GISCi

Gruppo Italiano Screening del Cervicocarcinoma

OSSERVATORIO NAZIONALE SCREENING

(CIN3) and cancers due to HPV 16 and 18 in Italy: Estimating the number of non-preventable cancer in different scenarios of age for starting screening in vaccinated women

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Rationale

- Cervical cancer incidence in Italy below the age of 30 is quiet low: 1.8/100.000 (AIRTum data)
- Over 70% of cancers in Italy are due to HPV 16-18 (ICO 2015)
- In young women the proportion of HPV 16-18 cancer is higher than in the geeneral population: >80% (Carozzi 2010)

Rationale

- It is necessary to estimate the incidence of cancers in vaccinated women before the age of screening;
- We need to estimate the proportion of HPV16-18 cancers by age.
- There are evidences that the proportion of HPV16-18 is higher in young women (deSanjose 2011; Giorgi Rossi 2012).

Age trend

	All ages	≤24 years	25–29 years	30–34 years	35–39 years	40–44 years	45–49 years	50–54 years	55–59 years	60–64 years	65–69 years	70–74 years	75–79 years	≥80 years
HPV types 16 and 18*														
n (%)	5289 (100%)	36 (0·7%)	139 (2·6%)	360 (6·8%)	622 (11·8%)	809 (15·3%)	818 (15·5%)	712 (13·5%)	594 (11·2%)	470 (8·9%)	303 (5·7%)	208 (3·9%)	125 (2·4%)	93 (1·8%)
Proportion of patients in age group with HPV 16 and 18 (%)	70·5%	75·0%	77·2%	77·3%	79·2%	76·7%	71·6%	69·4%	69·8%	68·3%	62·7%	54·5%	56·6%	54·4%
Other HPV types														
n (%)	2210 (100%)	12 (0·5%)	41 (1·9%)	106 (4·8%)	163 (7·4%)	246 (11·1%)	325 (14·7%)	314 (14·2%)	257 (11·6%)	218 (9·9%)	180 (8·1%)	174 (7·9%)	96 (4·3%)	78 (3·5%)
Proportion of patients in age group with other HPV types	29·5%	25·0%	22·8%	22·7%	20·8%	23·3%	28·4%	30·6%	30·2%	31·7%	37·3%	45·5%	43·4%	45·6%
Any type														
n	7499	48	180	466	785	1055	1143	1026	851	688	483	382	221	171

Data are based on the upper estimate attribution of several HPV types. HPV=human papillomavirus. *Test for linear trend p<0·0001.

Table: **Number and relative contribution of HPV genotypes in cases of invasive cervical cancer that tested positive for HPV DNA, by age group**

DeSanjosè Lancet oncol 2010, 2011

Trend by age: Italian studies

Table 3 HPV types 16/18 and HPV types 16/18/45 by histotype, study and age

		<=24	25-34	35-44	45-54	55-64	65+	All ages
Histological type								
Squamous cell carcinoma	16/18 (n)	1	40	108	85	61	69	364
	%	100,0	93,0	76,1	72,6	72,6	75,0	76,0
	16/18/45 (n)	1	41	118	94	64	72	390
	%	100	95,3	83,1	80,3	76,2	78,3	81,4
	Any type (n)	1	43	142	117	84	92	479
Adeno- and Adenosquamous cell carcinoma	16/18 (n)	0	5	15	5	10	8	43
	%	0	100	93,8	55,6	83,3	61,5	76,8
	16/18/45 (n)	1	5	15	6	11	11	49
	%	100	100	93,8	66,7	91,7	84,6	87,5
	Any type (n)	1	5	16	9	12	13	56

Included studies:
South: Carozzi 2010
IEO Milano: Sideri 2009
IFO Roma: Mariani 2010

Giorgi Rossi et al Infectious Agents and Cancer 2012

Method

The incidence of non-preventable cancers is estimated on the basis:

- Pre-screening overall incidence: ITACAN (Airtum) all active registries active in 1990-98.
- % of non 16-18 cancers **observed before screening program activation**.

As reference we adopted the incidence of cancer in the ‘90s in women <25

Relevant to establish if there is a calendar time trend in the HPV16-18 proportion.

