero** 9 casi per anno - 0.6%	28	**Collo dell'utero** 9 casi per anno - 0.3%

Tassi standardizzati di incidenza e mortalità 1994 – 201*
(dati consolidati)



Tassi standardizzati di incidenza e mortalità 1994 – 2014



- Incidenza (WSIR)
- Mortalità per cancro della cervice uterina in base al certificato di causa di morte (WSMRc)
- Mortalità attribuita alla cervice uterina in base alla sede del tumore riportata nel registro regionale (WSMRadj)*

* IBM 1996-2013; 1994-95 riallocati proporzionalmente secondo Loos AH et al. Sheep and goats… Eur J Cancer 2004

L'accuratezza delle cause di morte e la stima dei trend: il caso della cervice uterina

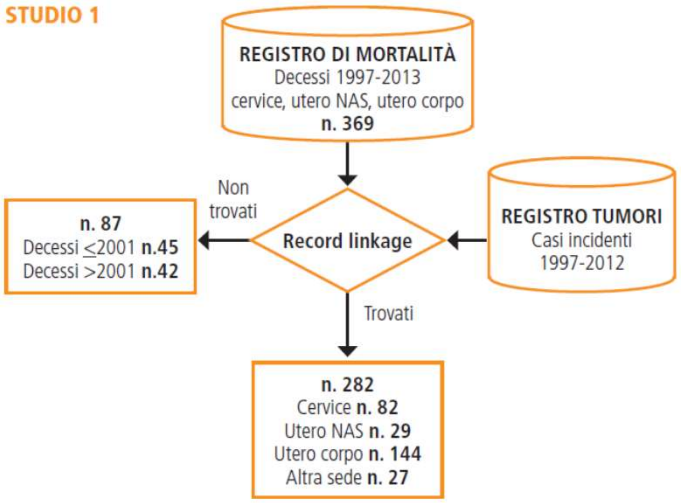
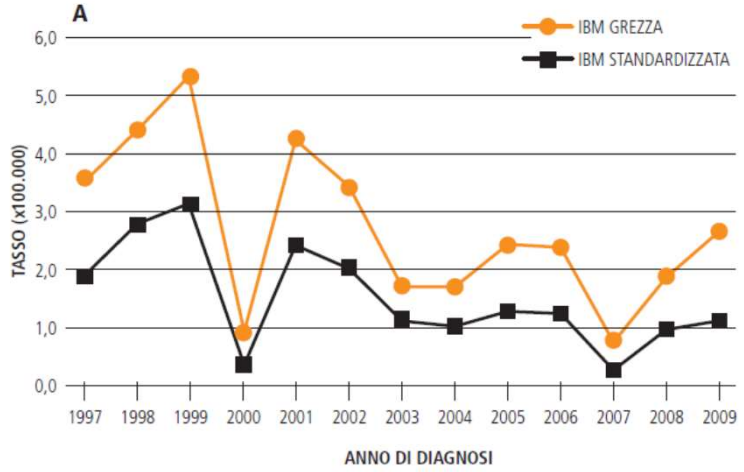
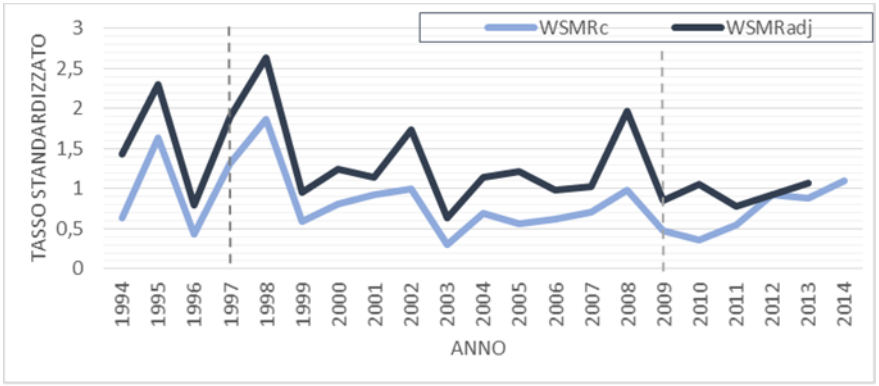


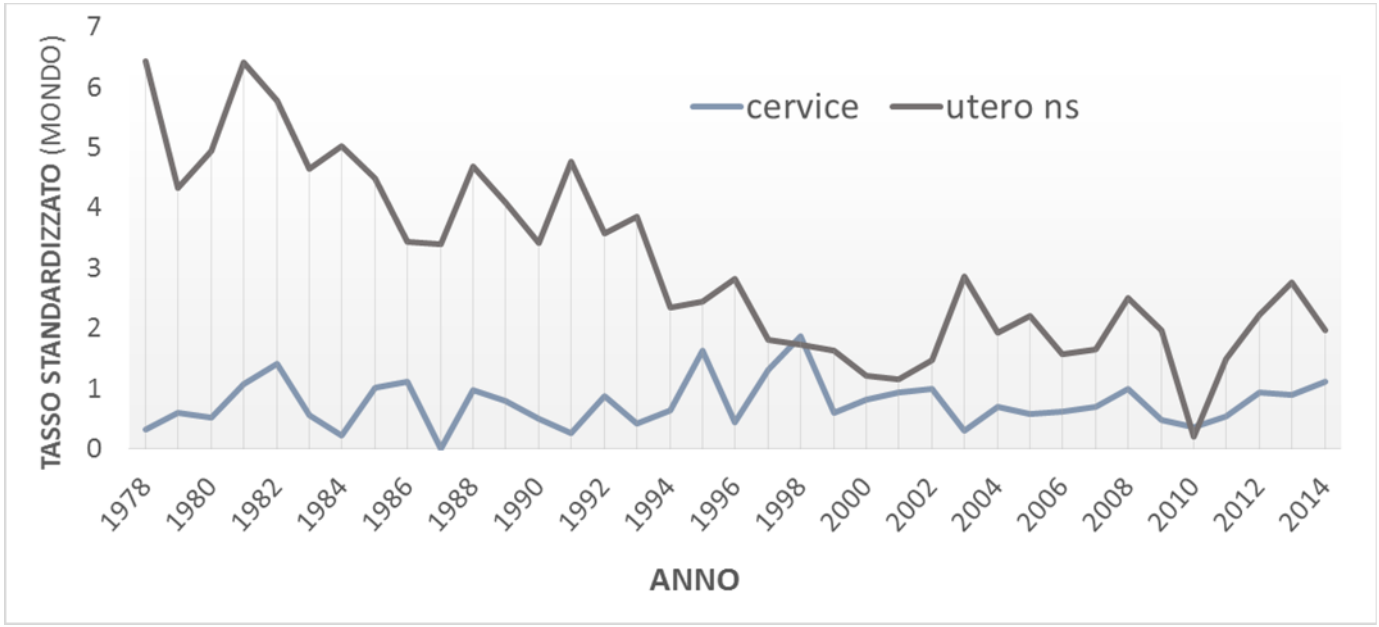
Figura 1. Diagramma di flusso dell'uso delle fonti nei due studi.
Figure 1. Flowchart of the use of the sources within the two studies.

Mancuso et al. Epidemiol Prev. 2016;40:157-63.



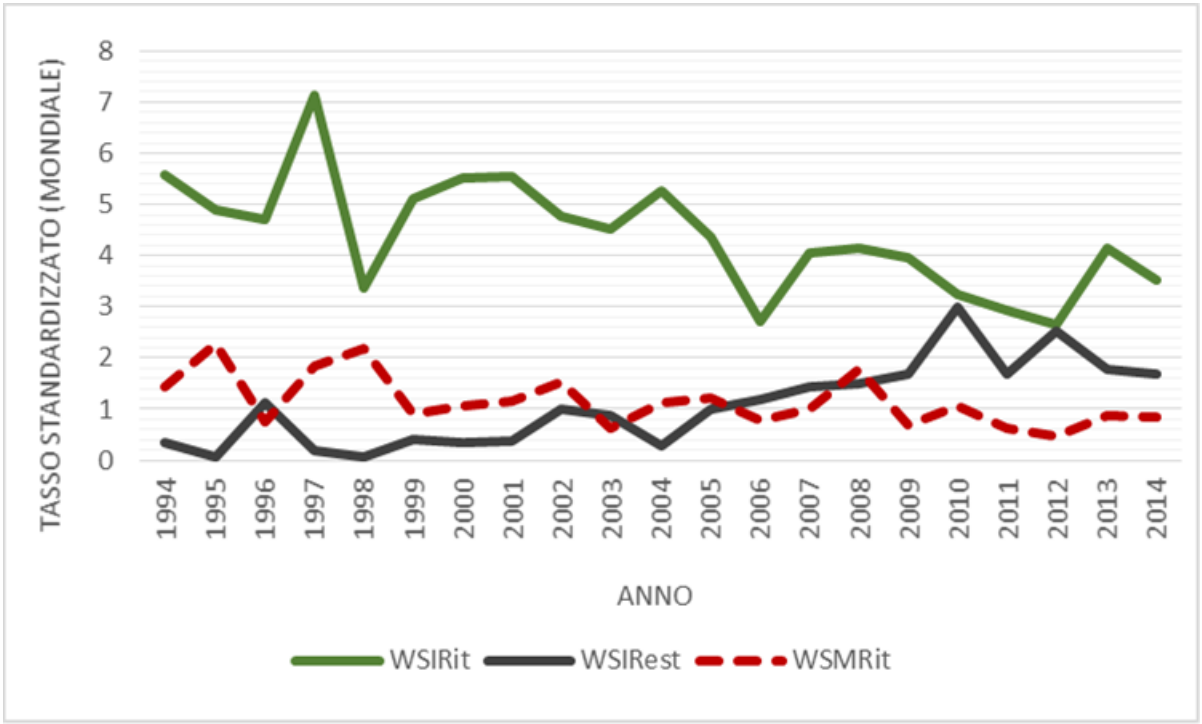


La mortalità in Umbria dagli anni ‘70 (fine)

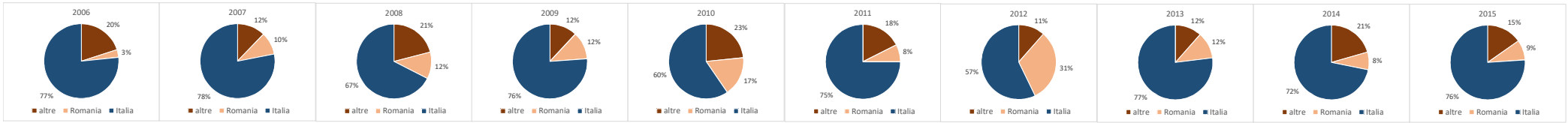


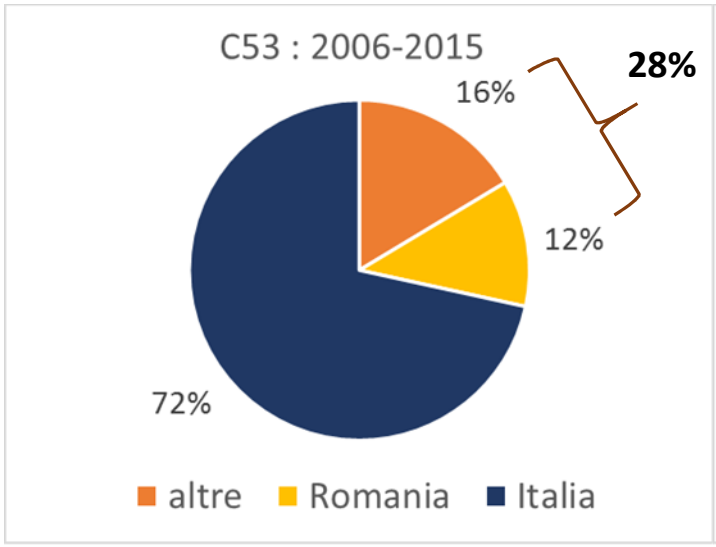
Composizione dei casi

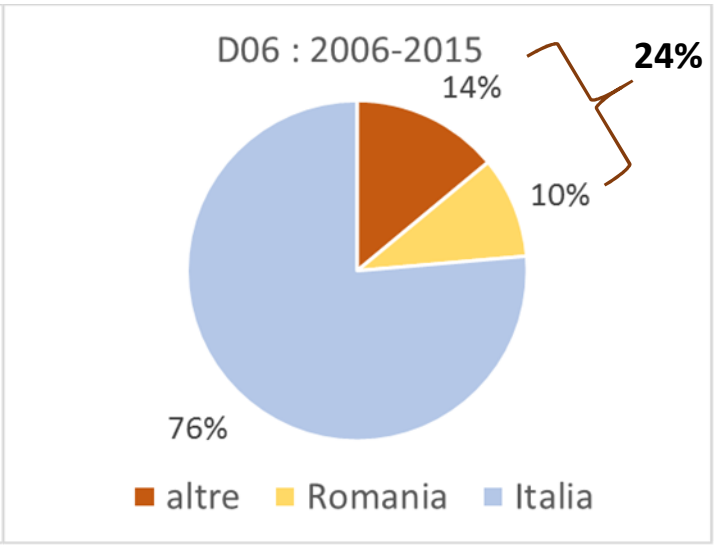
Tassi standardizzati di incidenza di carcinoma della cervice uterina per nate in Italia (verde) verso nate all'estero (grigio) e di mortalità per nate in Italia (rosso); periodo 1994 – 2014

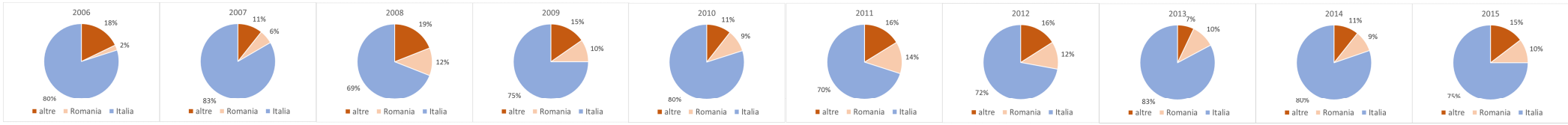


Distribuzione % dei casi di carcinoma infiltrante e CIN III per comune di nascita 2006-15

