e&p anno 39 (3) maggio-giugno 2015

WWW.EPIPREV.IT

[1]AOU Città della salute e della scienza, CPO Piemonte, Torino
[2]Servizio interaziendale di epidemiologia, AUSL Reggio Emilia
[3]IRCCS-Arcispedale S. Maria Nuova, Reggio Emilia
[4]Istituto oncologico veneto IRCSS
[5]Istituto per lo studio e la prevenzione oncologica (ISPO), Firenze

Corresponding author:
Guglielmo Ronco
guglielmo.ronco@cpo.it

A first survey of HPV-based screening in routine cervical cancer screening in Italy

Prima survey sull'utilizzo routinario del test HPV nello screening cervicale in Italia

Guglielmo Ronco,[1] Paolo Giorgi-Rossi,[2,3] Pamela Giubilato,[1] Annarosa Del Mistro,[4] Marco Zappa,[5] Francesca Carozzi[5] and the HPV screening survey working group

Abstract

Pilot HPV-based cervical screening programmes have recently started in Italy, partly on the strength of a large randomized trial. The Ministry of Health recommended that regions shift toward HPV-based screening in early 2013 and provided guidelines for its application (stand-alone HPV testing by validated methods, cytological triage of HPV positives, beginning at age 30-35, 5-year intervals). A first survey on the 2012 activity was conducted in 2013.

In 2012, 19 Italian organized cervical screening programmes from 10 regional programmes invited 311,856 women (8.0% of all women invited for cervical screening in 2012 in Italy) for HPV-based screening; 41.5% complied, with a decreasing North-South trend. Among screened women, 7.9% (range 4.3%-13.9%) were HPV positive, decreasing to 6.6% (range 4.0%-12.4%) when considering women aged 35-64 years. Among HPV positive women, 34.8% (with high variability between programmes: range 11.1%-59.3%) were judged to have ASC-US or more severe cytology (5.3% ASC-US, 26.6% L-SIL, 5.2% H-SIL). Out of all screened women, those referred to colposcopy based on HPV and cytology results were 2.9% (range 0.6%-4.8%), whereas they were 2.0% when considering only women aged 35-64 years.

(*Epidemiol Prev* 2015; 39(3) Suppl 1: 77-83)
Keywords: cervical cancer, mass screening, HPV test, Italy

Riassunto

Recentemente, in parte sull'onda dei risultati di un ampio trial randomizzato, in Italia sono stati attivati programmi pilota di screening cervicale basati sul test HPV. All'inizio del 2013 il Ministro della salute ha raccomandato alle Regioni di passare a screening basati sul test HPV e ha fornito linee guida per la sua applicazione (utilizzo del solo test HPV applicando metodi validati, triage citologico dei casi positivi al test, inizio all'età di 30-35 anni, intervalli di 5 anni). Una prima survey sull'attività del 2012 è stata condotta nel 2013.

Nel 2012, 19 programmi organizzati di screening cervicale afferenti a 10 regioni hanno invitato allo screening basato sul test HPV 311.856 donne (8,0% di tutte le donne invitate allo screening cervicale nel 2012 in Italia) . Di queste, il 41,5% ha aderito con un trend decrescente da Nord a Sud. Tra le donne sottoposte a screening, il 7,9% (range 4,3%-13,9%) era HPV positivo, percentuale che diminuisce al 6,6% (range: 4,0%-12,4%) se si considerano solo le donne di età fra 35 e 64 anni. Tra le donne positive all'HPV, il test citologico ha dato esito ASC-US o più grave (5,3% ASC-US; 26,6% L-SIL; 5,2% H-SIL) nel 34,8% dei casi (con un'alta variabilità fra programmi, range: 11,1%-59,3%).

Di tutte le donne sottoposte a screening, quelle inviate in colposcopia sulla base dei risultati del test HPV e degli esiti ctologici sono state il 2,9% (range: 0,6%-4,8%), percentuale che si abbassa al 2,0% se si considerano solo le donne di età fra 35 e 64 anni.

(*Epidemiol Prev* 2015; 39(3) Suppl 1: 77-83)
Parole chiave: cancro cervicale, scereening di massa, test HPV, Italia

INTRODUCTION

Testing for the DNA of oncogenic HPV types as a primary screening test for cervical cancer precursors has been intensively studied over the past few years.

Randomized controlled trials (RCTs) comparing HPV-based to cytology-based screening have been conducted in Sweden (Swedescreen[1]), the Netherlands (POBASCAM[2]), England (ARTISTIC[3]), Italy (NTCC[4]), India,[5] Finland,[6] and Canada (CCCast[7] and FOCAL[8]).

The first four studies[1-4] published data on two screening rounds showing increased detection of high-grade CIN at the first round and decreased detection in the second when comparing the HPV and cytology groups. This proves that HPV-based screening allows earlier detection of persistent high-grade CIN than cytology. In addition, the Indian study showed a reduced incidence of cervical cancer mortality and advanced cancers after a once-in-a-lifetime screen by HPV.[5] These findings were confirmed by a pooled analysis of the RCTs that published results on two screening rounds with respect to invasive cancer incidence, which provided direct evidence of increased protection with HPV-based screening.[9]