Calendar time trend, Italy

Table 4 HPV types 16/18 and HPV types 16/18/45 by histotype, study and year of diagnosis

		1999°	*2000*	*2001*	*2002*	*2003*	*2004*	*2005*	*2006*	*2007*	*2008*	*All years*
Histological type												
Squamous cell carcinoma	**16/18 (n)**	16	23	30	34	56	60	62	62	13	9	365
	%	*64,0*	*74,2*	*73,2*	*66,7*	*73,7*	*76,9*	*75,6*	*89,9*	*81,3*	*81,8*	*75,9*
	16/18/45 (n)	18	24	30	37	64	65	68	63	14	9	392
	%	*72,0*	*77,4*	*73,2*	*72,5*	*84,2*	*83,3*	*82,9*	*91,3*	*87,5*	*81,8*	*81,5*
	Any type (n)	26	31	41	51	76	78	82	69	16	11	481
Adeno- and Adeno-squamous cell carcinoma	**16/18 (n)**	0	2	1	3	6	5	9	10	7	0	43
	%	-	*50,0*	*50,0*	*75,0*	*85,7*	*100,0*	*75*	*83,3*	*70*	-	76,8
	16/18/45 (n)	0	2	2	4	6	5	11	11	8	0	49
	%	-	*50,0*	*100,0*	*100,0*	*85,7*	*100,0*	*91,7*	*91,7*	*80*	-	*87,5*
	Any type (n)	0	4	2	4	7	5	12	12	10	0	56

Giorgi Rossi et al Infectious Agents and Cancer 2012

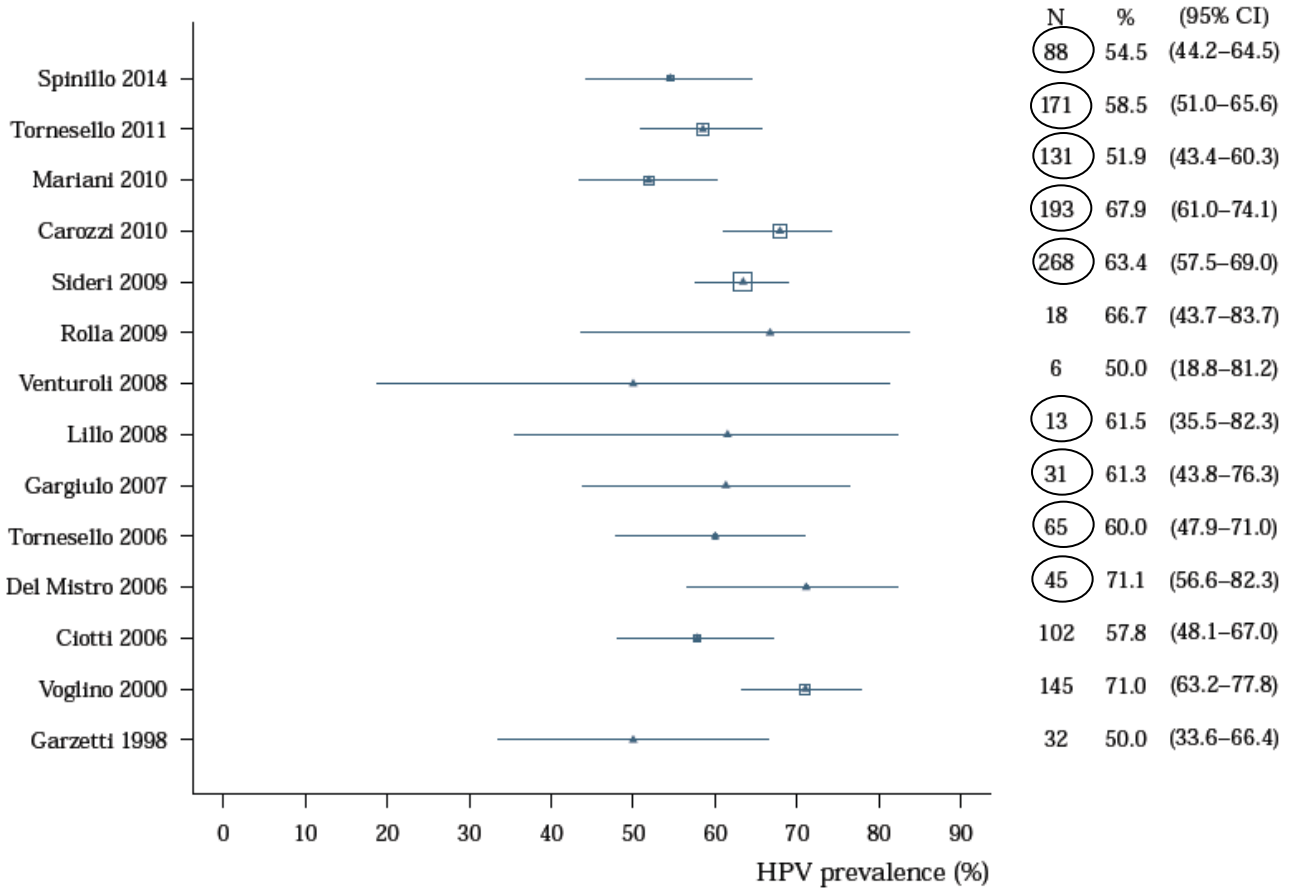
Table 13: Prevalence of HPV 16/18 in women with normal cytology, precancerous cervical lesions and invasive cervical cancer in Europe