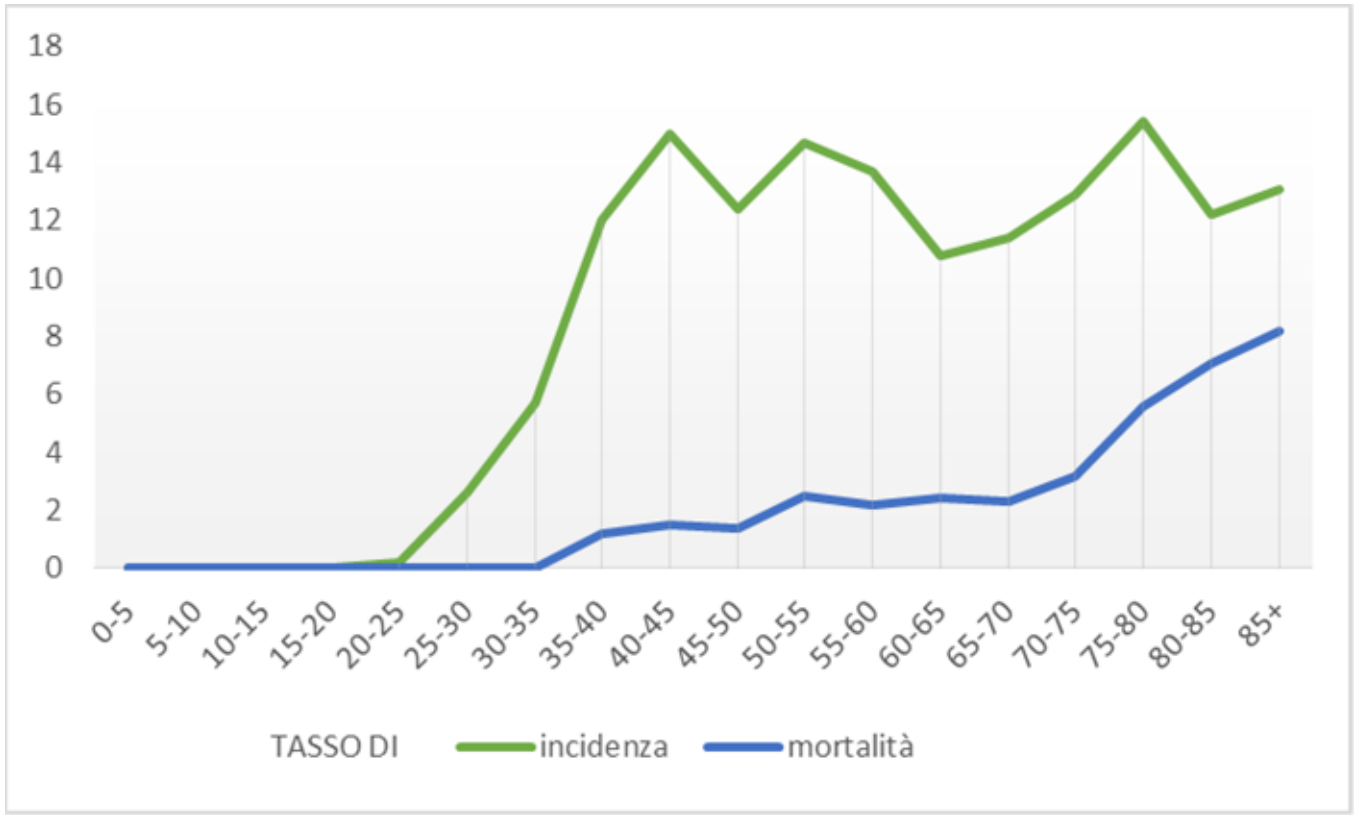




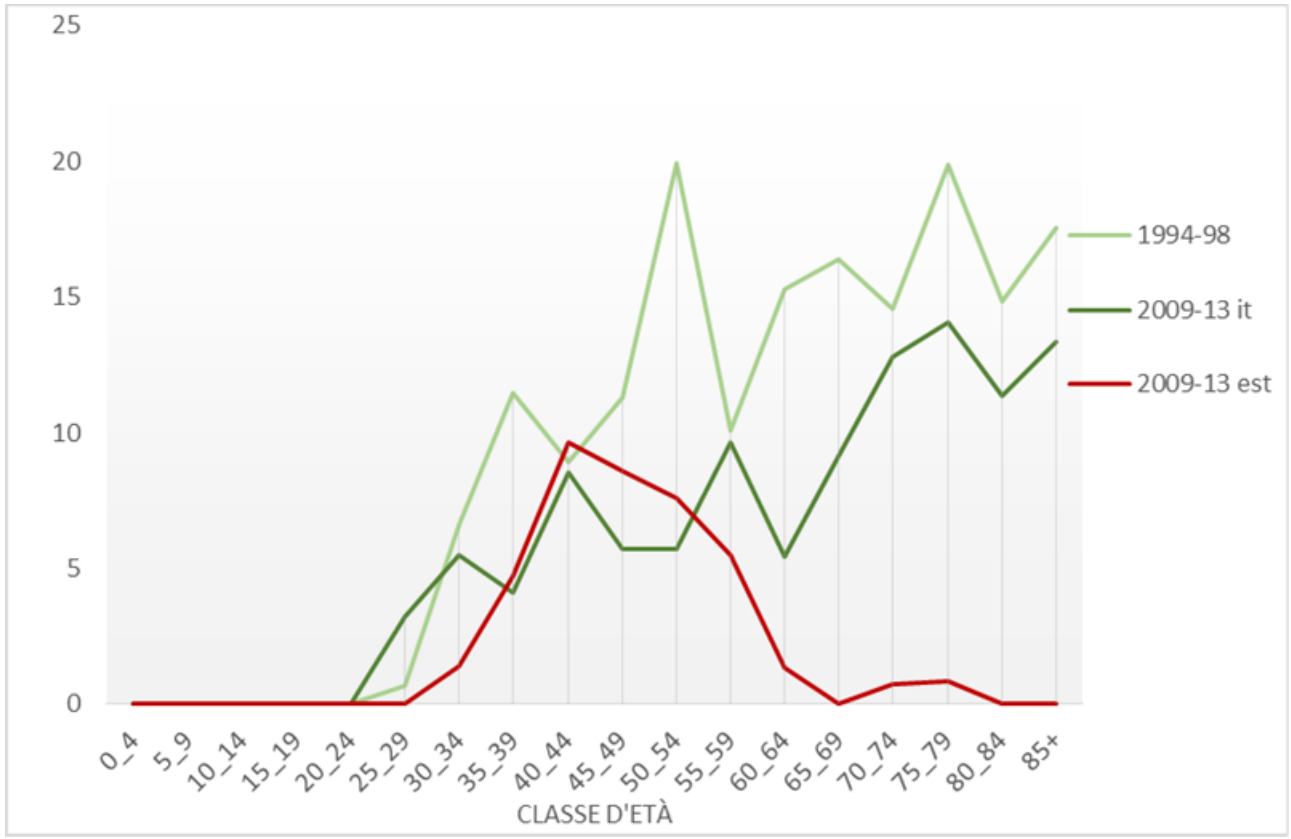




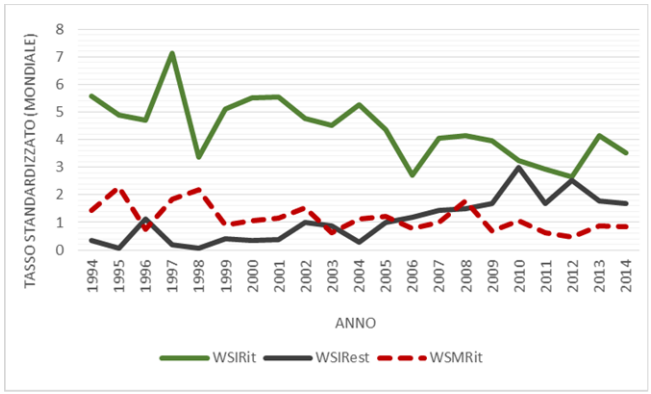
Tassi età specifici 1994-2014



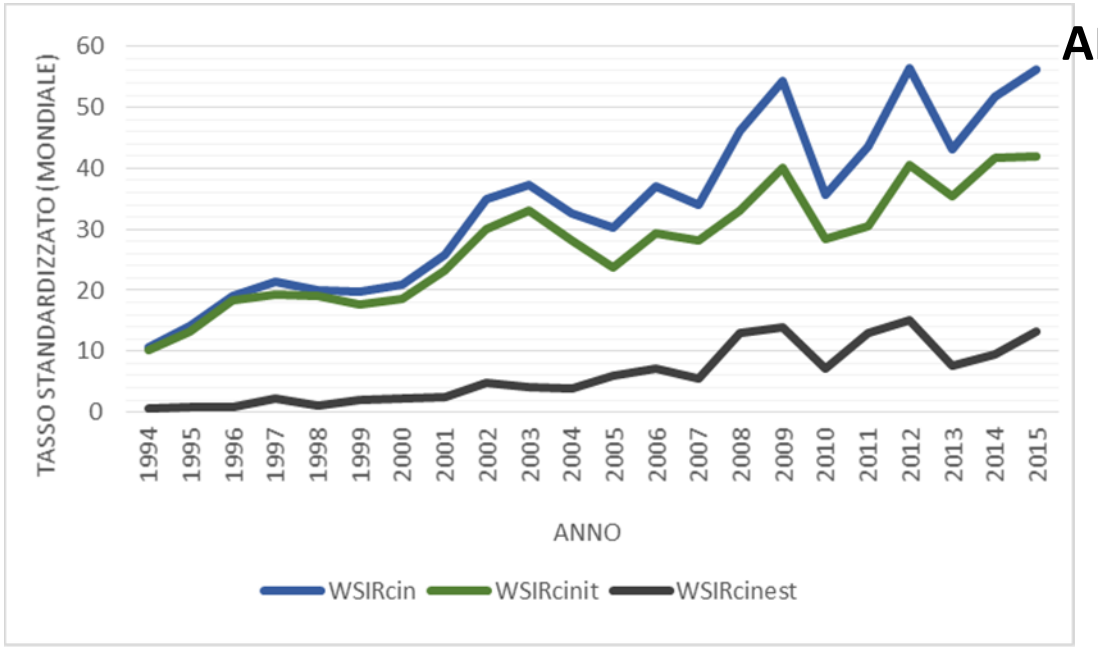
Distribuzione per età, periodo e comune di nascita – tassi età specifici di incidenza



Tassi standardizzati di incidenza complessivo (blu), nate in Italia (verde) verso nate all'estero (grigio) di CIN III (D06) - periodo 1994 – 2015



Carcinoma infiltrante (C53)



APC +5.9%

CIN III (D06)

RISULTATI (CIN3)

	n	%
Totale	3000	100
Classe di età		
<25 anni	136	4.5
25-64 anni	2795	93.2
≥65 anni	69	2.3
Paese di nascita		
Italia	2467	82
Estero	533	18

CARATTERISTICHE DELLE DONNE CON DIAGNOSI DI CIN3 (D06). UMBRIA, 1994-2013

INCIDENZA DI CIN3

Periodo	n	Tasso grezzo	Tasso standard. (95% IC)
1994-1998	395	18.78	19.33 (17.44-21.42)
1999-2003	654	30.59	30.99 (28.63-33.56)
2004-2008	861	38.25	38.66 (36.09-41.42)
2009-2013	1090	46.96	48.97 (46.10-52.06)

Classificazioni delle lesioni cervicali

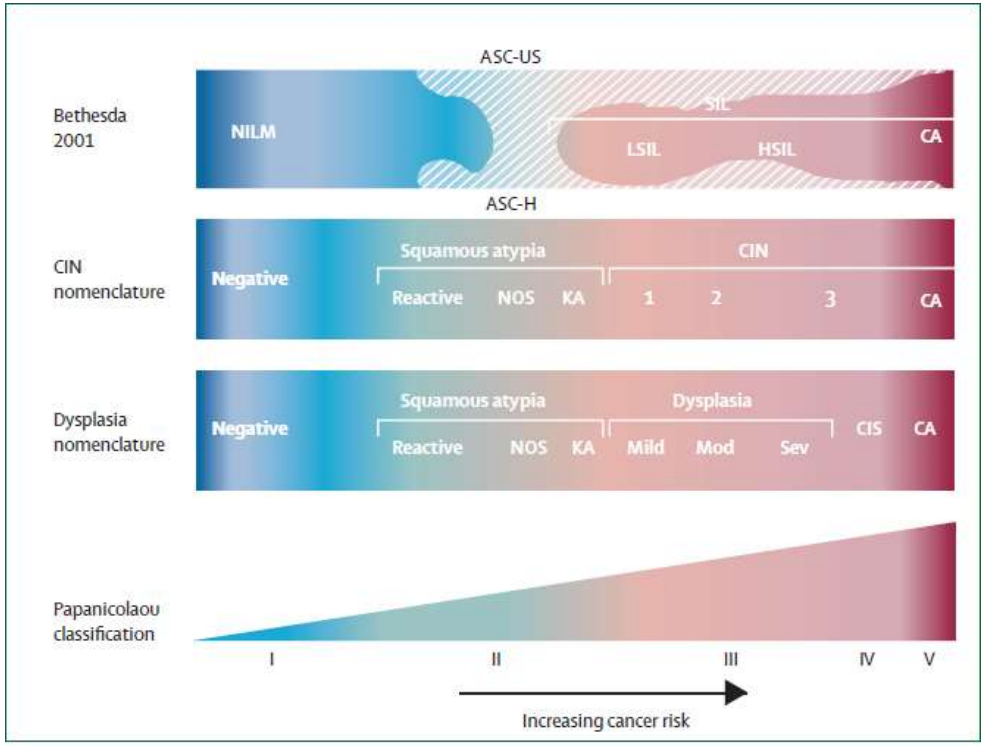


Figure 4: **Comparative classifications of HPV-related microscopic abnormalities**
To discuss HPV infection and cervical cancer with colleagues from other settings requires understanding the many different terms used. Equivocal interpretations of ASC-US (atypical squamous cells of undetermined significance) and ASC-H (atypical squamous cells, cannot rule out high-grade squamous intraeptithelial lesions) are noted with stippling, the amount and colour of which suggests the expected frequencies within the differential diagnosis. Adapted from Sherman.[36]

Persistent infection

- **In unscreened** populations, the **peak risk** of invasive cervical cancer occurs earlier than for most adult cancers, peaking or reaching a plateau from about **35 to 55 years of age**.

- This distribution is due to the fact that cervical cancers originate mainly from **HPV infections transmitted sexually in late adolescence and early adulthood**

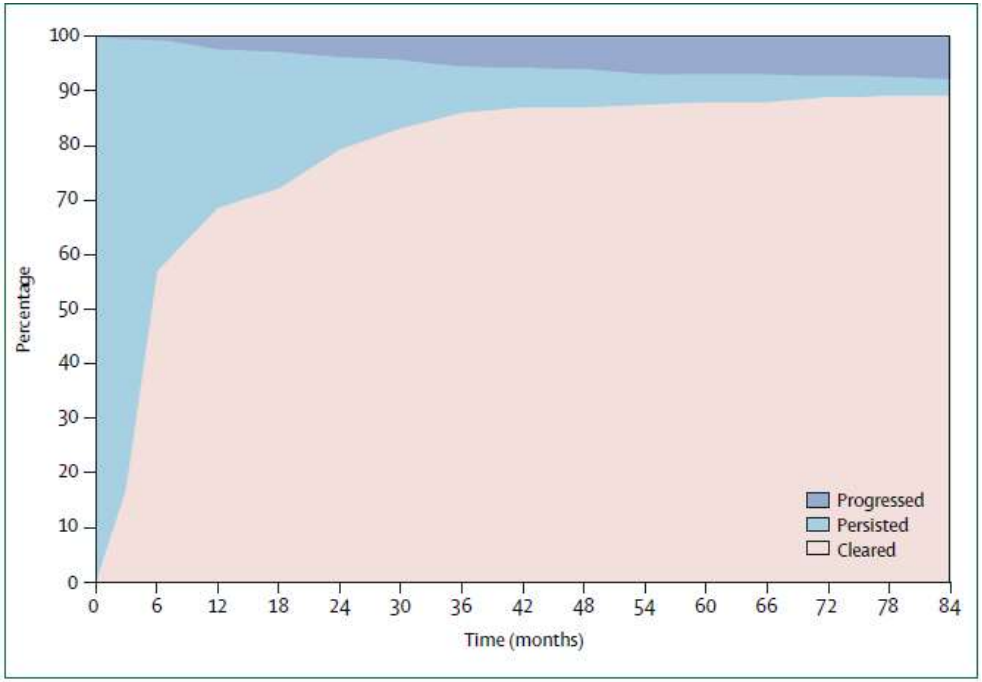


***Figure 5*: Average clearance, persistence, and progression of carcinogenic HPV infections**
Carcinogenic HPV infections detected by DNA testing tend to resolve quickly within a year of detection. Details vary by population, cytological status, and age, but this diagram of 777 infections found at enrolment visits of a large population-based cohort study (Guanacaste, Costa Rica; unpublished data) illustrates a typical pattern. Over time, the risk of a precancer diagnosis rises while the probability of eventual clearance among the still-persistent infections falls. Among women with no fertility concerns, treatment for carcinogenic infections, especially with HPV16 (the type most linked to risk of precancer and cancer), that persist beyond an appropriate period of watchful waiting (eg, 12–24 months), might be justified.

Studio IMPATTO - Changes in cervical cancer incidence following the introduction of organized screening in Italy

Serraino D, et al. Prev Med 2015; 75:56-63

Table 1
Distribution of 3557 women with ICCs, aged 25–74 years, by cancer registry area and periods before and after full-activation of OCSPs[a]. Italy, 1995–2008.

Cancer registry area	Included period	'Year-0' of OCSP full-activation[a]	Before OCSP full-activation[a]		After OCSP full-activation[a]		No. total ICCs
			No. years	No. ICCs	No. years	No. ICCs	
Northern Italy							
Friuli Venezia Giulia region	1995–2007	2000	5	305	8	400	705
Veneto region[b]	1997–2005	2000–02[c]	3–5[c]	123	4–6[c]	170	293
Parma province	1996–2008	2001	5	99	8	101	200
Modena province	1995–2005	1997	2	51	9	218	269
Ferrara province	1995–2005	1997	2	43	9	146	189
Romagna provinces[d]	1995–2005	1997	2	150	9	461	611
Central Italy							
Firenze province	1995–2005	2000	5	257	6	273	530
Umbria region	1995–2008	2000–02[c]	5	141	7–9[c]	212	353
Latina province	2001–2006	2003	2	44	4	71	115
Southern Italy							
Napoli province[e]	1996–2007	2000	4	76	8	114	190
Siracusa province	1999–2005	2003	4	56	3	46	102

Abbreviations: ICC, invasive cervical cancer; OCSP, organized cervical screening program.

[a] Calendar year during which at least 40% of target women had been invited to the OCSPs.

[b] Local Health Units n. 1, 3, 8, 13, 18, 20.

[c] Depending upon Local Health Unit.

[d] Provinces of Imola, Rimini, Cesena, Ravenna, and Forlì.

[e] Local Health Unit n. 4.

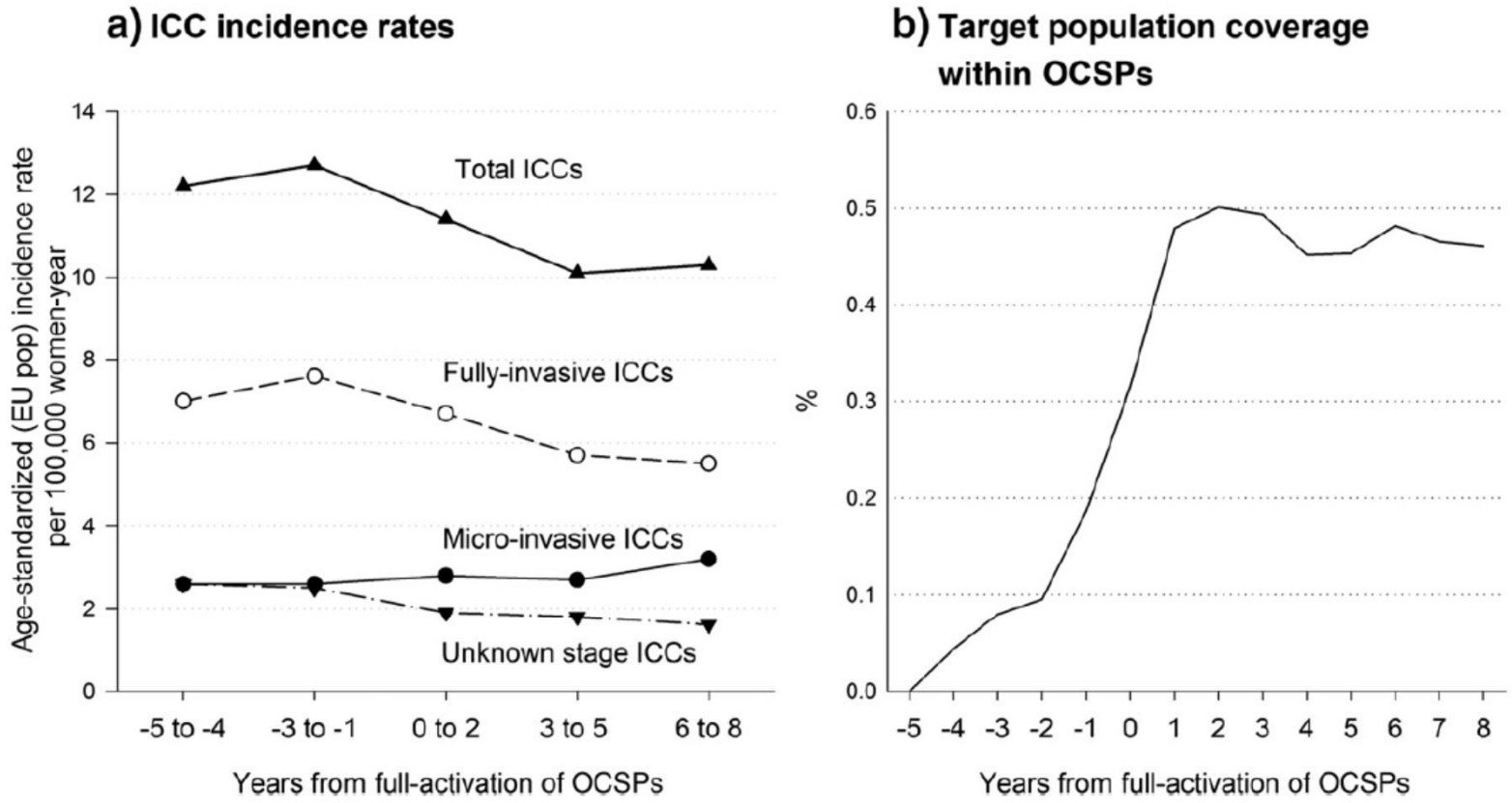


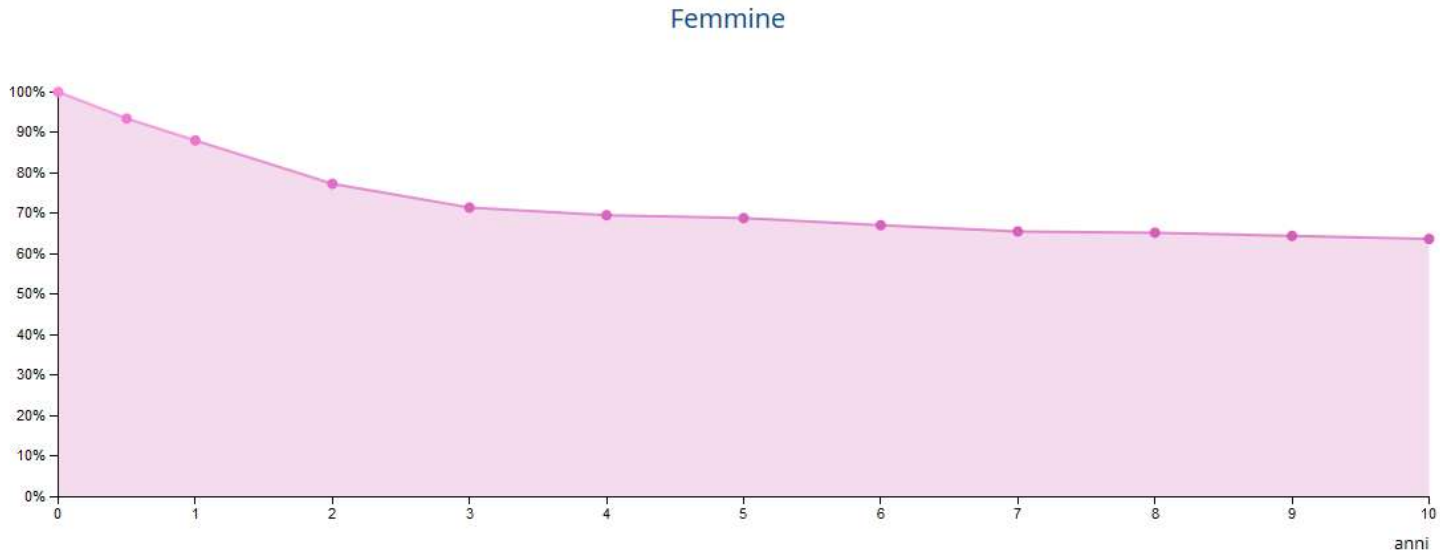
Fig. 1. (a) Invasive cervical cancer (ICC) age-standardized (European pop.) incidence rates (per 100,000 women-year) by stage at diagnosis and (b) proportion (%) of target women (25–64 years) having had a Pap-smear within organized cervical screening programs (OCSPs) in the previous 3 years in the study areas, according to years from full-activation of OCSPs[a]. Italy, women aged 25–74 years, 1995–2008. [a]Calendar year during which at least 40% of target women had been invited to OCSPs.

