

Epidemiologia delle lesioni ghiandolari

Paolo Giorgi Rossi

Servizio Epidemiologia, AUSL
Reggio Emilia

Argomenti trattati

- Incidenza: età, tipi correlati e trend
- L'epidemia latente
- L'efficacia dello screening con Pap test
- La sensibilità del Pap test e della colposcopia
- L'efficacia dello screening con HPV

L'incidenza

L'incidenza dell'adenocarcinoma della cervice uterina, Firenze 1985-2000

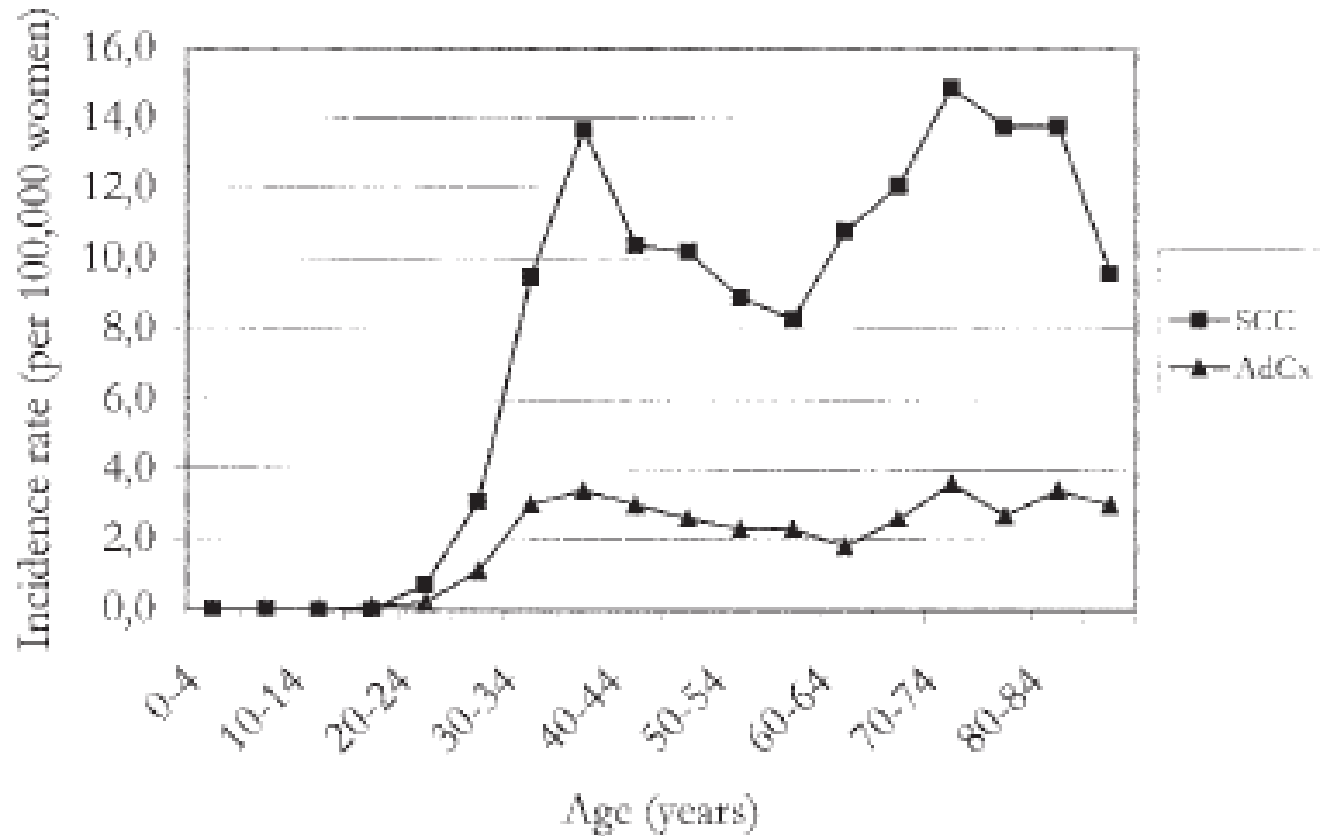
Età	Incidenza/100.000 (casi)
<25	0.1 (2)
25-44	1.3 (35)
45-64	2.0 (52)
65+	2.6 (56)
Tutte le età	1.2 (145)