Country /Region	Normal cytology		Low-grade lesions		High-grade lesions		Cervical cancer	
	No. tested	HPV Prev (95% CI)	No. tested	HPV Prev (95% CI)	No. tested	HPV Prev (95% CI)	No. tested	HPV Prev (95% CI)
Europe	180,090	3.8 (3.7-3.9)	20,452	26.9 (26.3-27.5)	19,390	54.1 (53.4-54.8)	16,690	73.4 (72.7-74.1)
Eastern Europe	7,818	9.7 (9.1-10.4)	842	31.6 (28.5-34.8)	696	59.3 (55.6-62.9)	1,601	84.8 (83.0-86.5)
Belarus	322	7.1 (4.8-10.5)	94	35.1 (26.2-45.2)	91	56.0 (45.8-65.8)	26	65.4 (46.2-80.6)
Bulgaria	-	- -	-	- -	-	- -	127	80.3 (72.6-86.3)
Czech Rep.	1,302	6.6 (5.4-8.1)	338	33.7 (28.9-38.9)	311	63.3 (57.9-68.5)	184	77.2 (70.6-82.6)
Hungary	-	- -	-	- -	75	61.3 (50.0-71.5)	44	95.5 (84.9-98.7)
Moldova	-	- -	-	- -	-	- -	-	- -
Poland	799	3.4 (2.3-4.9)	66	34.8 (24.5-46.9)	-	- -	1,014	88.1 (85.9-89.9)
Romania	801	10.1 (8.2-12.4)	250	19.6 (15.2-25.0)	128	45.3 (37.0-53.9)	-	- -
Russia	2,140	9.4 (8.2-10.7)	94	35.1 (26.2-45.2)	91	56.0 (45.8-65.8)	206	73.8 (67.4-79.3)
Slovakia	-	- -	-	- -	-	- -	-	- -
Ukraine	-	- -	-	- -	-	- -	-	- -
Northern Europe	86,821	4.2 (4.1-4.3)	4,949	30.6 (29.3-31.9)	6,383	55.4 (54.2-56.6)	4,276	76.6 (75.3-77.8)
Denmark	27,135	6.5 (6.2-6.8)	414	27.1 (23.0-31.5)	1,136	60.1 (57.2-62.9)	362	74.3 (69.6-78.5)
Estonia	-	- -	-	- -	-	- -	-	- -
Finland	-	- -	-	- -	-	- -	460	88.5 (85.2-91.1)
Iceland	-	- -	-	- -	441	59.0 (54.3-63.5)	140	72.1 (64.2-78.9)
Ireland	5,647	4.3 (3.8-4.9)	104	42.3 (33.3-51.9)	222	83.8 (78.4-88.1)	97	74.2 (64.7-81.9)
Latvia	-	- -	94	35.1 (26.2-45.2)	91	56.0 (45.8-65.8)	247	70.0 (64.1-75.4)
Lithuania	609	6.1 (4.4-8.3)	15	6.7 (1.2-29.8)	29	55.2 (37.5-71.6)	191	63.9 (56.9-70.4)
Norway	4,192	2.4 (2.0-2.9)	60	13.3 (6.9-24.2)	1,607	38.7 (36.4-41.1)	450	78.2 (74.2-81.8)
Sweden	6,789	2.4 (2.1-2.8)	1,494	32.9 (30.6-35.4)	383	48.0 (43.1-53.0)	780	70.4 (67.1-73.5)