Sopravvivenza per cancro della cervice uterina

Sopravvivenza relativa standardizzata 69% a 5 anni

Sopravvivenza standardizzata per fasce di età, pesi Corazziari - collo dell'utero

Periodo di studio: 1994-2013, follow-up al 31-12-2015.



* Ederer F, Heise H, Corazziari et al. - Standard cancer patient population for age standardising survival ratios - European Journal of Cancer 40 (2004) 2307–2316

- For cervical cancer, national estimates of 5-year survival range from less than 50% to more than 70%; regional variations are much wider, and improvements between 1995–99 and 2005–09 have generally been slight.... *(Umbria circa 75%)*

Studio Concord 2

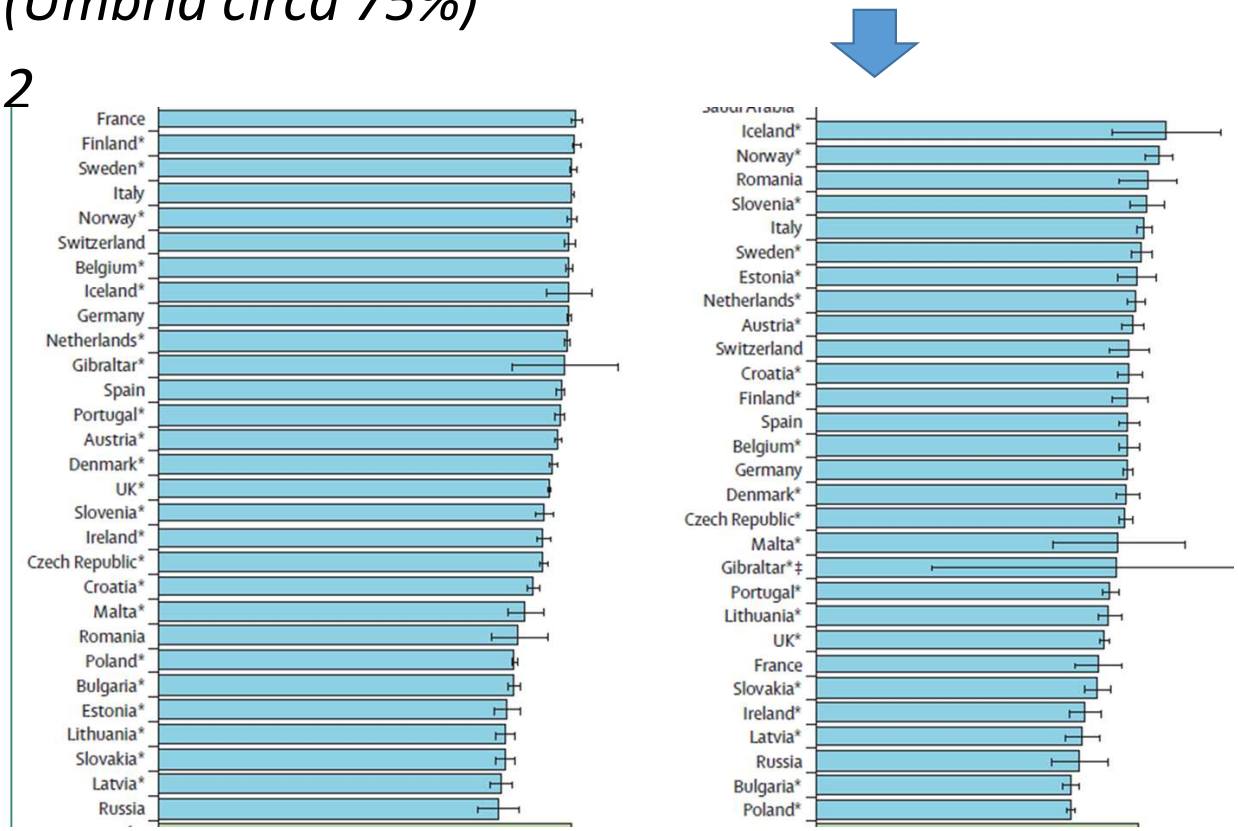
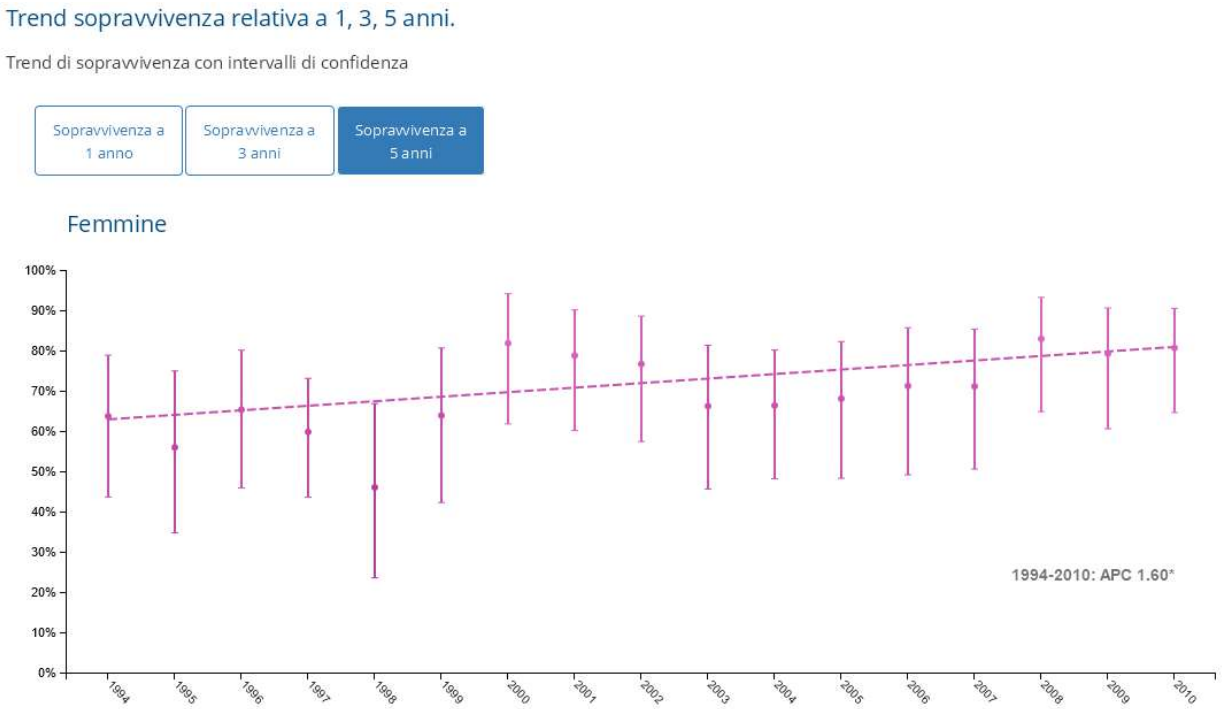
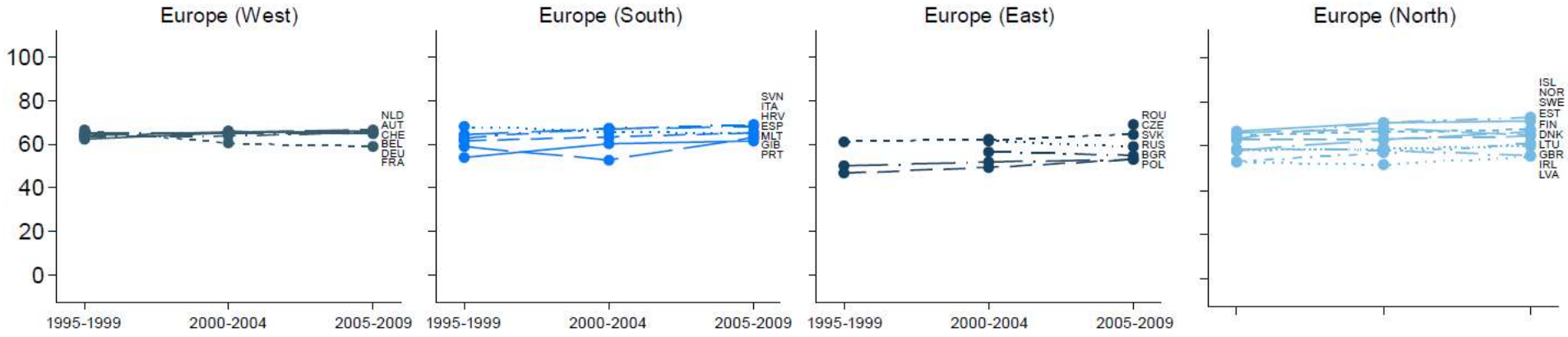


Figure 2: **Global distribution of age-standardised 5-year net survival (%) for women diagnosed aged 15–99 years with (A) breast cancer or (B) cervical cancer during 2005–09, by continent and country**
Survival estimates for each country are ranked from highest to lowest within each continent. Error bars represent 95% CIs. Survival estimates are flagged as follows: *100% coverage of national

The global burden of women's cancers: a grand challenge in global health. Ginsburg O et al. Lancet 2015

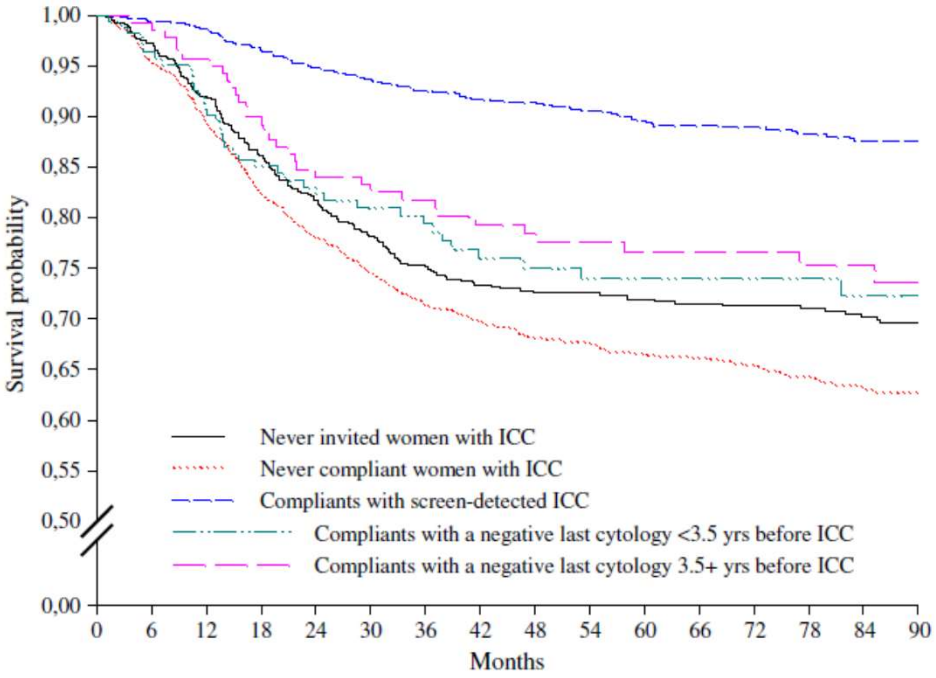
Trend della sopravvivenza relativa a 5 anni per i carcinomi infiltranti APC + 1.6





Sopravvivenza dei cancri invasivi e screening

- Screen-detected cancers were more frequently micro-invasive (42%) than non-screen-detected ones (14%), a result in line with previous studies …, indicating that Italian OCSPs allowed cancer down-staging.
- The survival of women with non-screen-detected ICC remained significantly lower as compared to women with screen-detected ICC, with or without adjustment for tumor stage. This indicates that OCSPs also had an effect on survival, beyond that related to tumor down-staging.

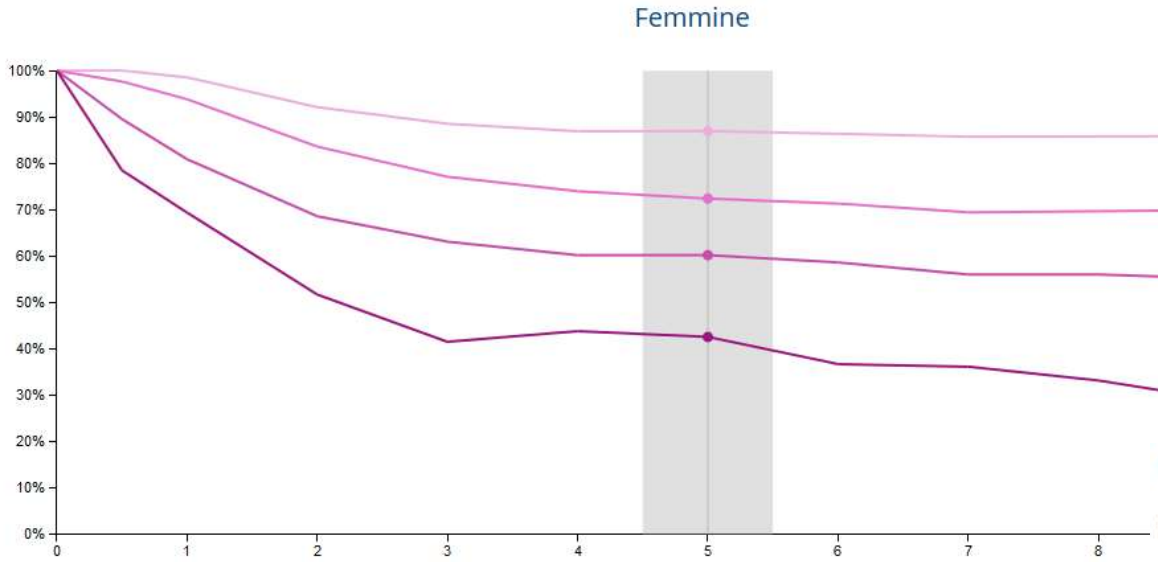


Screening patterns within organized programs and survival of Italian women with invasive cervical cancer Zucchetto A. Prev Med 2013

Sopravvivenza per classe d’età

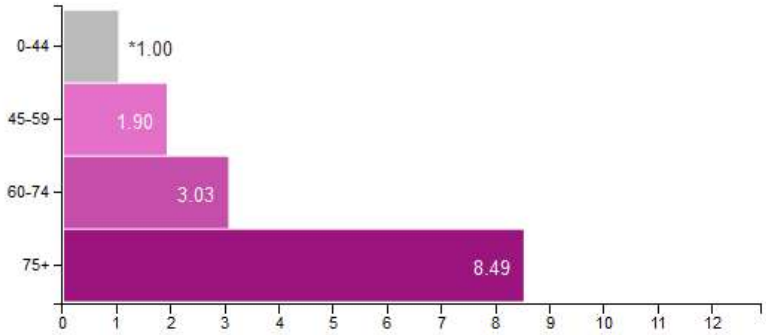
Sopravvivenza Relativa per fasce di età - collo dell'utero

Periodo di studio: 1994-2013, follow-up al 31-12-2015



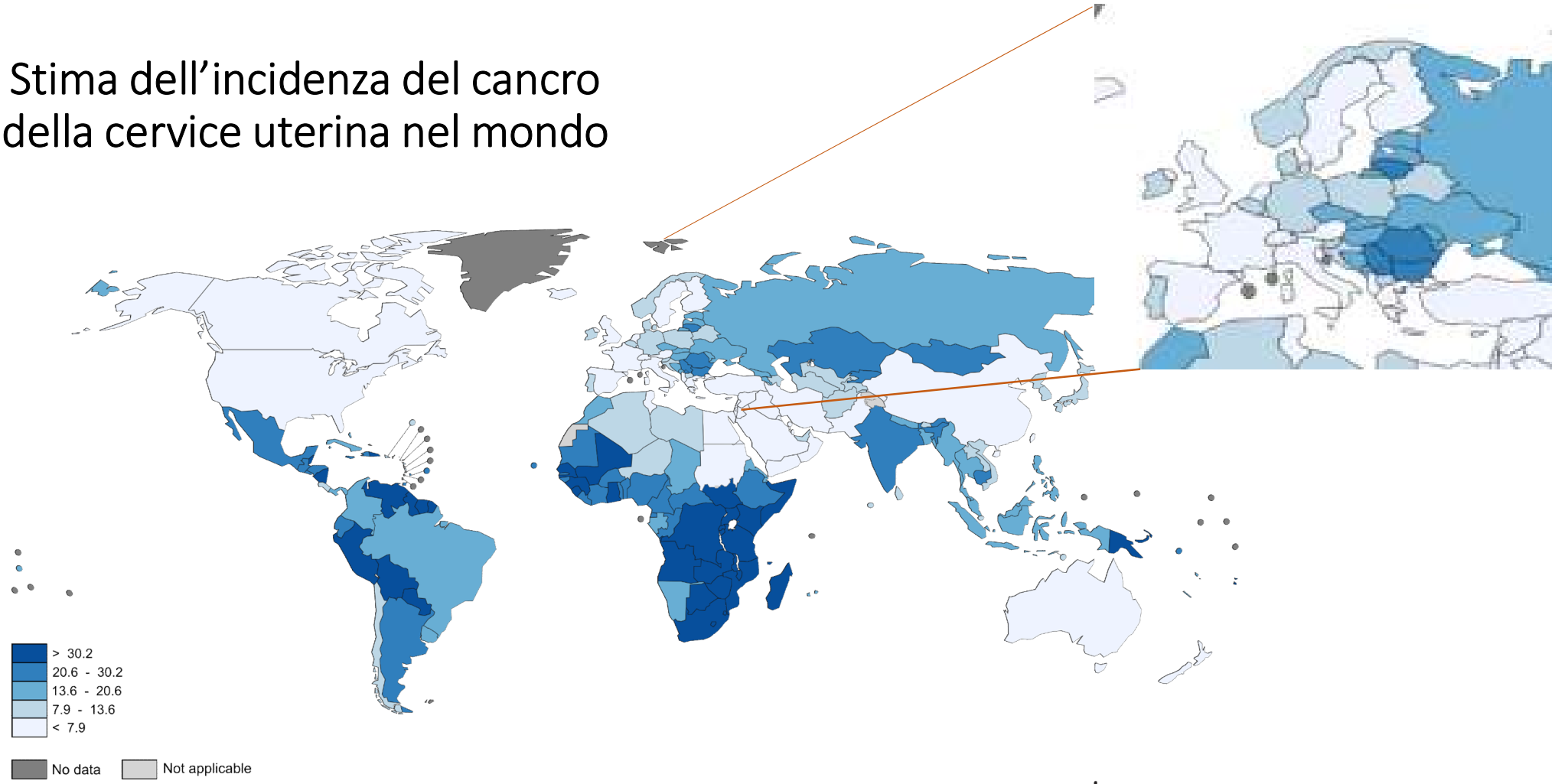
Femmine - Rischio relativo di morte per fasce di età

Rischio relativo di morte rapportato alla popolazione femminile di età 0-44.