Table 2

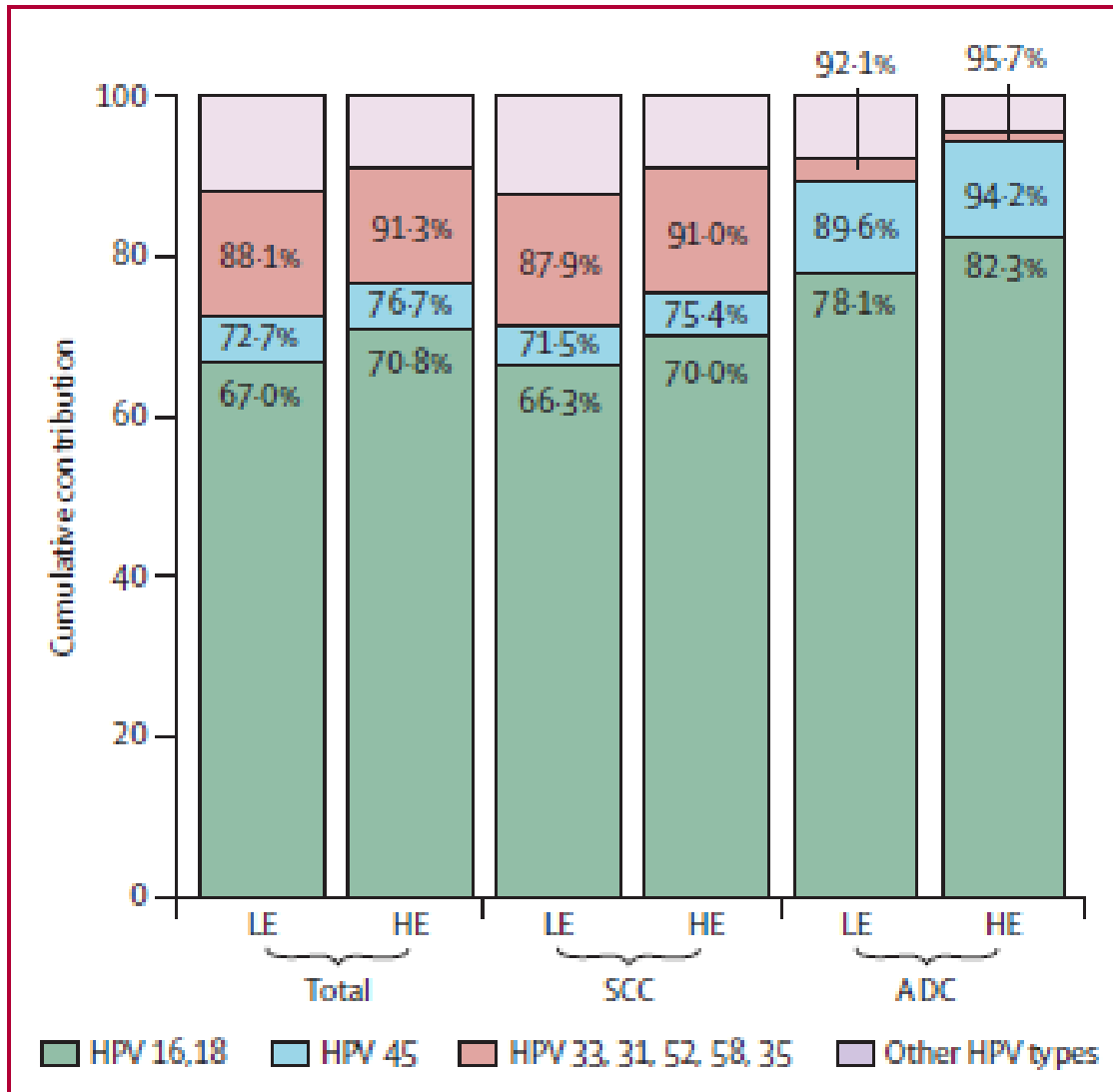
Age-adjusted incidence rates (cases/100,000 women adjusted on the European population) of cervical adenocarcinoma by age-groups and by calendar period. Tuscany Cancer Registry

Age-groups (years)	Calendar period and adjusted rate (cases/100,000 women)				
	1985–1988 (cases)	1989–1992 (cases)	1993–1996 (cases)	1997–2000 (cases)	All periods (cases)
<25	0.1 (1)	0 (0)	0 (0)	0.2 (1)	0.1 (2)
25–44	0.6 (4)	0.4 (3)	1.7 (11)	2.4 (17)	1.3 (35)
45–64	1.4 (10)	2.6 (17)	1.8 (12)	2.0 (13)	2.0 (52)
65+	1.5 (7)	2.7 (16)	3.2 (17)	2.8 (16)	2.6 (56)
All ages	0.7 (22)	1.1 (36)	1.3 (40)	1.5 (47)	1.2 (145)