UK	42,449	3.2 (3.0-3.4)	2,768	29.6 (27.9-31.3)	2,474	61.6 (59.7-63.5)	1,549	79.3 (77.2-81.2)
Southern Europe	31,831	3.8 (3.6-4.0)	10,607	25.5 (24.7-26.3)	5,249	51.1 (49.7-52.4)	3,970	67.8 (66.3-69.2)
Albania	-	- -	-	- -	-	- -	-	- -
Andorra	-	- -	-	- -	-	- -	-	- -
Bosnia & H.	-	- -	-	- -	-	- -	297	68.0 (62.5-73.1)
Croatia	205	18.0 (13.4-23.9)	1,271	13.5 (11.8-15.5)	941	20.6 (18.2-23.3)	117	82.9 (75.1-88.7)
Cyprus	-	- -	-	- -	-	- -	-	- -
Greece	6,506	2.8 (2.4-3.2)	1,990	21.6 (19.9-23.5)	290	56.9 (51.1-62.5)	342	53.2 (47.9-58.4)
Italy	15,093	4.1 (3.8-4.4)	4,647	29.3 (28.0-30.6)	1,825	63.2 (60.9-65.4)	1,308	72.3 (69.8-74.7)
Macedonia	-	- -	-	- -	-	- -	-	- -
Malta	-	- -	-	- -	-	- -	-	- -
Montenegro	-	- -	-	- -	-	- -	-	- -
Portugal	425	5.6 (3.8-8.3)	444	45.3 (40.7-49.9)	1,051	56.2 (53.2-59.2)	168	81.5 (75.0-86.7)
San Marino	-	- -	-	- -	-	- -	-	- -
Serbia	-	- -	-	- -	-	- -	-	- -
Slovenia	4,199	4.8 (4.2-5.5)	69	33.3 (23.4-45.1)	304	64.5 (58.9-69.6)	264	77.7 (72.3-82.3)
Spain	5,403	2.7 (2.3-3.2)	2,186	23.9 (22.1-25.7)	838	45.6 (42.2-49.0)	1,474	62.8 (60.3-65.3)
Western Europe	56,074	2.6 (2.5-2.7)	4,054	25.1 (23.8-26.5)	3,959	58.3 (56.8-59.8)	3,100	78.3 (76.8-79.7)
Austria	-	- -	-	- -	204	60.3 (53.4-66.8)	200	78.5 (72.3-83.6)
Belgium	13,414	3.6 (3.3-3.9)	1,205	26.4 (24.0-29.0)	463	51.8 (47.3-56.4)	120	78.3 (70.1-84.8)
France	4,764	4.7 (4.1-5.3)	1,818	25.5 (23.6-27.6)	1,585	57.3 (54.8-59.7)	1,484	74.8 (72.5-76.9)
Germany	10,988	3.2 (2.9-3.5)	688	21.2 (18.3-24.4)	819	50.5 (47.1-54.0)	69	76.8 (65.6-85.2)
Liechtenstein	-	- -	-	- -	-	- -	-	- -
Luxembourg	-	- -	-	- -	-	- -	58	89.7 (79.2-95.2)
Monaco	-	- -	-	- -	-	- -	-	- -
Netherlands	26,908	1.5 (1.4-1.7)	207	22.7 (17.5-28.9)	855	70.2 (67.0-73.1)	1,169	82.2 (79.9-84.3)
Switzerland	-	- -	136	30.9 (23.7-39.1)	33	75.8 (59.0-87.2)	-	- -