La classifica internazionale

Stima dell'incidenza del cancro della cervice uterina nel mondo



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data source: GLOBOCAN 2012
Map production: IARC
World Health Organization

World Health Organization

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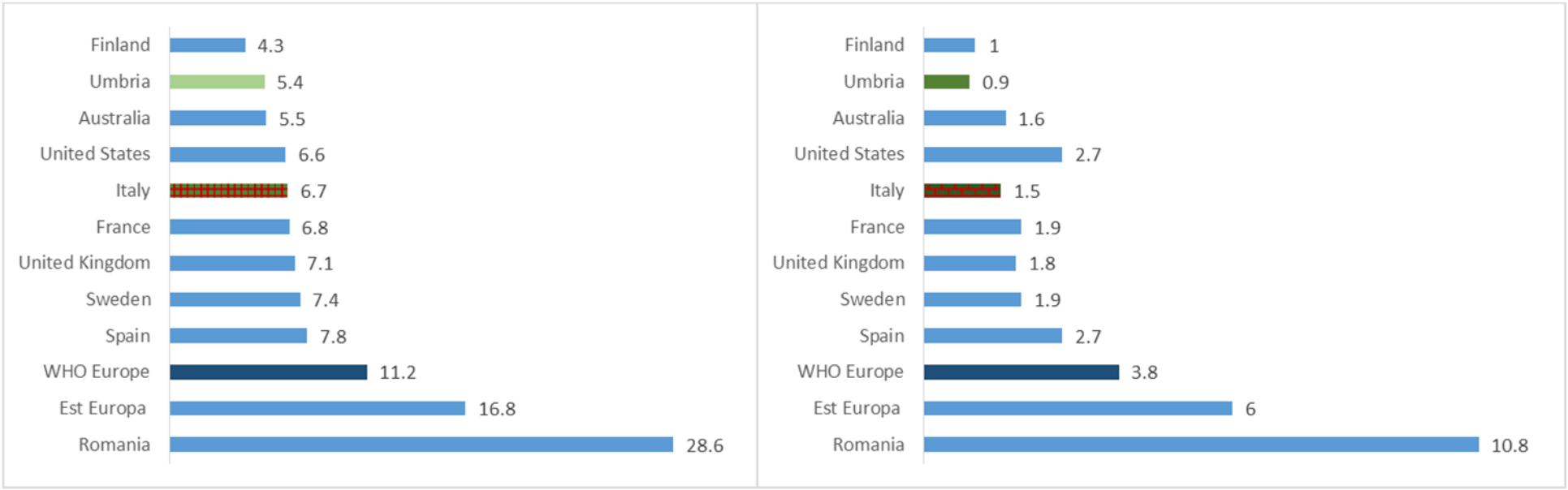
Tasso standardizzato di incidenza (mondo) e mortalità, 2012. Confronto internazionale (Globocan)



Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray, F. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11. Lyon, France: International Agency for Research on Cancer; 2013. Available from: http://globocan.iarc.fr, accessed on day/month/year.

Umbria - Finlandia

- The mass screening programme in Finland introduced in the mid-1960s and the 80% declines seen there from the mid-1960s to the early-1990s is a cornerstone of the evidence for the effective- ness of organised cytological screening [36]; it is worth noting that the age-adjusted (world) incidence rates of cervical cancer at their peak in Finland (circa 1962–65 [6], of 17.3) are of a similar or lesser order of magnitude than the corresponding rates observed today in almost half of the countries studied in the combined regions

Patterns and Trends in Human Papillomavirus-Related Diseases in Central and Eastern Europe and Central Asia
Bray F et al. Vaccine 2013

Determinanti dei trend del cervicocarcinoma invasivo

- The varying period and cohort patterns in ICC trends across countries can be largely attributed to two independent factors:

(1) the existence, duration, and quality of screening programmes over calendar time; and

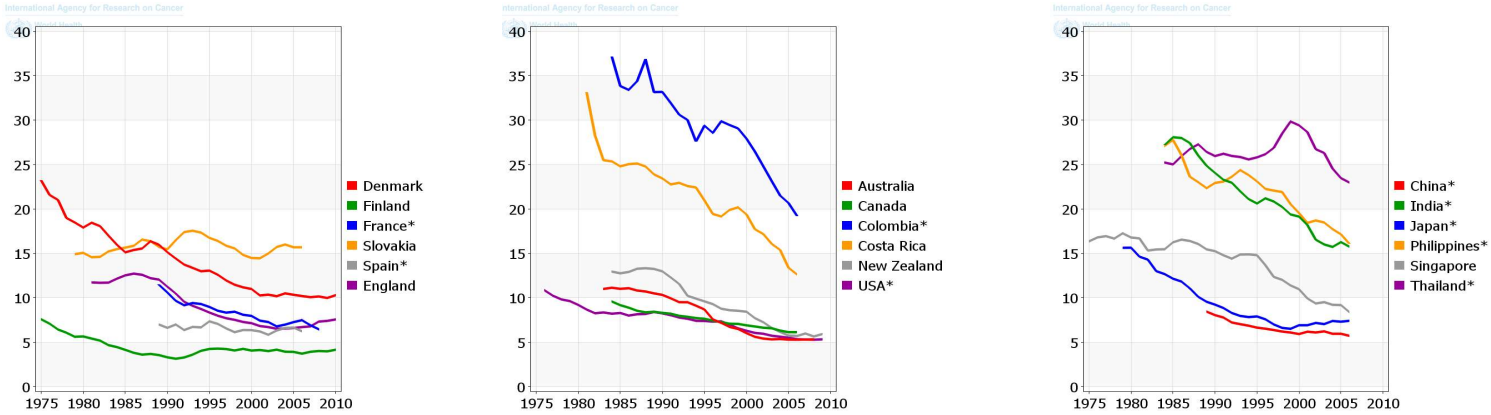
(2) changes in ICC risk factors, notably sexual behavior and, hence, the probability of HPV exposure, affecting consecutive generations of women

Vaccarella S et al. European Journal of Cancer (2013) 49, 3262– 3273

EPIDEMIOLOGIA DEL CANCRO DELLA CERVICE

- L'incidenza del cancro della cervice mostra in molti Paesi un trend decrescente

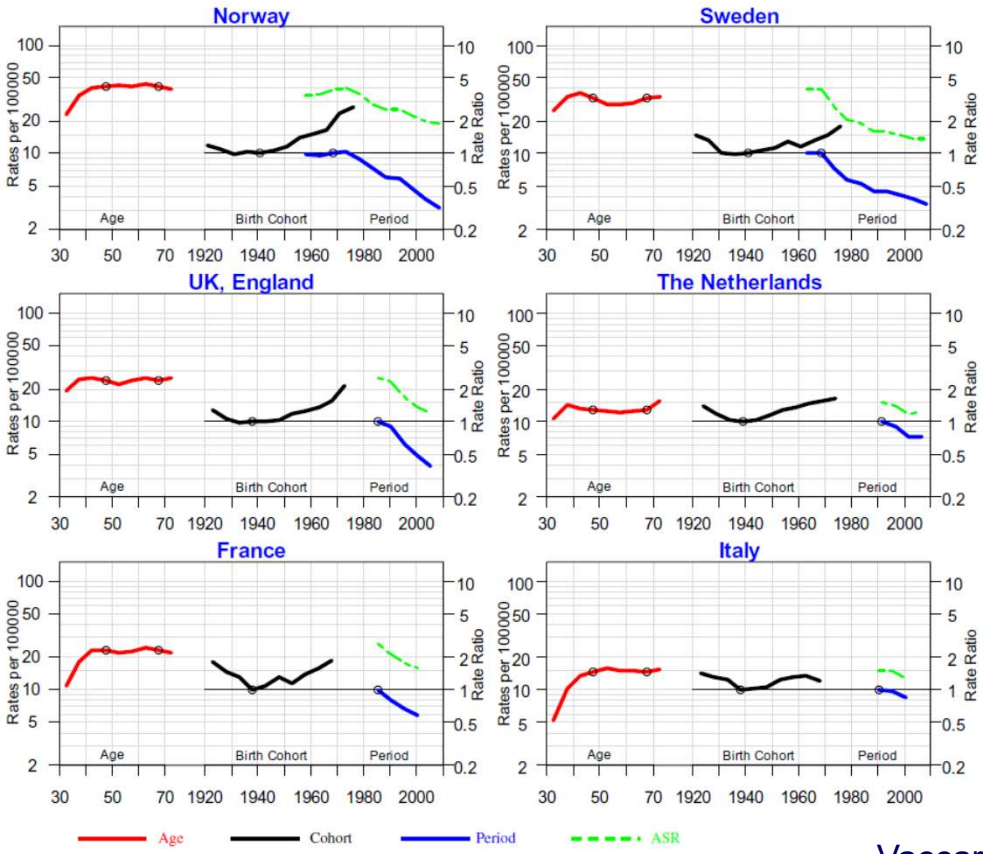
- Tale riduzione è dovuta principalmente allo sviluppo di programmi organizzati di screening, che portano alla precoce identificazione di precursori del cancro invasivo.



Trends in incidence of cervical cancer in selected countries: age-standardised rate per 100,000

GLOBOCAN 2012 (IARC) :

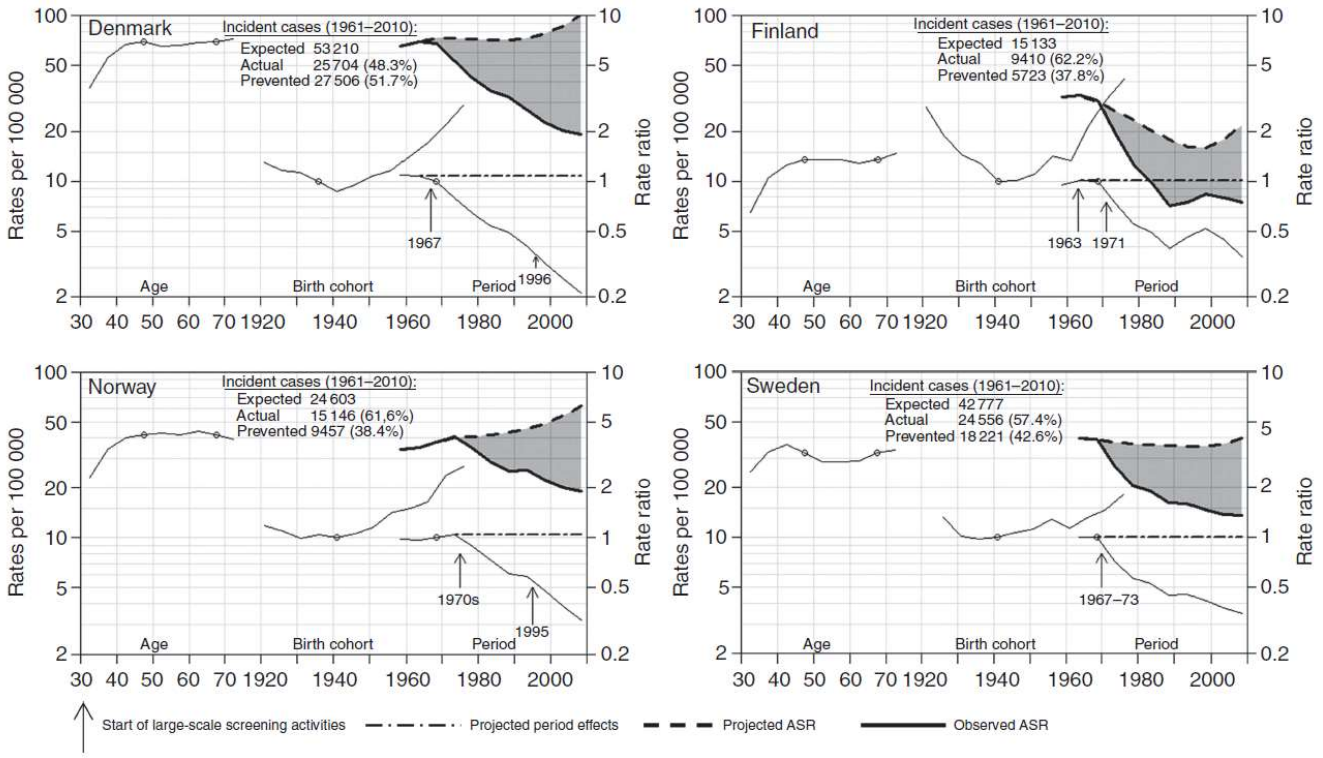
Worldwide trends in cervical cancer incidence: Impact of screening against changes in disease risk factors



- Effetto coorte di nascita,
- (*meno marcato in Italia rispetto agli scandinavi*) Many aspects of sexual behaviour,…have changed substantially starting from generations of women born during or after the Second World War
- Effetto periodo
- the beneficial impact of screening in counteracting the underlying cohort-specific increases in ICC risk

Vaccarella S et al. European Journal of Cancer (2013) 49, 3262– 3273

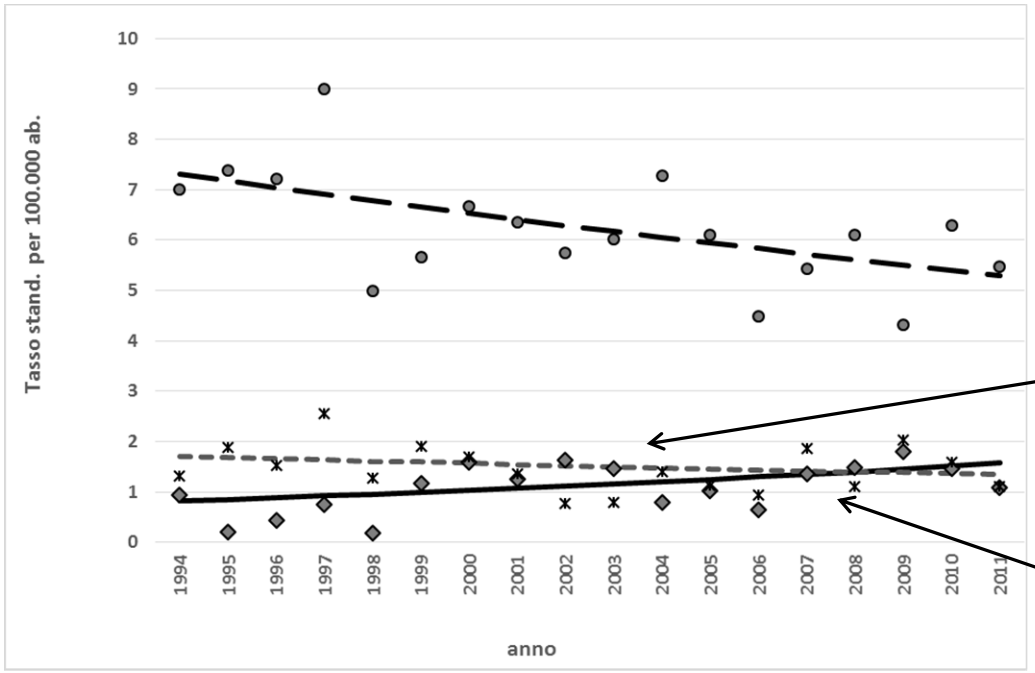
Ruolo dello screening



50 years of screening in the Nordic countries: quantifying the effects on cervical cancer incidence Vaccarella S et al. BJC 2014

- **Screening programmes might have prevented a HPV-driven epidemic of cervical cancer in Nordic countries**.
- According to extrapolations from cohort effects, cervical cancer incidence **rates** in the Nordic countries **would have been otherwise comparable to the highest incidence rates currently detected in low-income countries**
- might not exclude, however, that the initial impact of screening may be partly obscured by the early detection of microinvasive cancers

Andamento dell'incidenza per cancro della cervice uterina per ISTOTIPO



SCC: CR Squamoso

OCC: CR morfologia indefinita

AC: Adenocarcinoma

Indicatore	Periodo	APC**	95% IC	P-Value
SCC	1994 - 2011	**-1.9***	-3.3; -0.4	0.0
AC	1994 - 2011	**3.9**	-0.3; 8.3	0.1
OCC	1994 - 2011	**-1.4**	-4.4;1.6	0.3

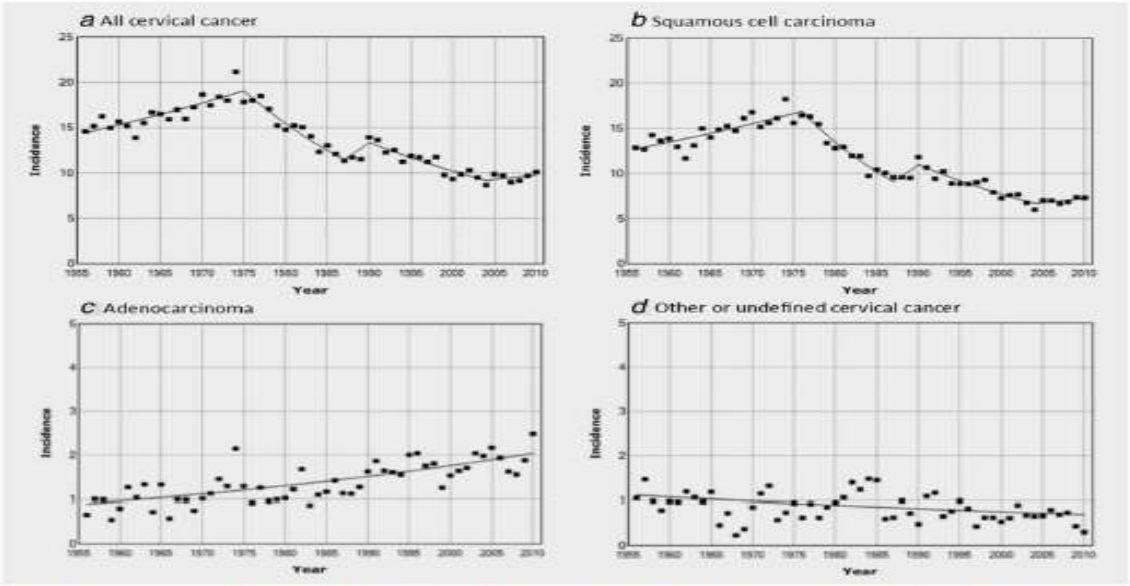


Figure 2. Age-standardised (w) incidence rate of cancer of the uterine cervix per 100,000 woman-years as a function of calendar year, by morphology. Dots represent observed rates and lines those fitted using joinpoint regression.