L'incidenza dell'adenocarcinoma della cervice uterina, Olanda



Tipi HPV correlati

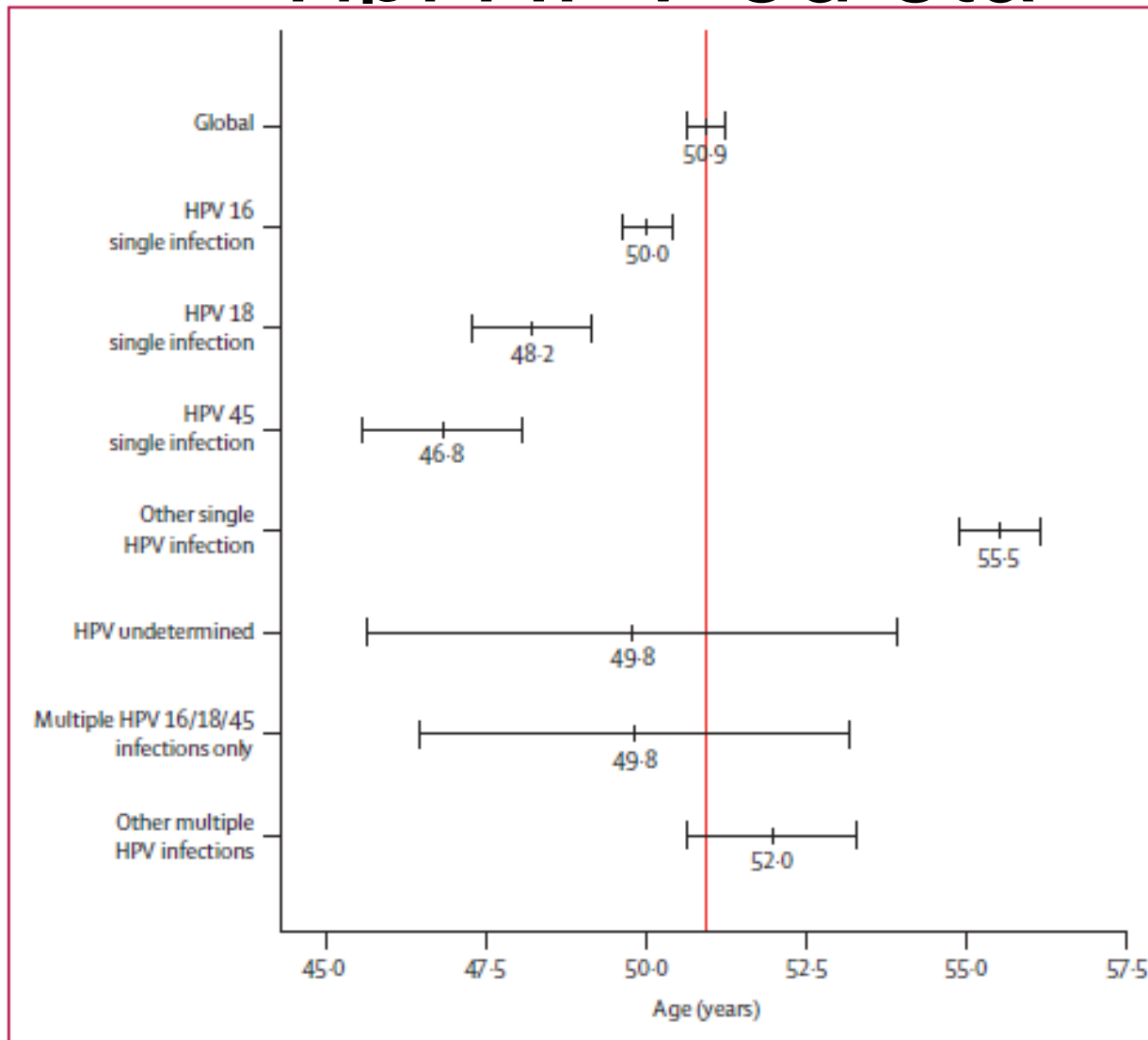


Tipi della famiglia alpha 7 maggiormente correlati ad adenocarcinoma

TABLE I – TYPE-SPECIFIC PREVALENCE OF 19 HPV TYPES IN ADENO/
ADENOSQUAMOUS CARCINOMA (ADC) AND SQUAMOUS CELL
CARCINOMA (SCC) OF THE CERVIX, AND CORRESPONDING
ADC:SCC PREVALENCE RATIOS

HPV type/species	SCC		ADC		ADC:SCC prevalence ratio (95% CI)
	N	%	N	%	
Any HPV	11,693	90.1	2,373	80.3	0.90 (0.89–0.92)
Any multiple	7,253	9.1	1,408	8.5	0.98 (0.75–1.28)
Alpha 7					
18	11,786	12.2	2,512	37.9	3.16 (2.91–3.43)
39	7,058	1.5	1,289	0.8	0.64 (0.33–1.23)
45	7,849	3.8	1,616	5.6	1.65 (1.29–2.12)
59	6,882	1.0	1,430	1.1	1.64 (0.92–2.92)
68	6,704	0.5	1,209	0.6	1.60 (0.62–4.09)
70	6,384	0.4	989	0.3	0.82 (0.25–2.71)
Alpha 9					
16	11,878	56.6	2,521	35.3	0.57 (0.54–0.60)
31	9,071	3.6	1,639	2.0	0.49 (0.34–0.72)
33	10,309	5.2	2,005	2.1	0.39 (0.28–0.53)
35	8,340	1.5	1,530	0.7	0.69 (0.36–1.33)
52	8,737	3.5	1,573	1.3	0.52 (0.33–0.80)
58	9,088	5.9	1,613	1.9	0.39 (0.27–0.56)
Other					
6	9,049	0.4	1,497	0.1	0.09 (0.01–0.74)
11	8,400	0.2	1,308	0.1	0.55 (0.07–4.32)
51	7,281	1.0	1,286	0.2	0.26 (0.06–1.04)
56	7,232	1.0	1,445	0.2	0.23 (0.07–0.76)
66	6,969	0.3	1,131	0.3	0.98 (0.28–3.38)
73	5,929	0.3	774	0.0	–
82	6,135	0.2	828	0.0	–

Tipi HPV ed età



Trend in Olanda

TABLE I—INCIDENCE OF CERVICAL CANCER IN THE NETHERLANDS, 1989–1998¹

Year	SCC		AdCx		Other		Total	
	Cases	ESR	Cases	ESR	Cases	ESR	Cases	ESR
1989	556	7.1	114	1.4	49	0.6	719	9.1
1990	561	7.0	144	1.8	55	0.7	761	9.5
1991	537	6.4	135	1.7	61	0.8	737	8.9
1992	556	6.8	139	1.6	53	0.6	752	9.1
1993	523	6.3	143	1.7	53	0.6	722	8.6
1994	539	6.2	131	1.6	45	0.5	715	8.3
1995	547	6.4	141	1.7	34	0.4	725	8.5
1996	532	6.1	136	1.6	47	0.5	719	8.2
1997	535	6.1	157	1.8	37	0.4	729	8.3
1998	546	6.1	154	1.7	29	0.3	733	8.2
EAPC	−1.6%		1.2%		−8.0%		−1.6%	
<i>p</i>	0.001		0.71		0.002		<0.001	

¹SCC, squamous cell carcinoma; ESR, estimated standardized rate; EAPC, estimated annual percent change.

anno	Incidenza/100.000 (casi)
1989	1.4 (114)
1990	1.8 (144)
1991	1.7 (135)
1992	1.6 (139)
1993	1.7 (143)
1994	1.6 (131)
1995	1.7 (141)
1996	1.6 (136)
1997	1.8 (157)
1998	1.7 (154)