Available data in Italy: ICO systematic review for Europe

No way to estimate HPV16-18 proportion by age and calendar time from published data.

Figure 33: Prevalence of HPV 16 among women with invasive cervical cancer in Italy by study



Finale Ligure: we dedided to make a pooled anlysis of existing studies starting from individual data

ro l' HPV

ICO Dec 2014

lata as of 30 Jun 2014).

Methods (2)

Pooled analysis %HPV 16-18:

- We decided to work on cancers only since there are enough cases.
- Analysis of age trend
- Analysis of time trend
- Analysis of interaction of age and time trends by histology
- Statistical analysis:
  - Models with age in classes and as continuous variable
  - Observed proportion.

Available cases by laboratory

Center	CIN3		Squamous cell carcinoma		Adeno and Anenosquamous cell carcinoma		Other		Total	
	N	%	N	%	N	%	N	%	N	%
Laboratorio 1										
Brescia	108	10.5	4	0.6					112	6.4
Laboratorio 2										
HSR			9	1.4	4	4.3			13	0.7
Laboratorio 3										
IEO			242	38.8	7	7.4	2	40	251	14.4
Laboratorio 4										
IFO			106	17	17	18.1	3	60	126	7.2
Laboratorio 5										
PD			29	4.7	3	3.2			32	1.8
VI			14	2.2	2	2.1			16	0.9
Laboratorio 6										
Pavia	532	51.9	63	10.1	25	26.6			620	35.5
Laboratorio 7										
Campania	37	3.6	46	7.4					83	4.7
Laboratorio 8										
Lazio	111	10.8	47	7.5	22	23.4			180	10.3
Sardegna	40	3.9	2	0.3	3	3.2			45	2.6
Sicilia	9	0.9	5	0.8					14	0.8
Toscana	121	11.8	12	1.9					133	7.6
Abruzzo	67	6.5	45	7.2	11	11.7			123	7.0
ALL	**1025**		**624**		**94**		**5**		**1748**	

Agre trend confirmed

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		?24	25-34	35-44	45-54	55-64	65+	All ages
Squamous cell carcinoma	**16/18 (n)**	1	51	129	101	78	79	439
	%	100.0	91.1	75.4	70.1	72.9	68.7	73.9
	16/18/45 (n)	1	52	141	111	81	84	470
	%	100.0	92.9	82.5	77.1	75.7	73.0	79.1
	Any type	1	56	171	144	107	115	594
Adeno and Anenosquamous cell carcinoma	**16/18 (n)**	0	13	17	13	12	9	64
	%	0.0	92.9	68.0	65.0	75	64.3	71.1
	16/18/45 (n)	1	13	17	14	13	12	70
	%	100.0	92.9	68.0	70.0	81.2	85.7	77.8
	Any type	1	14	25	20	16	14	90

Calendar time trend: not evident

		1997-1999	2000-2002	2003-2005	2006-2008	2009-2011	2012-2013	All years
Squamous cell carcinoma	**16/18 (n)**	48	91	180	95	16	10	440
	%	70.6	70.0	74.7	81.9	66.7	58.8	73.8
	16/18/45 (n)	52	95	199	98	18	10	472
	%	76.5	73.1	82.6	84.5	75.0	58.8	79.2
	Any type	68	130	241	116	24	17	596
Adeno and Anenosquamous cell carcinoma	**16/18 (n)**	4	8	21	20	5	6	64
	%	66.7	57.1	77.8	71.4	62.5	85.7	71.1
	16/18/45 (n)	4	10	23	22	5	6	70
	%	66.7	71.4	85.2	78.6	62.5	85.7	77.8
	Any type	6	14	27	28	8	7	90

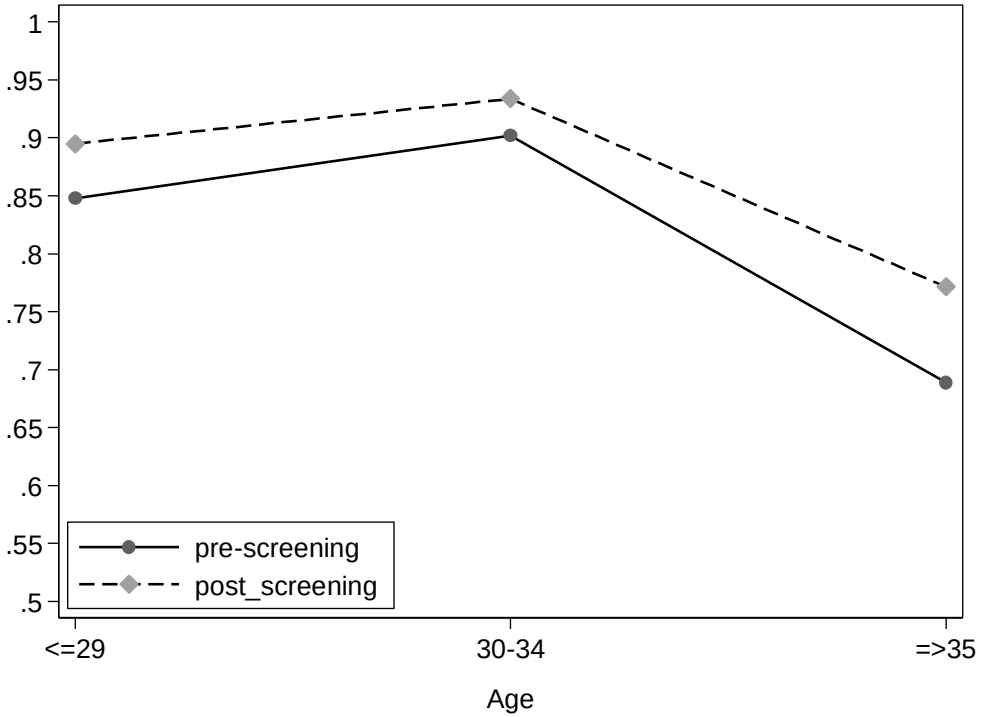
Time trend based on screening program activation