Table 2. Calendar year periods with distinct cervical cancer trends as defined by joinpoint analyses by morphology

Morphology	Joinpoint (95% CI)	Period	APC (95% CI)
All morphologies		1956–1975	1.5 (1.0 to 1.9)
	1975 (1959–1978)	1975–1987	−4.1 (−5.1 to −3.2)
	1987 (1973–1990)	1987–1990	5.2 (−10.6 to 23.8)
	1990 (1985–1998)	1990–2004	−2.6 (−3.4 to −1.8)
	2004 (1989–2008)	2004–2010	1.1 (−1.7 to 3.9)
Squamous cell cancer		1956–1976	1.4 (1.0 to 1.9)
	1976 (1973–1978)	1976–1987	−5.4 (−6.6 to −4.2)
	1987 (1981–1989)	1987–1990	6.4 (−11.2 to 27.5)
	1990 (1988–2000)	1990–2004	−3.5 (−4.4 to −2.5)
	2004 (1997–2008)	2004–2010	1.4 (−1.9 to 4.8)
Adenocarcinoma		1956–2010	1.5 (1.1 to 1.9)
Other or undefined cancer		1956–2010	−0.9 (−1.4 to −0.3)

Abbreviation: APC: annual percentage change.

Cervical cancer prevented by screening: Long-term incidence trends by morphology in Norway. Lönnberg S et al. Int J Cancer. (2015)

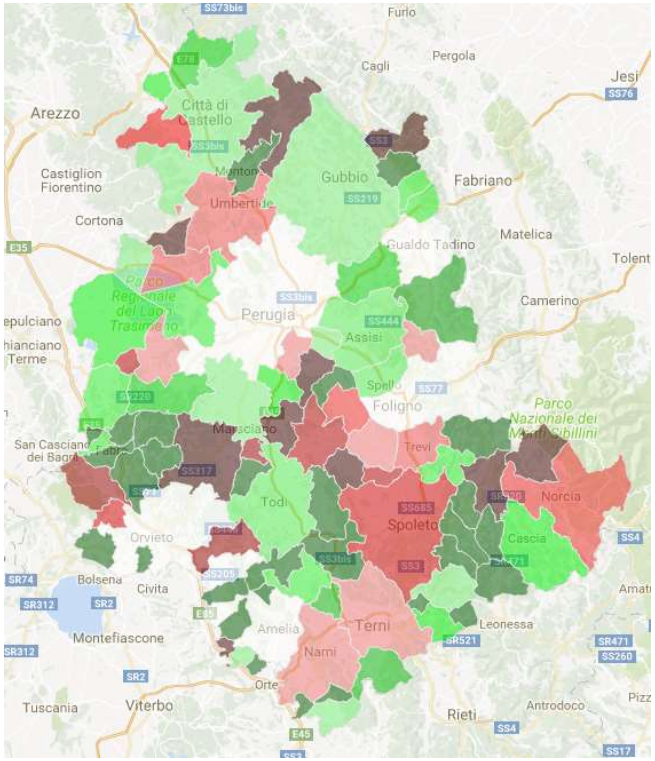
In poorly screened populations, squamous cell carcinomas constitute most cases of cervical cancer.
In regions with good cervical cancer screening programmes, the proportion of adenocarcinomas is increased (15–20%) compared with unscreened populations, presumably because they arise from the poorly sampled glands of the canal or from poorly recognised precursor lesions.
Beyond the relative increase, absolute rates of cervical adenocarcinomas are thought to have increased in various countries over the past two to three decades, for uncertain reasons (HPV18)

Controllo della patologia

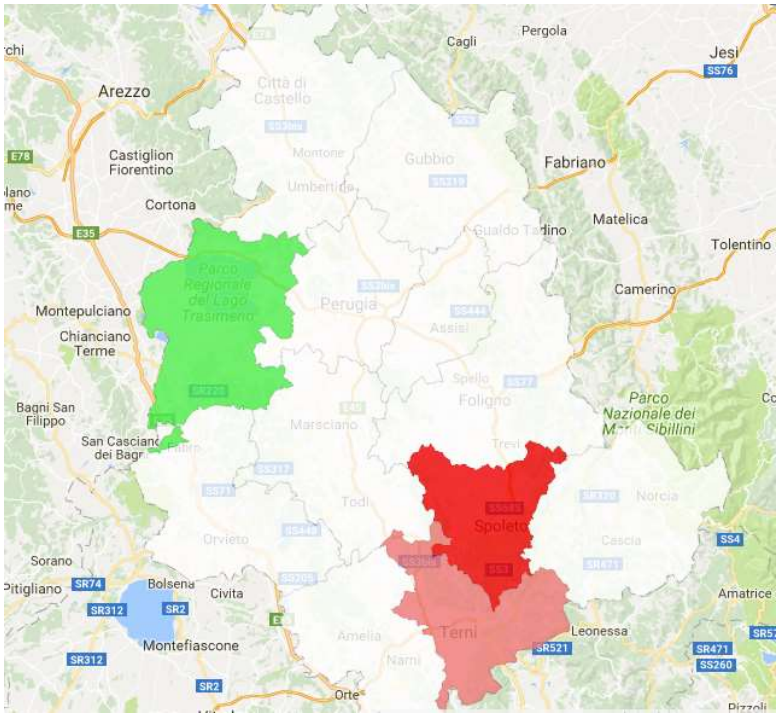
- Grazie allo screening regionale il danno alla salute delle donne legato al carcinoma della cervice uterina è molto ridotto
- La vaccinazione, in prospettiva, consentirà un controllo ancora maggiore, esteso anche ad altre patologie legate ad HPV
- I risultati conseguiti nella lotta contro le patologie HPV correlate rappresentano un modello di sanità pubblica che andrebbe esteso ed adeguatamente pubblicizzato

Comunque fare di più

Mappa dell'incidenza del carcinoma cervicale infiltrante in Umbria 2001-2013



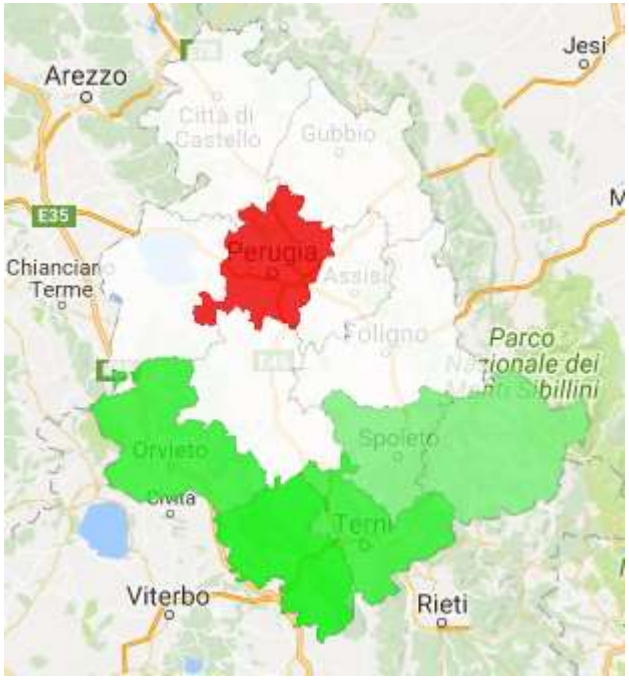
Per comuni



Per distretti

Mappa dell'incidenza del carcinoma cervicale infiltrante e delle CIN III in Umbria 2001-2013

Carcinoma infiltrante (ICD X C53)



CIN 3 (ICD X D06)

Eastern Europe

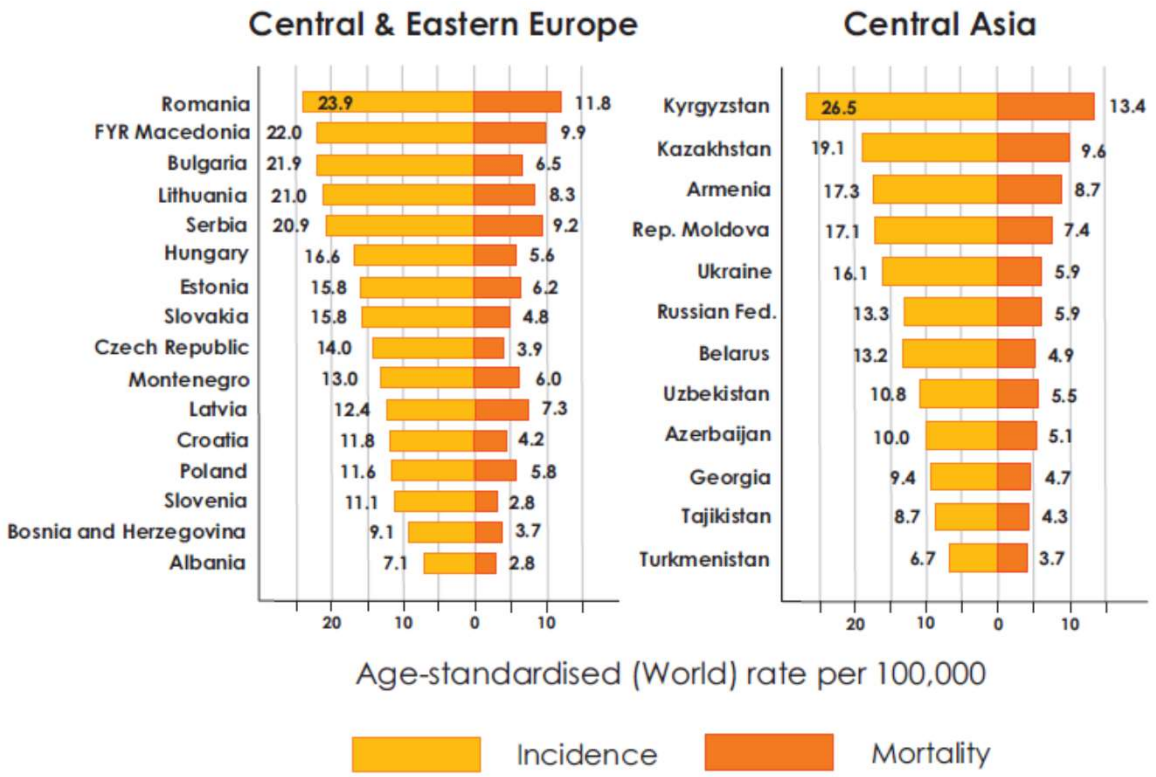
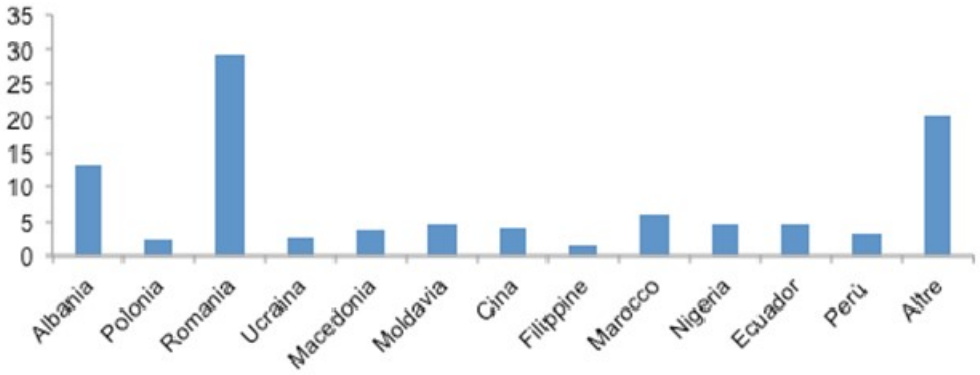


Fig. 1. Estimated cervical cancer age standardised(world) incidence (left), mortality (right), all ages, in the regions of Central and Eastern Europe and in Central Asia, 2008. Data source: Globocan2008 [4].

Trends in cervical cancer incidence and mortality in the Baltic countries, Bulgaria and Romania. Arbyn M et al. International Journal of Cancer 2011

IVG tra le donne straniere

- In Umbria nel 2013 risiedevano 55.956 donne di cittadinanza straniera. Le più rappresentate erano le rumene (circa 16.000, il 28,5%), …
- è possibile affermare che esse contribuiscano in maniera preminente alle IVG tra le donne straniere…
- Oltre la metà delle donne rumene erano in possesso di un elevato **livello di istruzione …**contrariamente a quanto osservato tra le donne di cittadinanza estera nel complesso.
- …donne rumene che prima di effettuare l'IVG nell'anno 2011 si erano già sottoposte ad IVG è risultata particolarmente elevata, 48,4%;



Fonte: Relazione sull'interruzione volontaria di gravidanza nella Regione Umbria negli anni 2011-2013

Lotta ad HPV: la situazione in Romania

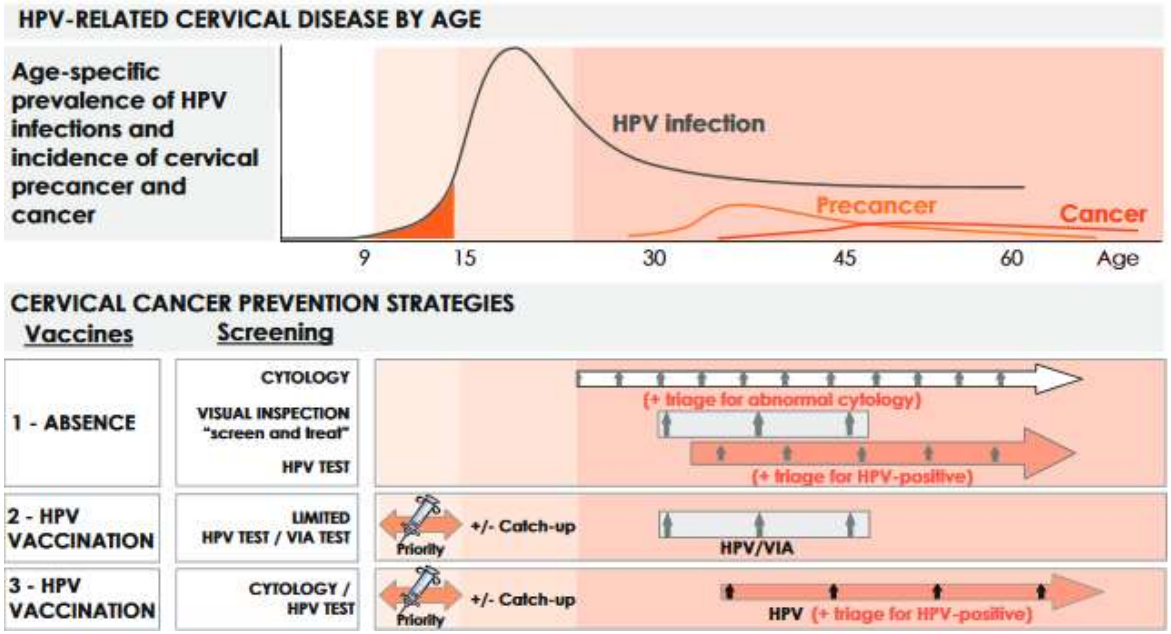
- Romania performs opportunistic screening based on regional organization…The reported coverage in this opportunistic setting is extremely low—between 0.6 and 3.2%...the screening infrastructure in the country is insufficient and financial resources are less than 10% of the necessary amount…
- In Romania, a national school-based programme to vaccinate females aged 11 was first launched in 2008, but was temporarily suspended during the first year due to low acceptance—only about 2% of the target population received the vaccine.
- The government analysed the reasons for the low uptake and subsequently implemented a novel information campaign prior to a re-launch in February 2010. To the best of the authors' knowledge, the relaunched HPV vaccination programme in Romania was stopped at the end of 2011 due to a negative public reaction and lack of proper communication.
- This resulted in low coverage in the target population, which did not reach 5%.

Poljak M et al. Cervical Cancer Screening Practices and Current Status of Vaccination Implementation in Central and Eastern Europe. Vaccine 2013

Indicazioni

Interventi per ridurre le diseguaglianze nell'accesso alla prevenzione:

- Su base geografica:
  - Promozione dello screening mirata alle aree con minore partecipazione
  - Aumento delle coperture vaccinali
- Su base etnica
  - Promozione dello screening mediante interventi adattati
  - In generale interventi di promozione della salute
- Auto-prelievo proposto a non-aderenti



Sette i morti che caddero - li
Raggiungemmo a piedi.
Mille siamo gli uccisori

11. Ensure your children take part in vaccination programmes for:

hepatitis B (for newborns);

human papillomavirus (HPV) (for girls).

12. Take part in organised cancer screening programmes for:

bowel cancer (men and women);

breast cancer (women);

cervical cancer (women).

European Code against Cancer 4th Edition: 12 ways to reduce your cancer risk. Schutz et al. Cancer Epidemiology 2015

Fine

Prevention of cervical cancer

- Prevention of cervical cancer includes both
- primary prevention, through HPV vaccination and education about safe sexual practices, and
  - There is some evidence that health education programmes that promote abstinence, conscientious condom use, or both, could reduce the risk of cervical cancer at the population level
- secondary prevention through cervical cancer screening.

Evoluzione dello screening

HPV DNA e Pap Test

- Testing for HR (high risk)-HPV has been investigated as a primary screening test in several randomized clinical trials. Cross-sectional as well as longitudinal studies have consistently demonstrated the superiority of HPV testing, compared with Pap testing, to prevent invasive cervical cancer by detecting high-grade precancerous lesions.
- However, HPV testing is also associated with a lower specificity, especially in younger women.32
- By 2018, screening programs in Italy will rely more on HPV testing than cytology,

Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomized controlled trials

- The rate ratio for invasive cervical carcinoma among all women from recruitment to end of follow-up was 0·60 (95% CI 0·40–0·89), with no heterogeneity between studies (p=0·52).
- Detection of invasive cervical carcinoma was similar between screening methods during the first 2·5 years of follow-up (0·79, 0·46–1·36) but was significantly lower in the experimental arm thereafter (0·45, 0·25–0·81). In women with a negative screening test at entry, the rate ratio was 0·30 (0·15–0·60).
- HPV-based screening provides 60–70% greater protection against invasive cervical carcinomas compared with cytology.