Trend a Firenze 1985-2000

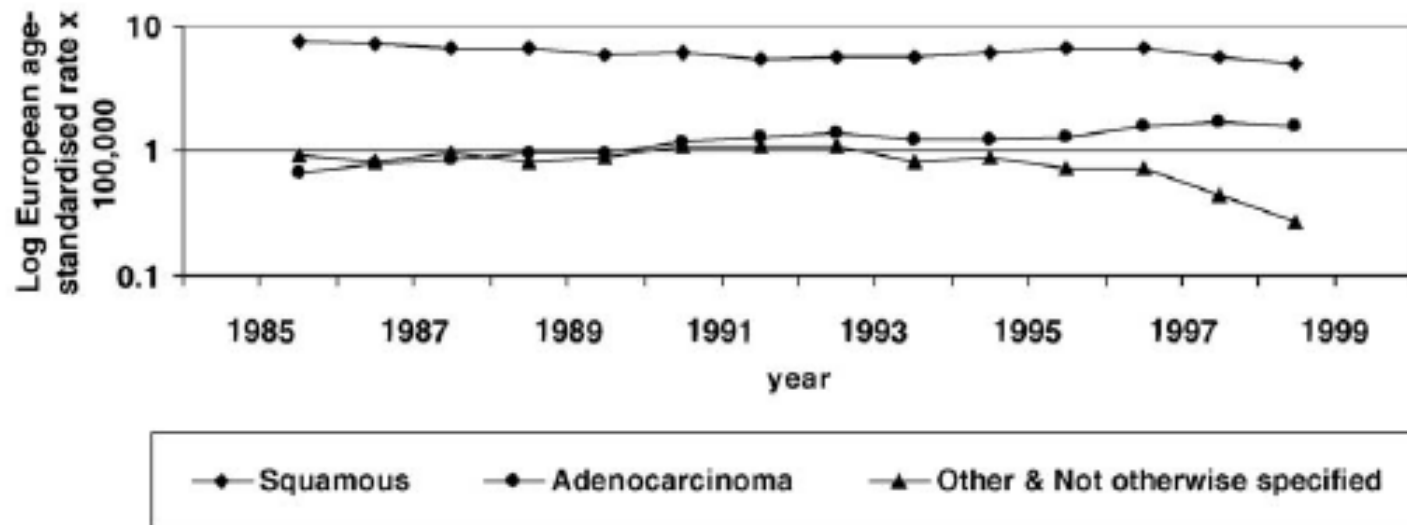
Table 2

Age-adjusted incidence rates (cases/100,000 women adjusted on the European population) of cervical adenocarcinoma by age-groups and by calendar period. Tuscany Cancer Registry

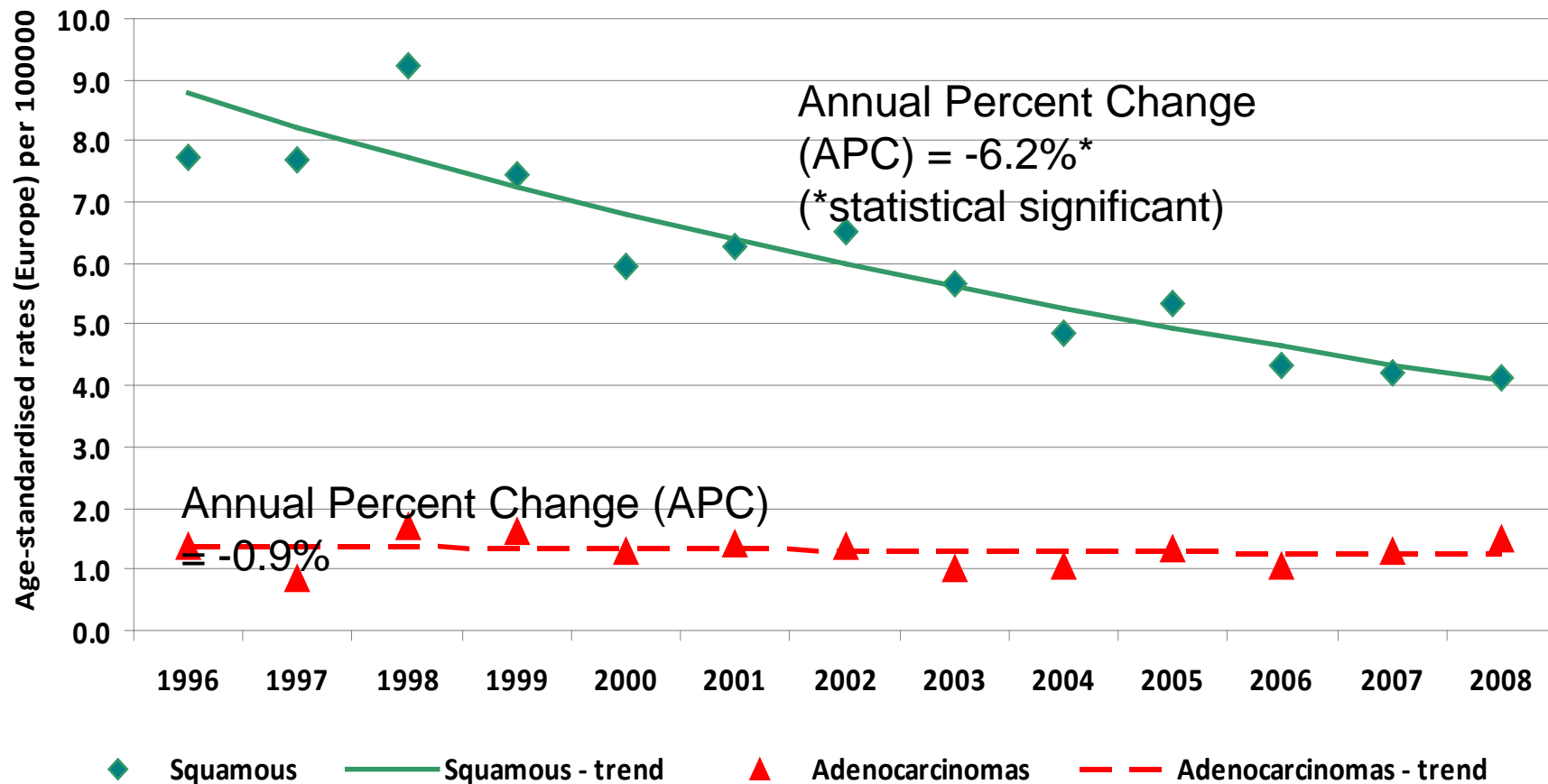
Age-groups (years)	Calendar period and adjusted rate (cases/100,000 women)				
	1985–1988 (cases)	1989–1992 (cases)	1993–1996 (cases)	1997–2000 (cases)	All periods (cases)
<25	0.1 (1)	0 (0)	0 (0)	0.2 (1)	0.1 (2)
25–44	0.6 (4)	0.4 (3)	1.7 (11)	2.4 (17)	1.3 (35)
45–64	1.4 (10)	2.6 (17)	1.8 (12)	2.0 (13)	2.0 (52)
65+	1.5 (7)	2.7 (16)	3.2 (17)	2.8 (16)	2.6 (56)
All ages	0.7 (22)	1.1 (36)	1.3 (40)	1.5 (47)	1.2 (145)