Calendar time for each case has been classified as pre- or post- screening activation according to the residence province (or region) and year: when >=50% of the target population has been invited for the first round of screening the area was considered as post-screening; when the program was not yet active or invited <50% the area was considere pre-screening (Zucchetto et al. Prev Med 2015)

Age and preriod effect on HPV 16-18 proportion in cancers

HPV types 16/18	OR	95%CI	P-value
Model 1			
age	0.98	0.97 – 0.99	0.002
post vs pre screening org	1.53	0.95 – 2.44	0.078
Model 2			
Age			
<29 vs >35	2.57	0.71 – 9.31	0.149
30-34 vs >35	4.28	1.64 – 11.19	0.003
post vs pre screening org	1.54	0.96 – 2.47	0.071

Estimated proportions of HPV16-18 cancers by age class (pre/post-screening)



	<=29	**30-34**	**≥ 35**
Pre screening	0.85 (0.69 – 1.01)	0.90 (0.81 – 0.98)	0.69 (0.64 – 0.73)
Post screening	0.90 (0.77 – 1.02)	0.93 (0.87 – 0.99)	0.77 (0.71 – 0.84)

Estimate of non-preventable cancers in the Italian population

	<15	15-19	20-24	25-29	30-34
incidenza 90-98	0	0,1000	0,4000	2,4000	6,6000
numero casi atteso senza vaccinazione	0	1,5012	6,4935	43,1292	140,2673
incidenza non-16-18 (tasso grezzo)	0	0,0100	0,0400	0,2400	0,6600
numero casi non 16-18	0	0,1501	0,6493	4,3129	14,0267
incidenza non-16-18 (modello età in continuo)	0	0,0190	0,0800	0,5040	1,5180
numero casi non 16-18	0	0,2852	1,2987	9,0571	32,2615
incidenza non-16-18 (modello età in classi)	0	0,0630	0,0240	0,2400	2,0460
numero casi non 16-18	0	0,9458	0,3896	4,3129	43,4829

Actual situation (no vaccination starting age 25): 8 cases per year

Cases in vaccinated staring screening at 25: 0.8-1.6 cases per year

Cases in vaccinated starting at 30: 5.1-10.5 cases per year

Cases in vaccinated starting at 35: 19.1-42.8 cases per year

Conclusions

- Non preventable cancers according to the actual screening starting age (25) with the 1990-98 incidence were 8 per year.
- The number of non-preventable cancers in vaccinated women with **starting age at 30** when projected to the Italian 2015 population would be from 5 to 10 cancers according to the estimate methods.

NB: the model is strongly influenced by one cancer due to HPV 45 occurred in a 22 years old women.

Proposta del Comitato Tecnico

C'è un forte razionale per proporre l'innalzamento dell'età di inizio dello screening a 30 anni per le ragazze vaccinate naïve (vaccinate nel dodicesimo

2.1	**There is a strong rational for proposing an increase in the starting age for screening to 30 for girls vaccinated in their twelfth year. […]**	**For girls vaccinated in their twelfth year (+/- 1 year), it accepts the proposal to increase the starting age for screening to 30, with full consent.**

Per le ragazze vaccinate nel dodicesimo anno di vita (+/- 1 anno), la Giuria accetta con consenso pieno la proposta di innalzamento dell'età di inizio dello screening a 30 anni.

Grazie per l'attenzione

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