Ronco G et al. Lancet 2014; 383: 524–32

Rischio di sviluppare un carcinoma infiltrante

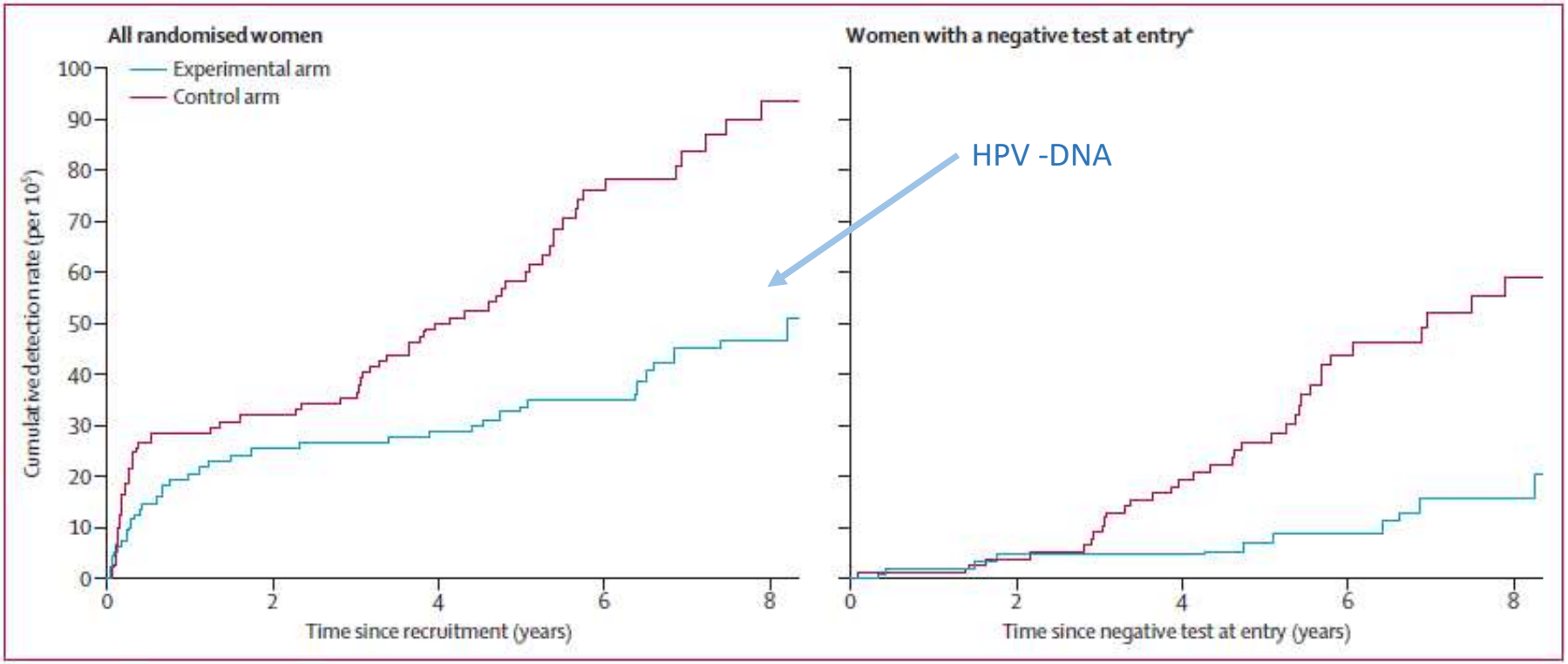


Figure 2: **Cumulative detection of invasive cervical carcinoma**

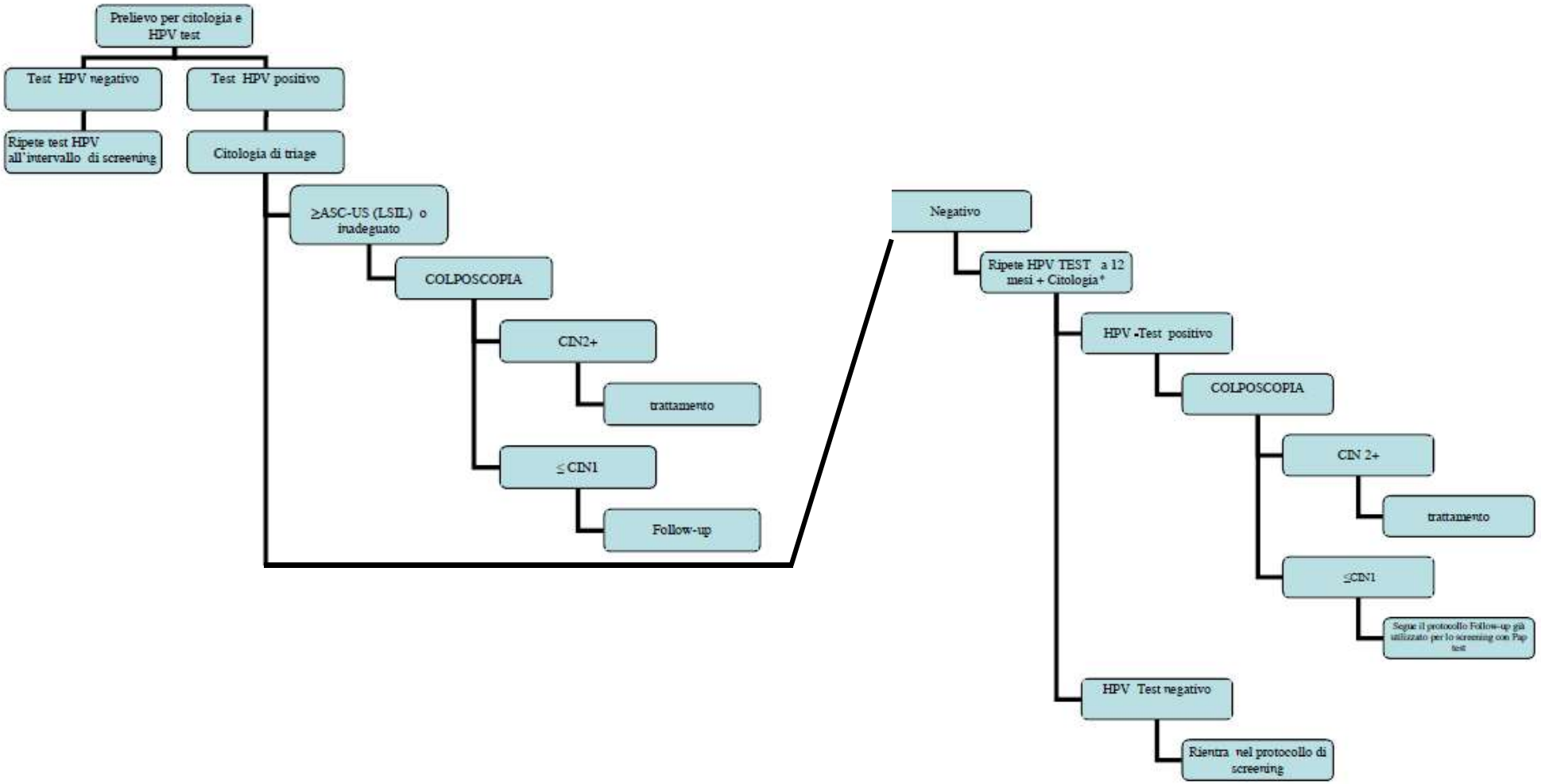
*Observations are censored 2·5 years after CIN2 or CIN3 detection, if any.

Raccomandazioni sul test HR-HPV come test di screening primario - 12 maggio 2017

- I risultati degli studi clinici randomizzati sull'applicazione di test molecolari per la ricerca di HPV nei programmi di screening hanno dimostrato che in donne di età superiore a 30 anni il test HPV è più efficace del pap test nel rilevare la presenza o il rischio di sviluppare carcinomi e lesioni di alto grado (2).

- Il sistema utilizzato deve essere in grado di individuare tutto il gruppo di HPV ad alto rischio (HR-HPV:16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59)

Figura 1. Protocollo screening cervicale con test HPV primario e citologia di triage.



Il programma di screening per la prevenzione del tumore della cervice uterina in Umbria

- E' rivolto a tutte le donne tra i 25 e i 64 anni di età (circa 250.000 donne)

- Dal **2007** per le donne con diagnosi citologica al Pap-test di ASCUS e LSIL viene effettuata come triage la ricerca del Papillomavirus con la metodica della citologia in fase liquida (LBC); questo permette di inviare a colposcopia solo l'1% circa delle donne screenate, percentuale tra le più basse in Italia

- Nel **2013** si è completato il 5° round ed è stato avviato lo screening con HPV primario su una parte del territorio regionale per le donne tra i 35 e i 64 anni

- Nel **2014** lo screening con HPV primario è stato avviato su tutta la regione

Non solo lesioni cervicali

Patologie correlate ad HPV

- Human papillomavirus (HPV) infection is the most common sexually transmitted infection [1].
- It is rapidly acquired after initiation of sexual activity and prophylactic prevention should be conducted before sexual debut [2].
- Infection with low-risk HPV types can cause recurrent respiratory papillomatosis and anogenital warts; 90 % of these cases are attributable to HPV 6 and 11 [3].
- Persistent infections with high-risk HPV types can cause pre-oncogenic lesions that can lead to cancer in several anatomic sites. The highest burden of disease is shouldered by those infected with high-risk HPV types 16 and 18,

HPV è causa di altri tumori maligni e patologie

	Less developed regions	More developed regions	World
Hepatitis B and C viruses	520 000 (32·0%)	80 000 (19·4%)	600 000 (29·5%)
Human papillomavirus	490 000 (30·2%)	120 000 (29·2%)	610 000 (30·0%)
Helicobacter pylori	470 000 (28·9%)	190 000 (46·2%)	660 000 (32·5%)
Epstein-Barr virus	96 000 (5·9%)	16 000 (3·9%)	110 000 (5·4%)
Human herpes virus type 8	39 000 (2·4%)	4100 (1·0%)	43 000 (2·1%)
Human T-cell lymphotropic virus type 1	660 (0·0%)	1500 (0·4%)	2100 (0·1%)
Opisthorchis viverrini and *Clonorchis sinensis*	2000 (0·1%)	0 (0·0%)	2000 (0·1%)
Schistosoma haematobium	6000 (0·4%)	0 (0·0%)	6000 (0·3%)
Total	1 600 000 (100·0%)	410 000 (100·0%)	2 000 000 (100·0%)

Data are number of new cancer cases attributed to a particular infectious agent (proportion of the total number of new cases attributed to infection that is attributable to a specific agent). *Numbers are rounded to two significant digits.

Table 2: **Number of new cancer cases* in 2008 attributable to infection, by infectious agent and development status**

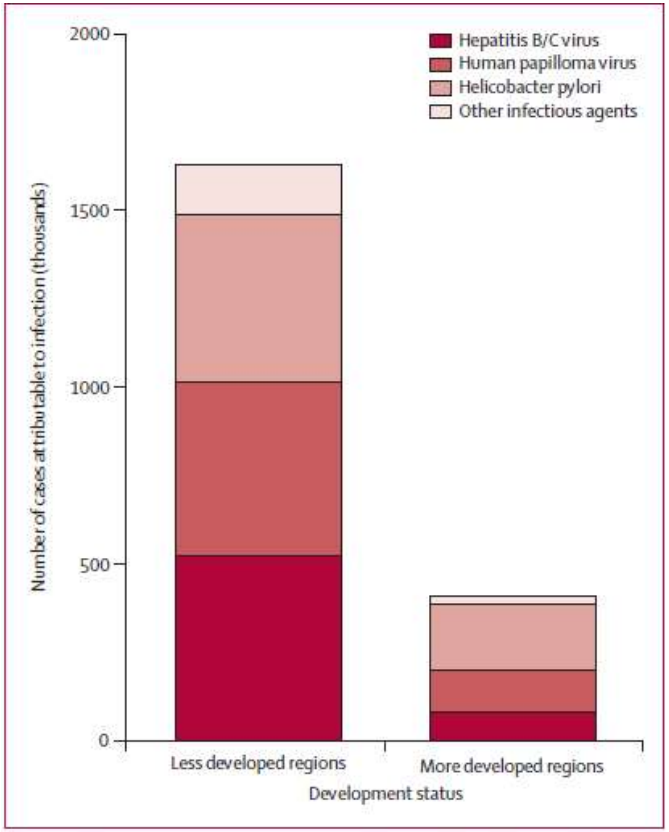


Figure 2: **Number of new cancer cases in 2008 attributable to infection, by infectious agent and development status**

Sebbene la proporzione sia simile,

- The burden of cervical cancer is disproportionately high (>80%) in the developing world.
- Not only is cervical cancer the most prevalent and important cancer in women in several developing countries, but also the societal importance of the disease is accentuated even further by the young average age at death, often when women are still raising families.

HPV-related cancers

Human papillomavirus (HPV; high-risk types)						
Cervix uteri carcinoma (C53)	Case–control	PCR in tumour tissue or cells	>100	World	100%	High-risk HPV types are considered a necessary cause of cervical cancer. Strong data
Penile carcinoma† (C60)	Case–control	PCR in tumour tissue	NR‡	World	50%	Assumption is that detection of high-risk HPV DNA in tumour tissue signifies cancer attributable to HPV Data based on one meta-analysis.[16] Limited data
Anal carcinoma† (C21)	Case–control	PCR in tumour tissue	NR‡	World	88%	Same assumption as for penile cancer Data based on one meta-analysis.[17] Strong data
Vulvar carcinoma† (C51)	Case–control	PCR in tumour tissue	NR‡	World	43%	Same assumption as for penile cancer Data based on one meta-analysis.[17] Limited data
Vaginal carcinoma† (C52)	Case–control	PCR in tumour tissue	NR‡	World	70%	Same assumption as for penile cancer Data based on one meta-analysis.[17] Limited data
Oropharynx† including tonsils and base of tongue (C01, C09–C10)	Case–control	PCR in tumour tissue with HPV E6 or E7 expression	NR‡	North America Northern and western Europe Eastern Europe Southern Europe Australia Japan Rest of world	56% 39% 38% 17% 45% 52% 13%	Few prevalence studies available for less developed regions Same assumption as for penile cancer, except for the difficulty separating strong effect of tobacco and alcohol. Limited data

TABLE 1
Estimated Percentage Attributable to Human Papillomavirus*

Cancer Site	% Attributable to HPV	Reference	Among HPV-positive, % Attributable to HPV-16 and HPV-18	Reference(s)
Cervix	100	Parkin & Bray 2006[2]	70	Munoz 2004[49]
Vagina	40	Parkin & Bray 2006[2]	80	Daling 2002[50]
Vulva	40	Parkin & Bray 2006[2]	80	Trimble 1996[51]; Iwasawa 1997[52]
Penis	40	Parkin & Bray 2006[2]	63	Rubin 2001[53]
Anus	90	Parkin & Bray 2006[2]	92	Daling 2004[54]; Frisch 1999[55]
Oral cavity	25	Kreimer 2005[3]	95	Kreimer 2005[3]
Oropharynx	35	Kreimer 2005[3]	89	Kreimer 2005[3]

HPV indicates human papillomavirus.

*This table was adapted from Parkin & Bray 2006[2] with updates based on Kreimer 2005.[3] See text for further discussion of HPV-attributable fractions.

EUROGIN 2011 roadmap on prevention and treatment of HPV-related disease

Table 1. Cancers associated with high-risk HPV infection and with HPV16 or 18 infection

Site (ICD-10 code)	Attributable to hrHPV	Of which HPV16/18	Number of cancers		
			Total	Attributable to hrHPV	Attributable to HPV16/18
Cervix (C53)	100%[2]	71%[4]	529,500[5]	529,500	375,945
Penis (C60)	47%[6]	74%[6]	26,300[7]	12,361	9,098
Vulva (C51)	40%[8]	93%[8]	30,000[7]	12,000	11,100
Vagina (C52)	70%[8]	93%[8]	15,000[7]	10,500	9,750
Anus (female) (C21)	84%[8]	94%[8]	15,900[7]	13,356	12,561
Anus (male) (C21)	84%[8]	94%[8]	14,500[7]	12,180	11,455
Oro-pharynx (female) (C01, C09-C10)	19%[9, 1]	89.3%[10]	12,600[11]	2,394	2,138
Oro-pharynx (male) (C01, C09-C10)	19%[9, 1]	89.3%[10]	48,900[11]	9,291	8,299
All sites (females)	9.4%	6.8%	6,044,710[11]	567,750	411,494
All sites (males)	0.5%	0.4%	6,617,844[11]	33,832	28,852
All sites (both sexes)	4.8%	3.5%	12,662,554[11]	601,582	440,346

Zona di trasformazione

- For reasons that we do not understand, persistent HPV infections cause cancers mainly at the transformation zones between different kinds of epithelium (eg, cervix, anus, and oropharynx).
- Illustrating the importance of the transformation zone, cancer-associated (carcinogenic) HPV infections are equally common in cervical and vaginal specimens;
- however, cervical cancer is the second most common tumour in women worldwide, whereas vaginal cancer is exceedingly rare

Immunizzazione

HPV L1 virus-like-particle (VLP) vaccines

- HPV L1 virus-like-particle (VLP) vaccines are based on the self-assembly of recombinant L1 protein into non-infectious capsids that contain no genetic material.
- Intramuscular injection of the vaccine induces high titres of neutralising antibody, more than 50 times the titres induced by natural infection

Vaccines

two prophylactic vaccines are licensed to protect against HPV infection:

- a quadrivalent vaccine, which targets HPV 6, 11, 16 and 18 (and HPV 31 by cross- protection), and
- a bivalent vaccine targeting HPV 16 and 18 (which cross-protects against HPV 31, 33 and 45) [8].
- The efficacy of each vaccine against HPV infection and related diseases has been established by large randomized clinical trials (RCTs) using intraepithelial neoplasia as surrogate end points [9–11].
- A second-generation HPV 9-valent vaccine (9vHPV) targeting five additional HPV types (against HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58) was approved in December 2014 by the US Food and Drug Administration

National- and state-level impact and cost-effectiveness of nonavalent HPV vaccination in the United States

- The nonavalent vaccine produces greater health benefits than the bivalent and quadrivalent vaccines
- at a lower societal cost.
- Because of the impact of herd immunity, any expansion in coverage will be much more effective in reducing cancer incidence and healthcare costs if targeted in those states with the lowest coverage

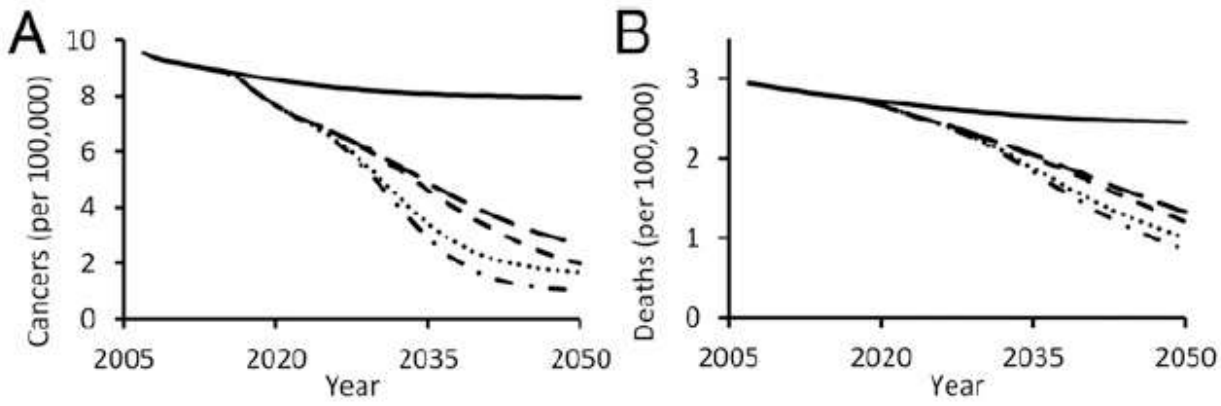


Fig. 2. Impact through 2050 of no vaccination (solid line), 2vHPV/4vHPV continued at current adolescent coverage (long dashed line), 9vHPV at current coverage (short dashed line), 2vHPV/4vHPV at 100% coverage (dotted line), and 9vHPV at 100% coverage (dashed and dotted line) on annual HPV-associated cervical cancers (*A*) and annual HPV-associated cervical cancer mortality (*B*).