1985-88	1989-92	1993-96	1997-2000
0.7 (22)	1.1 (36)	1.3 (40)	1.5 (47)

Trend a Firenze



L'incidenza dell'adenocarcinoma della cervice uterina, Emilia-Romagna



1.3/100000

Nel 1996 circa 10% dei Ca invasivi

Nel 2008 circa il 30% dei Ca invasivi

L'epidemia che abbiamo evitato

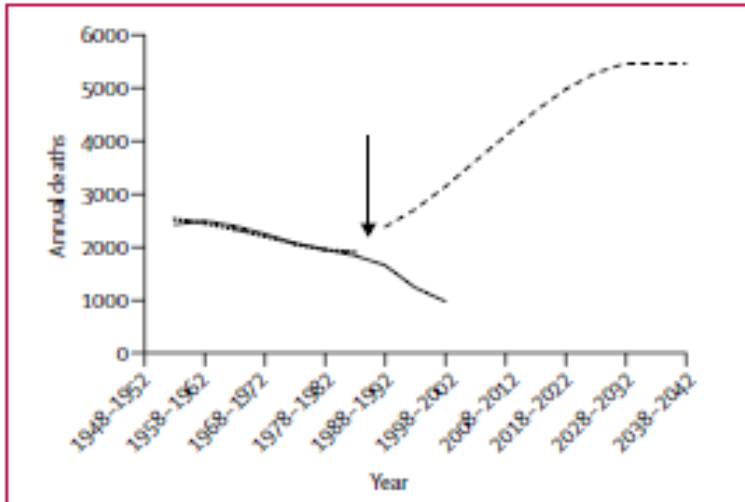
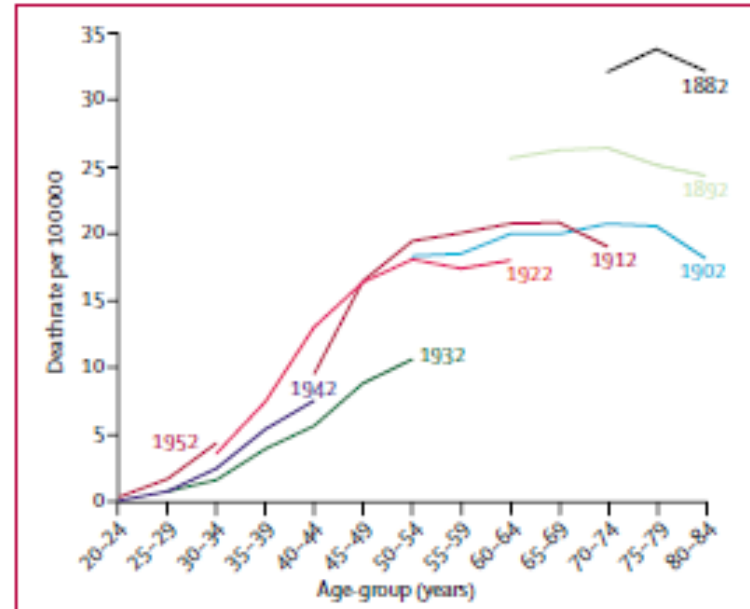


Figure 4: Projected cervical cancer deaths in women younger than 85 years without any screening (England and Wales)



Peto et al Lancet 2005

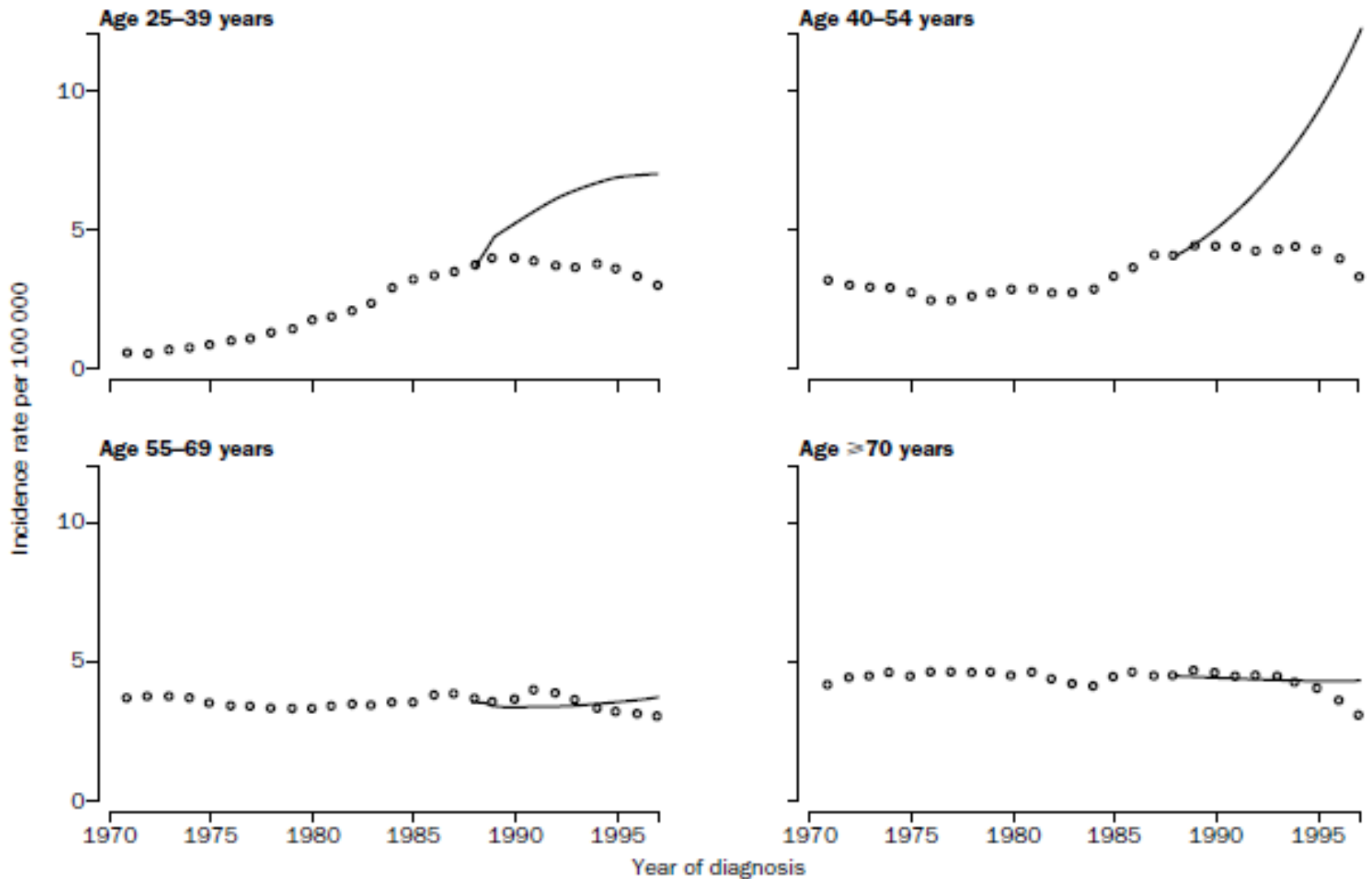


Figure 1: Trends in age-specific incidence of adenocarcinoma of the cervix in five registries with available data 1971-97
 Open circles=3-year running averages of actual rates. Continuous curves are rates predicted from age-cohort model fitted to data from England 1971-87.

Conclusioni incidenza

- Malattia rara, al di sotto di soglia per giustificare screening
- Simile correlazione ad HPV rispetto a squamoso, ma con maggiore prevalenza 18 e 45
- Sostanzialmente stabile negli ultimi decenni
- Squamoso in calo drastico, sebbene abbiamo indizi di un'epidemia "silente" contenuta dallo screening.

Efficacia Pap test

Efficacia del Pap a Firenze

Table 2 Distribution of the cases (overall including not otherwise specified (NOS) and other cancers and divided by squamous cancer and adenocarcinomas) and controls by history of screening. OR of developing a fully invasive cervical cancer by time since last test^a, adjusted for civil status and birth place

Time since last test ^a	Controls No. (%)	Squamous		Adenocarcinoma		All cases	
		No. (%)	OR (95% CI)	No. (%)	OR (95% CI)	No. (%)	OR (95% CI)
< 3 years	187 (22.5)	11 (7.4)	0.15 (0.07–0.30)	9 (17.0)	0.65 (0.26–1.65)	22 (10.6)	0.25 (0.15–0.42)
3– < 6 years	171 (20.5)	11 (7.4)	0.20 (0.10–0.39)	13 (24.5)	0.99 (0.43–2.29)	26 (12.5)	0.34 (0.21–0.56)
≥ 6 years	237 (28.5)	48 (32.4)	0.56 (0.36–0.87)	10 (18.9)	0.54 (0.24–1.23)	59 (28.4)	0.56 (0.38–0.82)
Never screened	237 (28.5)	78 (52.7)	1.0 ^b	21 (39.6)	1.0 ^b	101 (48.6)	1.0 ^b

^aExcluding tests performed the year before the index date. ^bBaseline. OR = odds ratios; CI = confidence interval.

Efficacia del Pap a Trento

Morfologia	Odds Ratio	95%CI
Squamoso	0.23	0.09-0.58
adenocarcinoma	0.24	0.07-0.78

Nessun effetto sotto i 40 anni

Efficacia in Australia

Table I Relative protection against adenocarcinoma of the cervix in relation to timing and number of negative cytology reports and past history of abnormality

<i>Risk factor</i>	<i>No. of cases</i>	<i>No. of controls</i>	<i>Relative protection^a</i>	<i>95% CI</i>
Time since last negative report (years)				
10+	6	24	1.0	
5-9.9	19	49	0.6	0.2-1.8
3-4.9	33	68	0.5	0.2-1.4
2-2.9	13	54	0.9	0.3-3.1
1-1.9	20	110	1.3	0.4-4.0
0-0.9	22	147	1.6	0.5-5.0
Number of negative reports				
2	39	137	1.0	
3	29	107	0.9	0.5-1.7
4	18	77	1.0	0.5-1.9
5	12	47	0.8	0.4-1.8
6	6	32	1.1	0.4-3.0
7+	9	52	1.2	0.5-3.0
Past history of cervical abnormality				
No	105	433	1.0	
Yes	8	19	0.5	0.2-1.3

^aAfter adjustment for the other variables.

Efficacia del Pap in Giappone

TABLE 3. Odds ratios according to histological type and age

	Screening history	Cases	Controls	Odds ratio	95% confidence interval
Histological type					
Squamous cell-carcinoma	Ever	80 (45.7)	293 (83.7)	0.13***	0.077-0.215
	Never	96 (54.3)	57 (16.3)	1.0	
Adenocarcinoma	Ever	17 (73.9)	39 (84.8)	0.40 n.s.	0.091-1.753
	Never	6 (26.1)	7 (15.2)	1.0	
Age (years)					
35-49	Ever	52 (50.0)	180 (86.5)	0.15***	0.078-0.280
	Never	52 (50.0)	28 (13.5)	1.0	
50-79	Ever	45 (47.9)	153 (81.4)	0.14***	0.065-0.281
	Never	49 (52.1)	35 (18.6)	1.0	

*** $p < 0.001$

n.s., not significant.