PNAS 2016; 113:5107–5112

Target

- Since their licensure in 2006, HPV vaccines have been progressively introduced in many countries, mainly targeting young adolescent girls aged (9)10–14 years.
- An HPV vaccination coverage of 70% in women has been regarded as the threshold for optimum cost-effectiveness.
- A meta-analysis showed that a vaccination coverage of at least 50% delivered a 68% reduction in HPV types 16 and 18 and a 61% reduction in anogenital warts between the prevaccination and post-vaccination periods.
- Coverage will also affect the management of cervical cancer screening programmes. These programmes will need to be adjusted to the number of vaccinated females who will enter screening ages.

Efficacy

- Clinical trials have shown that HPV vaccines have more than 90% effi cacy in preventing high-grade cervical lesions caused by human papillomavirus types 16 and 18,[2,3]
- which are the two HPV types known to cause 70–80% of cervical cancers and large proportions of other anogenital and oropharyngeal cancers.
- The quadrivalent vaccine has shown similar efficacy in the prevention of anogenital warts caused by HPV types 6 and 11.
- Furthermore, both vaccines have shown lower—but still substantial—efficacy against related non-vaccine oncogenic human papillomavirus types.[4,5]

2 Garland SM, Hernandez-Avila M, Wheeler CM, et al. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. N Engl J Med 2007; 356: 1928–43.
3 Paavonen J, Naud P, Salmeron J, et al. Effi cacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women. Lancet 2009; 374: 301–14.
4 Bonanni P, Boccalini S, Bechini A. Effi cacy, duration of immunity and cross protection after HPV vaccination: a review of the evidence. Vaccine 2009; 27 (suppl 1): A46–53.
5 Malagon T, Drolet M, Boily MC, et al. Cross-protective effi cacy of two human papillomavirus vaccines: a systematic review and meta-analysis. Lancet Infect Dis 2012; 12: 781–89.

Safety

- The vaccine had an acceptable safety profile and induced robust and long-lasting antibody responses.
- Safety outcomes between groups were generally similar.
- Furthermore, HPV vaccination among Asian populations has a favorable safety profile, with only slightly higher risks of local (RR: 1.89; 95% CI 1.65-2.17) and systemic (RR: 1.33; 95% CI 1.18-1.50) adverse events in vaccinated individuals compared with controls.
- Serious adverse events occurred in 285 (10%) of 2881 women in the vaccine group and 267 (9%) of 2871 in the control group; five (<1%) and eight (<1%) of these events, respectively, were believed to be related to vaccination.

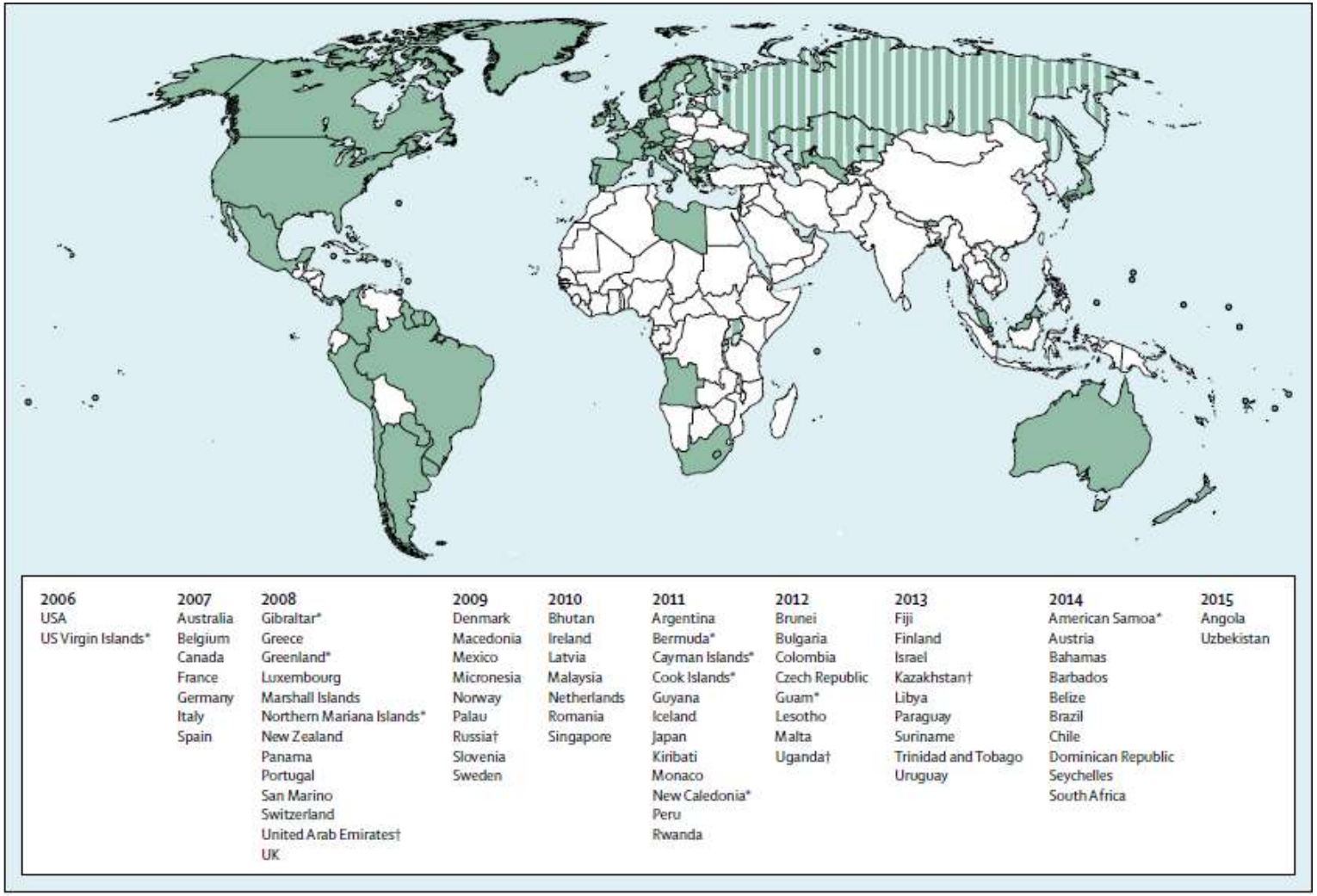
Table 4.
Safety and pregnancy outcomes up to month 48 (total vaccinated cohort)

	Vaccine group (n=2881)	Placebo group (n=2871)
Safety outcomes		
Solicited injection-site symptoms[*†] during 7-day post-vaccination period		
All	2443 (85%)	1910 (67%)
Grade 3[†]	394 (14%)	88 (3%)
General solicited symptoms[†] during 7-day post-vaccination period		
All	1878 (65%)	1659 (58%)
Related to vaccine	1181 (41%)	1025 (36%)
Grade 3[‡]	217 (8%)	169 (6%)
Unsolicited symptoms during 30-day post-vaccination period		
All	1154 (40%)	1164 (41%)
Related to vaccine	246 (9%)	192 (7%)
Grade 3[§]	207 (7%)	184 (6%)
Serious adverse events[¶]		
All	285 (10%)	267 (9%)
Related to vaccine	5 (<1%)	8 (<1%)
Medically significant conditions[‖]	1169 (41%)	1136 (40%)
New-onset chronic diseases[**]	142 (5%)	162 (6%)
New-onset autoimmune diseases[**]	6 (<1%)	7 (<1%)
Deaths[††]	14 (<1%)	3 (<1%)
Pregnancy outcomes[‡‡]		
Total pregnancies	357	358
Ongoing pregnancies	2 (1%)	1 (<1%)
Normal infant	257 (72%)	250 (70%)
Congenital anomaly[§§]	4 (1%)	7 (2%)
Spontaneous abortion[¶¶]	67 (19%)	67 (19%)
Elective termination[¶¶]	20 (6%)	23 (6%)
Therapeutic abortion	0	1 (<1%)
Ectopic pregnancy	5 (1%)	6 (2%)
Stillbirth	0	2 (1%)
Lost to follow-up	2 (1%)	1 (<1%)

Safe

- CDC and WHO have concluded from the literature that there is no association with the HPV vaccine and serious adverse effects.
- *However, there has been a concerted effort in places such as the United States to suggest that the HPV vaccine may cause serious adverse effects including brain damage*

HPV global vaccination coverage



2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
USA	Australia	Gibraltar*	Denmark	Bhutan	Argentina	Brunei	Fiji	American Samoa*	Angola
US Virgin Islands*	Belgium	Greece	Macedonia	Ireland	Bermuda*	Bulgaria	Finland	Austria	Uzbekistan
	Canada	Greenland*	Mexico	Latvia	Cayman Islands*	Colombia	Israel	Bahamas	
	France	Luxembourg	Micronesia	Malaysia	Cook Islands*	Czech Republic	Kazakhstan†	Barbados	
	Germany	Marshall Islands	Norway	Netherlands	Guyana	Guam*	Libya	Belize	
	Italy	Northern Mariana Islands*	Palau	Romania	Iceland	Lesotho	Paraguay	Brazil	
	Spain	New Zealand	Russia†	Singapore	Japan	Malta	Suriname	Chile	
		Panama	Slovenia		Kiribati	Uganda†	Trinidad and Tobago	Dominican Republic	
		Portugal	Sweden		Monaco		Uruguay	Seychelles	
		San Marino			New Caledonia*			South Africa	
		Switzerland			Peru				
		United Arab Emirates†			Rwanda				
		UK							

***Figure 1*: Countries that have introduced a publicly funded national human papillomavirus vaccination programme since 2006, by year**
Striped sections indicate implementation in a part of the country. French Polynesia, Liechtenstein, and Niue have reported vaccine programmes, but no information was available about year of introduction. *Special territory. †Partial implementation.

Despite accounting for only 14% of annual cervical cancer cases, on the basis of our estimations, high income countries accounted for almost 70% of vaccinated women worldwide by the end of 2014.

Furthermore, these same countries had already largely invested in cervical cancer screening programmes that were successful in lowering and stabilising cervical cancer rates

mostly to pre-adolescent females, but some extended the coverage to older cohorts using catch-up strategies

However, high-income countries show the lowest levels of vaccination coverage among targeted primary groups, achieving globally less than 50% coverage, mostly due to the strong influence of underperforming countries such as the USA, France, or Germany in the final estimates.

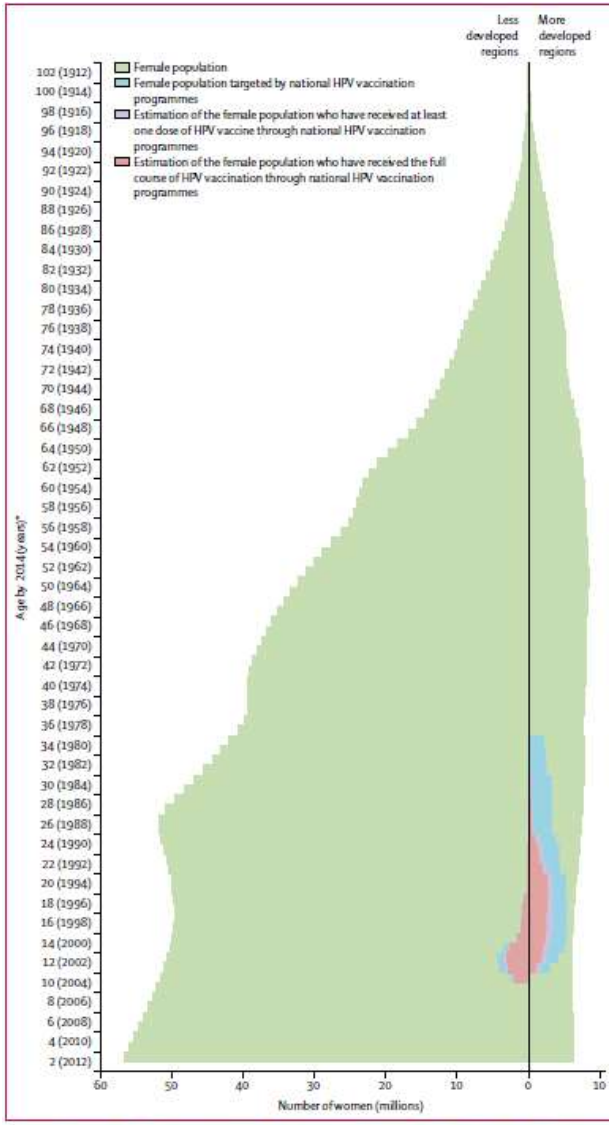
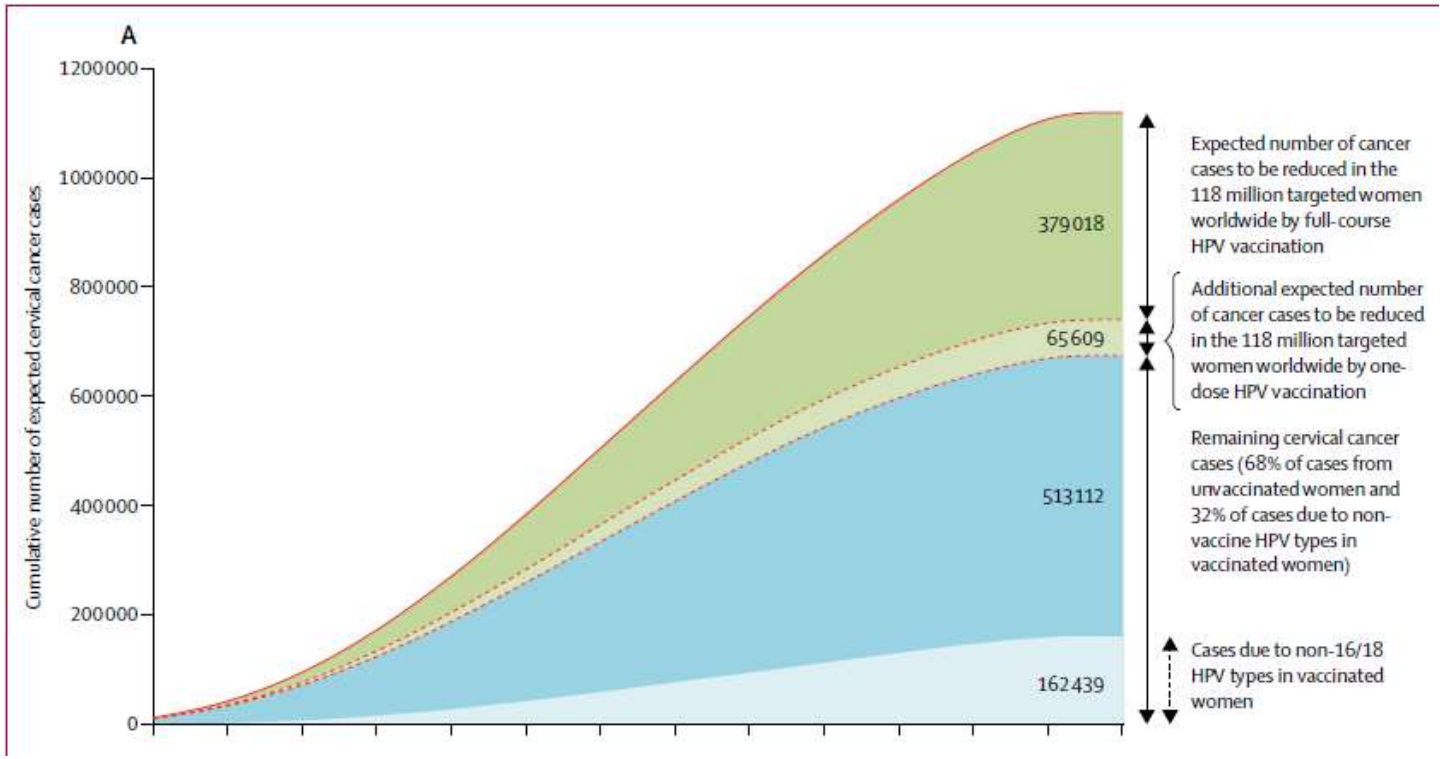


Figure 2: Female population pyramid by development level and age distribution of women targeted by national HPV vaccination programmes

Effetto previsto degli attuali livelli di vaccinazione

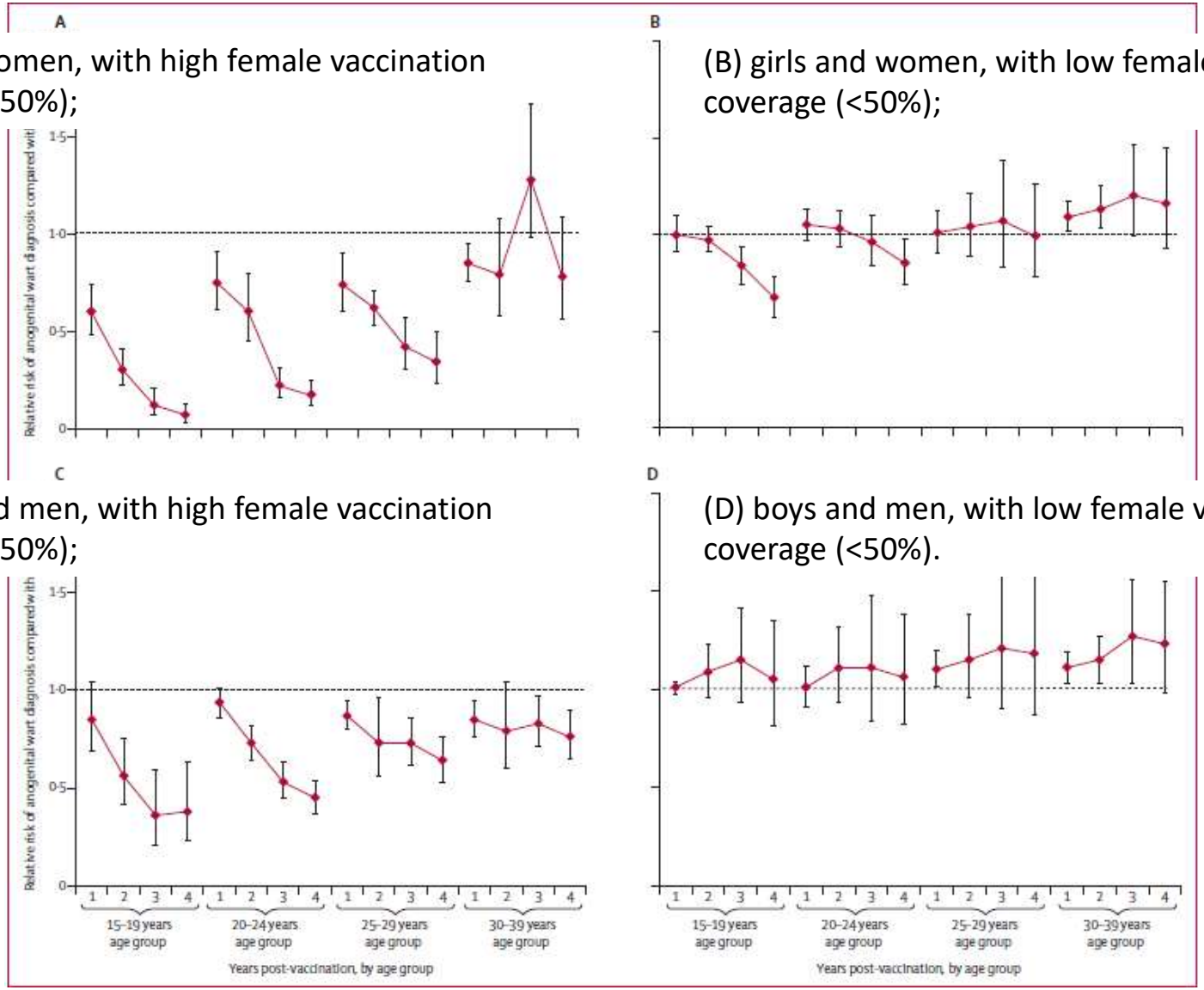


Effetti precoci delle campagne di vaccinazione

- In countries with high vaccination coverage, HPV16 and HPV18 infection, and anogenital warts decreased by more than 60% in girls younger than 20 years of age, starting after the first year of the vaccination programmes.
- Furthermore, in these countries, our results suggest evidence of vaccine crossprotection and herd effects, with significant reductions in
  - HPV31, HPV33, and HPV45 infection in girls younger than 20 years of age, and
  - in anogenital warts in men and older women.
- strong evidence that HPV vaccination is highly effective and can provide cross-protection outside trial settings, and reinforce the need for early vaccination and high vaccination coverage to maximise populationlevel effectiveness and herd effects