() = %

	Ever-invited (N = 2611) No. (%)	Never-invited (N = 657) No. (%)	OR ^a (95% CI)	Total (N = 3268) No.
<i>Age at ICC diagnosis (years)</i>				
25–34	261 (78.4)	72 (21.6)	0.98 (0.72–1.34)	333
35–44	793 (78.7)	215 (21.3)	1 ^b	1008
45–54	753 (78.6)	205 (21.4)	0.99 (0.80–1.24)	958
55–65	804 (83.0)	165 (17.0)	0.71 (0.57–0.90)	969
<i>Years between OCSF start and ICC diagnosis</i>				
≥ 6	1128 (90.8)	114 (9.2)	1 ^b	1242
3–5	781 (78.1)	219 (21.9)	2.79 (2.19–3.57)	1000
0–2	702 (68.4)	324 (31.6)	4.62 (3.66–5.84)	1026
<i>Area of residence</i>				
North	1919 (80.8)	455 (19.2)	1 ^b	2374
Centre	589 (79.8)	149 (20.2)	0.63 (0.51–0.79)	738
South/islands	103 (66.0)	53 (34.0)	2.71 (1.88–3.91)	156
<i>Country of birth^c</i>				
Italy	2280 (81.8)	506 (18.2)	1 ^b	2786
Foreign countries	267 (73.2)	98 (26.8)	2.19 (1.67–2.87)	365
<i>ICC histological type^c</i>				
Squamous cells	2001 (79.8)	508 (20.2)	1 ^b	2509
Other or NOS ^d	610 (80.5)	148 (19.5)	0.98 (0.79–1.21)	758

	Ever-compliant (N = 1430) No. (%)	Never-compliant (N = 1181) No. (%)	OR ^a (95% CI)	Total (N = 2611) No.
<i>Age at ICC diagnosis (years)</i>				
25–34	164 (62.8)	97 (37.2)	0.83 (0.63–1.11)	261
35–44	464 (58.5)	329 (41.5)	1 ^b	793
45–54	385 (51.1)	368 (48.9)	1.35 (1.10–1.65)	753
55–65	417 (51.9)	387 (48.1)	1.31 (1.07–1.60)	804
<i>Years between OCSF start and ICC diagnosis</i>				
≥ 6	601 (53.3)	527 (46.7)	1 ^b	1128
3–5	406 (52.0)	375 (48.0)	1.06 (0.88–1.28)	781
0–2	423 (60.3)	279 (39.7)	0.75 (0.62–0.91)	702
<i>Area of residence</i>				
North	1052 (54.8)	867 (45.2)	1 ^b	1919
Centre	358 (60.8)	231 (39.2)	0.79 (0.66–0.96)	589
South/islands	20 (19.4)	83 (80.6)	4.91 (2.99–8.08)	103
<i>Country of birth^c</i>				
Italy	1236 (54.2)	1044 (45.8)	1 ^b	2280
Foreign countries	162 (60.7)	105 (39.3)	0.80 (0.62–1.04)	267
<i>ICC histological type^c</i>				
Squamous cells	1078 (53.9)	923 (46.1)	1 ^b	2004
Other or NOS ^d	352 (57.7)	258 (42.3)	0.87 (0.73–1.05)	610

	Screen-detected ICC ^b (N = 1075) No. (%)	Non-screen-detected ICC ^c				Total (N = 1430) No.
		Last negative cytology <3.5 years before ICC diagnosis (N = 200)		Last negative cytology ≥3.5 years before ICC diagnosis (N = 155)		
		No. (%)	OR ^a (95% CI)	No. (%)	OR ^a (95% CI)	
<i>Age at ICC diagnosis (years)</i>						
25–34	130 (79.3)	22 (13.4)	1.03 (0.60–1.75)	12 (7.3)	0.60 (0.31–1.16)	164
35–44	352 (75.9)	58 (12.5)	1 ^d	54 (11.6)	1 ^d	464
45–54	288 (74.8)	52 (13.5)	1.10 (0.73–1.64)	45 (11.7)	1.02 (0.67–1.56)	385
55–65	305 (73.1)	68 (16.3)	1.35 (0.92–1.98)	44 (10.6)	0.94 (0.61–1.44)	417
<i>Years between OCSP start and ICC diagnosis^e</i>						
≥6	436 (72.6)	107 (17.8)	1 ^d	58 (9.7)	1 ^d	601
3.5–5	217 (75.3)	40 (13.9)	0.75 (0.50–1.12)	31 (10.8)	1.05 (0.66–1.68)	288
<i>Area of residence</i>						
North	853 (81.1)	147 (14.0)	1 ^d	52 (4.9)	1 ^d	1052
Centre	213 (59.5)	44 (12.3)	1.20 (0.83–1.74)	101 (28.2)	7.90 (5.46–11.42)	358
South/islands	9 (45.0)	9 (45.0)	5.76 (2.24–14.84)	2 (10.0)	3.90 (0.82–18.62)	20
<i>Country of birth^f</i>						
Italy	925 (74.8)	177 (14.3)	1 ^d	134 (10.8)	1 ^d	1236
Foreign countries	133 (82.1)	21 (13.0)	0.85 (0.52–1.40)	8 (4.9)	0.40 (0.19–0.85)	162
<i>ICC histological type^g</i>						
Squamous cells	871 (80.8)	109 (10.1)	1 ^d	98 (9.1)	1 ^d	1078
Other or NOS ^h	204 (58.0)	91 (25.9)	3.64 (2.65–5.02)	57 (16.2)	2.53 (1.76–3.63)	352

Sensibilità Pap e colposcopia

Table 3. ORs of cervical cancer associated with screening history, age at diagnosis, and FIGO stage by histological type*

Variable	All cancers			Squamous cell carcinomas			Nonsquamous cell carcinomas†		
	No. of case subjects	No. of control subjects	OR (95% CI)	No. of case subjects	No. of control subjects	OR (95% CI)	No. of case subjects	No. of control subjects	OR (95% CI)
All subjects	1230	6124		921	4588		309	1536	
Screening history									
Not screened	789	2836	2.52 (2.19 to 2.91)	628	2167	2.97 (2.51 to 3.50)	161	669	1.59 (1.20 to 2.11)
Screened‡	441	3288	1.00 (referent)	293	2421	1.00 (referent)	148	867	1.00 (referent)
Not screened	789	2836	3.53 (3.02 to 4.13)	628	2167	4.22 (3.50 to 5.08)	161	669	2.16 (1.60 to 2.93)
Screened, Pap smear normal	300	3097	1.00 (referent)	197	2289	1.00 (referent)	103	808	1.00 (referent)
Screened, Pap smear abnormal	141	191	7.55§ (5.88 to 9.69)	96	132	8.34§ (6.14 to 11.32)	45	59	6.07§ (3.88 to 9.49)
Screened, Pap smear normal	300	3097	1.00 (referent)	197	2289	1.00 (referent)	103	808	1.00 (referent)
Abnormal Pap smear, no biopsy	91	93	1.89§ (1.19 to 3.02)	63	67	1.90§ (1.08 to 3.36)	28	26	1.67§ (0.70 to 3.98)
Abnormal Pap smear with biopsy	50	98	1.00 (referent)	33	65	1.00 (referent)	17	33	1.00 (referent)

Sensibilità Pap e colposcopia

Table 6
Nonconcurrent False-Negative Pap Test and Colposcopic Examination Results

	1998-2001			2002-2004			All Years		
	Total	Preanalytic	Analytic	Total	Preanalytic	Analytic	Total	Preanalytic	Analytic
False-negative Pap test results									
Adjudicated histopathologic diagnosis									
SCC	5	3	2	3	3	0	8	6	2
Adenocarcinoma or AIS	24	18	6	29	17	12	53	35	18
CIN 2/3	118	100	18	82	61	21	200	161	39
CIN 1	203	148	55	355	257	98	558	405	153
Total	350	269	81	469	338	131	819	607	212
False-negative colposcopic results									
Adjudicated cytologic diagnosis									
SCC	0	0	0	1	1	0	1	1	0
Adenocarcinoma or AIS	0	0	0	3	3	0	3	3	0
HSIL	124	99	25	189	165	24	313	264	49
LSIL	399	261	138	1,228	920	308	1,627	1,181	446
Atypical (ASC-H or AGC)	13	13	0	147	147	0	160	160	0
Total	536	373	163	1,568	1,236	332	2,104	1,609	495

AGC, atypical glandular cells; AIS, adenocarcinoma in situ; ASC-H, atypical squamous cells, cannot exclude HSIL; CIN, cervical intraepithelial neoplasia; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; Pap, Papanicolaou; SCC, squamous cell carcinoma.

Valore predittivo negativo colpo

	Smear pattern			Total
	ED*	DN*	EC*	
Total no. smears	105	61	18	184
Colposcopy follow-up with biopsy	95	53	15	163
Colposcopy normal	31	16	5	52
No. normal colposcopies that were biopsied	27	16	5	48
Normal histology when colposcopy was normal	4	1	1	6
NPV of colposcopy (%)	14.9	6.3	20.0	12.5
Postcolposcopy probability of cervical lesion when colposcopy is normal (%)	85.2	93.8	80.0	87.5

Sensibilità Pap

Table 5. Sensitivity of cervical smears showing endocervical abnormalities (study group 2)

	Histology showing CGIN, AIS or endocervical adenocarcinoma
Total no. smears	101
Smears that suspected the endocervical disease and confirmed on histology (true positives)	67
Smears that did not report the endocervical lesion as endocervical glandular neoplasia (false negative)	34 (details in Figure 2)
False negative rate (%)	33.7
Sensitivity of smear for endocervical lesion (%)	66.3
Histological adenocarcinoma when smear suspected the endocervical adenocarcinoma	15
Smears that did not suspect the endocervical adenocarcinoma	15 (details in Figure 3)
False negative rate (smears not reported as endocervical adenocarcinoma) (%)	75
Sensitivity of smear for precise report of endocervical adenocarcinoma (%)	25

CGIN, cervical glandular intraepithelial neoplasia; AIS, adenocarcinoma *in situ*.

Efficacia HPV

	Pooled rate ratio* (95% CI)	I ² (p for heterogeneity between studies)
Morphology		
Squamous-cell carcinoma	0.78 (0.49-1.25)	0.0% (0.84)
Adenocarcinoma	0.31 (0.14-0.69)	0.0% (0.59)
Adenocarcinoma vs squamous-cell carcinoma	0.34 (0.12-0.90)	-
Stage		
1A	0.58 (0.34-1.01)	0.0% (0.82)
>1A	0.56 (0.31-1.00)	31.8% (0.22)
>1A vs 1A	0.86 (0.35-2.13)	-
Age at enrolment (years)		
<30†	0.98 (0.19-5.20)	0.0% (0.34)
30-34	0.36 (0.14-0.94)	7.2% (0.36)
35-49	0.64 (0.37-1.10)	0.0% (0.55)
≥50	0.68 (0.30-1.52)	36.5% (0.21)
<p>All randomised women are included, for the overall study period. *Estimates (experimental vs control arm) obtained by a study-adjusted fixed effects model.²⁴ †Women from Swedescreen and POBASCAM excluded.</p>		
<p>Table 4: Study-adjusted pooled relative detection rate of invasive cervical carcinoma, by morphology, stage, and age at enrolment</p>		

Conclusioni efficacia screening

- Efficacia del Pap differente da studio a studio, ma molto ridotta rispetto a squamosi
- Efficacia screening minore rispetto a squamoso ma rilevante: no aumento quando tutti i modelli predicono aumento.
- Sensibilità del Pap >50%
- Sensibilità colpo simile a squamosi?
- Efficacia HPV molto migliore di Pap

Conclusioni efficacia screening

- Maggiore efficacia del test HPV fa supporre che la minore efficacia sia dovuta a un problema di sensibilità del test
- La discreta sensibilità del Pap per lesioni prevalenti fa supporre un minore sojourn time di lesioni ghiandolari rilevabili con Pap rispetto a squamose