Population-level impact and herd effects following human papillomavirus vaccination programmes: a systematic review and meta-analysis. Drolet M Lancet Infect Dis 2015; 15: 565–80

Girls and women, with high female vaccination coverage (≥50%);



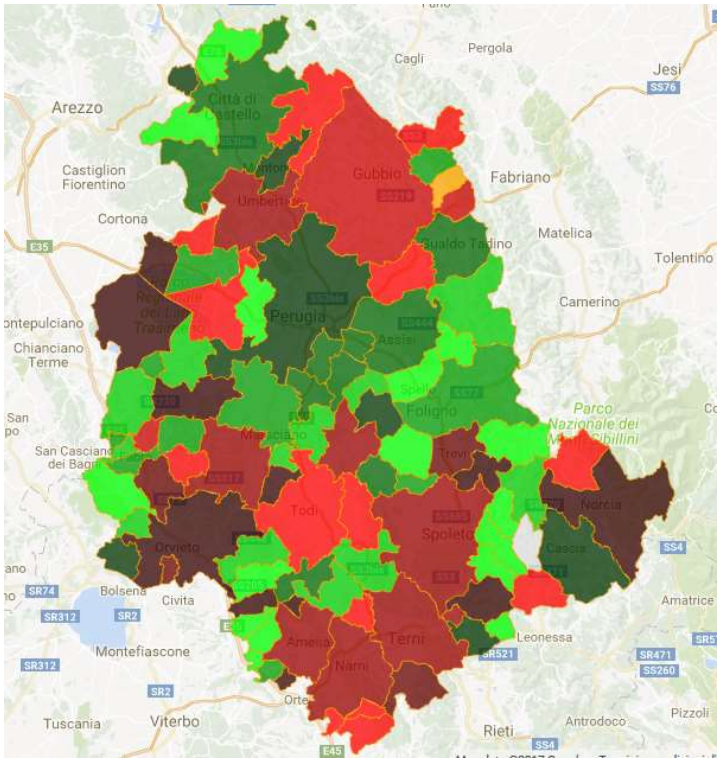
(B) girls and women, with low female vaccination coverage (<50%);

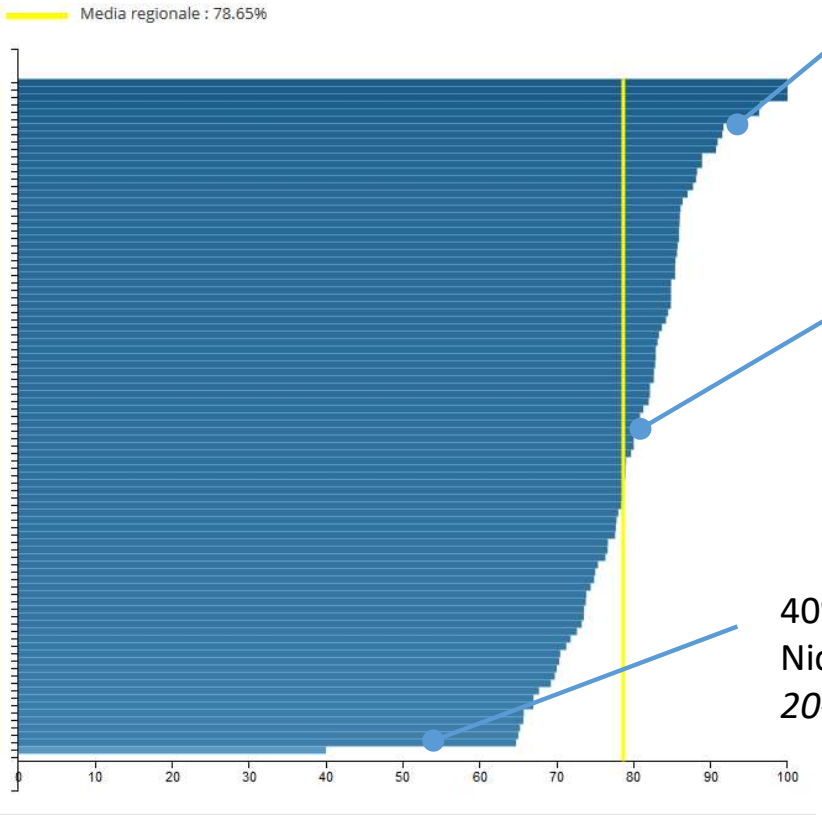
(C) boys and men, with high female vaccination coverage (≥50%);

(D) boys and men, with low female vaccination coverage (<50%).

Changes in anogenital wart diagnosis during the first 4 years after the introduction of human papillomavirus vaccination with the quadrivalent vaccine

Mappe della % di vaccinate contro HPV per comune 2009-2015 ; media regionale circa 79%





100% in alcuni comuni della Valnerina

82% Città di Castello *(IC 95% 80-84)*

40% Lisciano Niccone *(IC 95% 20-64)*

Mappatura provvisoria – in collaborazione con i Dr. Becchetti, Ciani, Santocchia, Valsenti, Gianfredi, Brunori, Bianconi

Male vaccination

- Extending the HPV vaccination programme to males was proposed to enhance the receptivity of females and males getting the HPV vaccine [15].
- This strategy would also contribute to reducing the HPV transmission and thus maximize the effect of the vaccination programme for cervical cancer.
- Moreover, HPV vaccines would prevent genital warts and non-cervical cancers caused by HPV infection, providing additional health benefits.
- Now increasing evidence demonstrates how important the burden of HPV-correlated diseases also is in men. Epidemiological data show that in Europe and the USA, the burden of HPV-related head and neck cancers is carried mainly by men (4 times more than women),

Vaccination strategy

- Few countries have implemented a universal HPV vaccination programme for males and females, … (Australia)

Cost-effectiveness: risultati non concordanti

- Marra et al. [71] found four studies assessing male vaccination against HPV and little detail was reported, since the main focus was the cost-effectiveness of female vaccination. Including males increased the cost per QALYg beyond the traditionally used cut-off of $50,000
- Seto et al. [28] concluded that male vaccination becomes cost-effective for low vaccination coverage in females and high vaccination coverage in males.
- Jiang et al. [29] performed a critical review of studies exploring the impact of HPV male vaccination: heterogeneity among these studies limited the conclusions regarding the absolute cost-effectiveness of male vaccination. Nevertheless, incorporating all HPV-related diseases combined with a suboptimal vaccine coverage rate among females could improve the cost-effectiveness profile of male vaccination
- Ben Hadj Yahia et al.: Extending vaccination to males does not seem to be cost-effective unless all HPV-related diseases are considered, vaccine coverage is below 40 % and/or the vaccine price is less than $75. [High risk: vaccine be extended to ‘high-risk’ men such as MSM who do not profit from female-only vaccination strategies or those men with HIV. Nevertheless, identification of the subpopulation is not feasible at the age of 12 years.]

Ben Hadj Yahia MG et al. Clin Drug Invest 2015

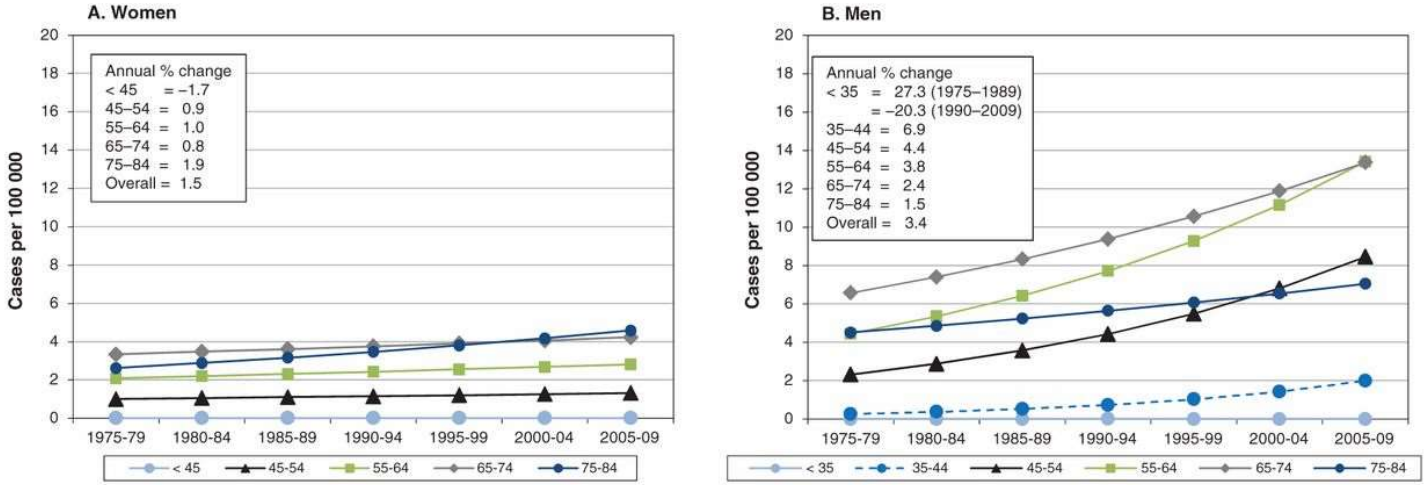
Increasing relevance of HPV in oropharingeal cancer

- Cancer registry-based studies, mostly from the Western countries, have reported a rising incidence of HPV-related HNC,
- despite an overall decrease in the incidence of HNC.[5–11]
- The overall decrease in the incidence of HNC in these countries can be largely attributed to the decline in the prevalence of cigarette smoking.
- A recent meta-analysis showed that HPV prevalence in head-and-neck tumors increased significantly from 41% prior to 2000 to 72% after 2004 and that HPV16 accounted for 96% of HPV-positive OSCC.[19]
- Further, HPV prevalence was higher among OSCC in North-America (60%) versus Europe (40%)

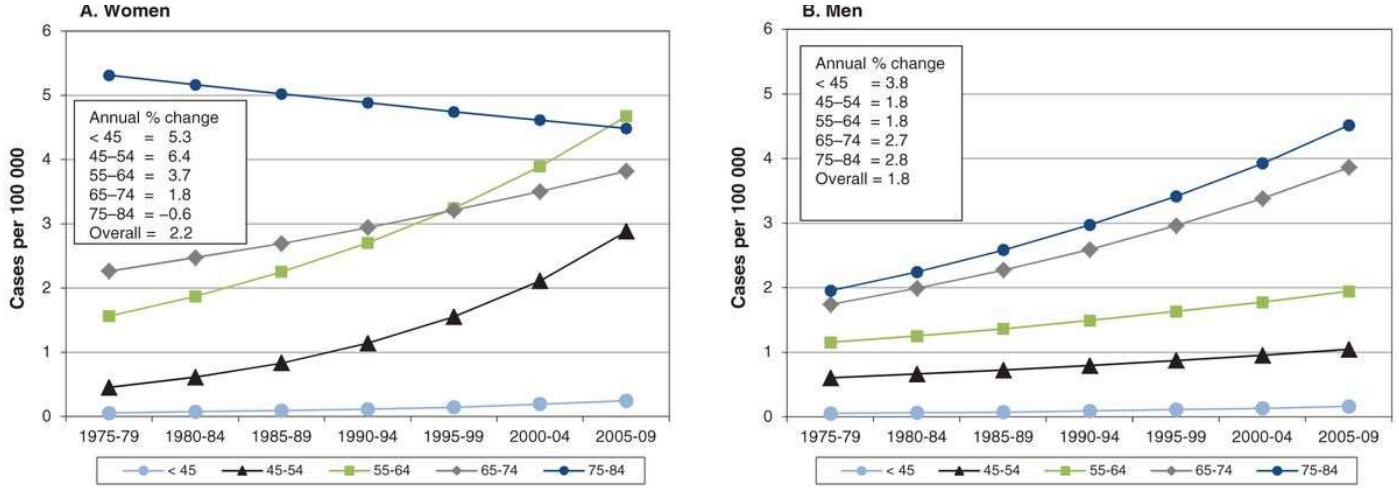
Increasing trend of HPV-related cancers

- Anal cancer incidence in southeast England increased in both men and women over the study period (1960–2004), by threefold in women and about 1.5-fold in men; the incidence is now higher in women than in men. Similar trends have been seen in Denmark (Frisch et al, 1993), the United States of America (Melbye et al, 1994; Johnson et al, 2004) and Sweden (Goldman et al, 1989). Increases have also been reported in Scotland (Brewster and Bhatti, 2006),
- The generational patterns seen in the cohort rates presented in this paper, with a marked change from around 1940, while not constituting proof, are compatible with the hypothesis that changes in sexual practices are a major contributor to the increases in anogenital cancers other than the cervix. Those born around 1940 would have been in their early twenties at the start of the 'sexual revolution' in the early 1960s.

An analysis of temporal and generational trends in the incidence of anal and other HPV-related cancers in Southeast England Br J Cancer. 2009 Feb 10; 100(3): 527–531.

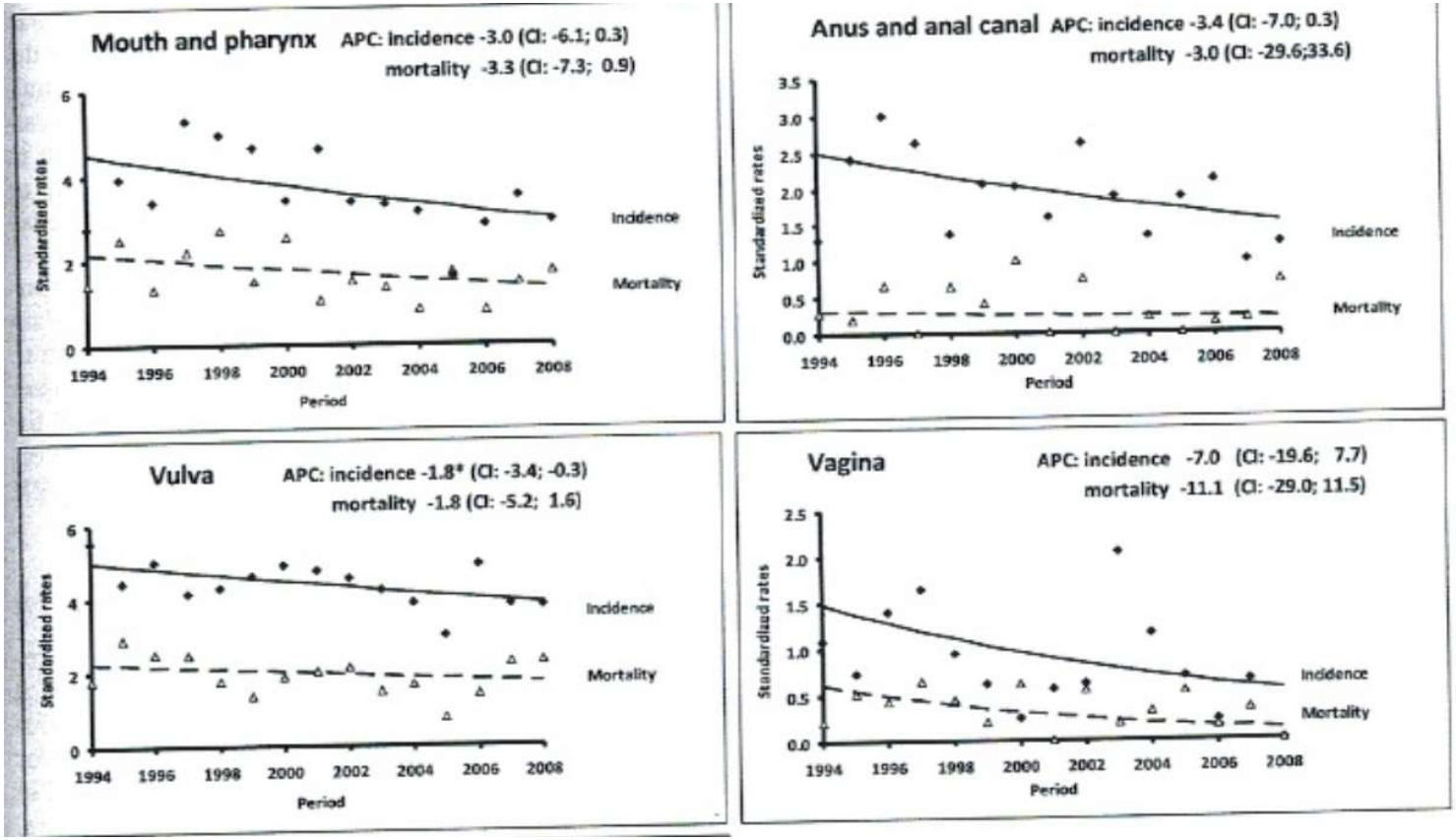


Age-specific trends in incidence of oropharyngeal cancers in Alberta, Canada, 1975–2009, among women (A) and men (B)



Age-specific trends in incidence of anal cancers in Alberta, Canada, 1975–2009, among women (A) and men (B)

Epidemiology of HPV-related female cancers in the Umbria region of Italy: pre-vaccination period



Public health value of universal HPV vaccination

- The cost-effectiveness of including boys into HPV vaccination programs should be re-assessed inview of the progressive drop of the economic burden of HPV-related diseases in men and women due to universal vaccination.
- The cost of the remarkable increase in anal and oropharyngeal HPV driven cancers in both sexes has been grossly underestimated or ignored.
- Conclusions: Steps must be taken by relevant bodies to achieve the target of universal vaccination. The analysis of HPV vaccination's clinical effectiveness vs. economic efficacy are supportive of the economic sustainability of vaccination programs both in women and men.
- In Europe, these achievements demand urgent attention to the social equity for both genders in healthcare. There is sufficient ethical, scientific, strategic and economic evidence to urge the European Community to develop and implement a coordinated and comprehensive strategy aimed at both genders and geographically balanced, to **eradicate cervical cancer and other diseases caused by HPV in Europe**

Audisio R. et al. Critical Reviews in Oncology/Hematology 97 (2016) 157–167

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