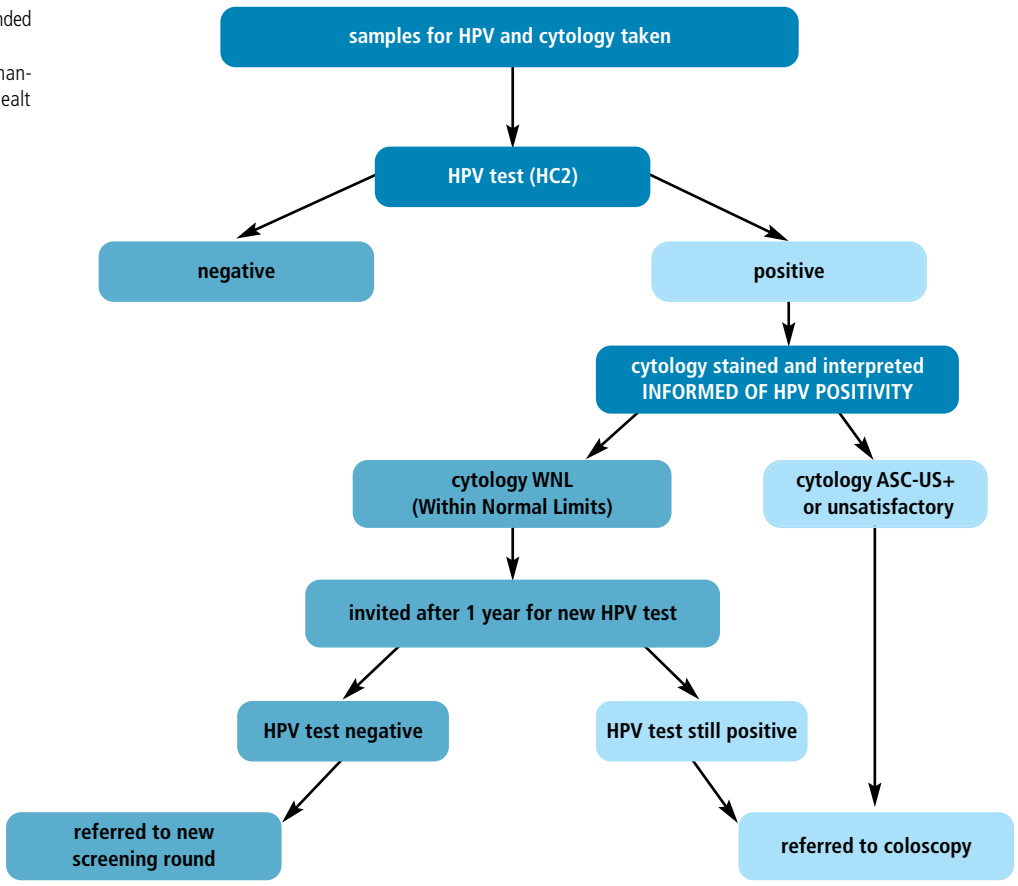
Over the past few years, partly on the strength of the NTCC experience, a number of pilot HPV-based screening projects have started up within Italian organized cervical screening programmes. They have mainly aimed at evaluating the feasibility of HPV-based screening in routine activity.

In the meanwhile, an Italian Health Technology Assessment report was published in 2012.[10] It concluded that HPV-based screening was more effective than cytology-based cervical screening and entailed little or no increase in negative effects if appropriate protocols were applied. This included using stand-alone HPV as a primary screening test, with only clinically validated DNA-HPV tests,[11] starting HPV-based screening at 30 to 35 years of age, adopting 5-year intervals and applying a «cytological triage» protocol. The latter entailed testing HPV-positive women for cytology (using material taken during the HPV sampling visit) and referring directly to colposcopy only women with ASC-US or more severe cytology, while retesting HPV-positive women with normal cytology after one year for stand-alone HPV and referring them to colposcopy only if HPV was still positive (figure 1).

Among other recommendations, the HTA report recommended strict monitoring of HPV-based screening. In early 2013, the Italian Ministry of Health adopted these recommendations as a guide for screening planning by regional health authorities.[12]

In 2013, a first Italian national survey of HPV-based screening was conducted as part of the yearly survey of cervical cancer screening by organized programmes.

Figure 1. Protocol recommended by the Italian HTA report.
Figura 1. Protocollo raccomandato dal report italiano di Healt Technology Assessment.



METHODS

Surveys designed to assess the level of implementation of organized cervical screening programmes in Italy and collect process indicators are conducted every year by the ONS (Osservatorio nazionale screening, National centre for screening monitoring) on behalf of the Italian Ministry of Health. Data are collected through a questionnaire as aggregated tables of data. Details are provided elsewhere.[13]

A survey section dedicated to HPV-based screening was added to the general survey in 2013, related to the 2012 activity. It was designed assuming that the protocol suggested by the HTA and Ministry guidelines was applied. As the protocol entails 1-year repeats for HPV-positive women with normal cytology, it was decided to split the collection of data on women invited each year for primary screening into two sections. The first section, including data on invitation and participation to the HPV test, its result and results of triage cytology, is collected in the year after the invitations. In September 2013, therefore, data were collected on women invited for primary HPV testing during 2012 and tested by April 2013. The second section, including 1-year repeats and colposcopies resulting both from cytology and 1-year repeat HPV tests, were collected during 2014 for women invited for primary testing in 2012.

In addition to these data, information on the screening protocol applied was also collected.

RESULTS

Extension of HPV-based screening and participation

In 2012, 19 Italian programmes from 10 regions invited women for HPV-based screening (table 1). Eleven of them were from northern Italy, 3 from central Italy, and 5 from southern Italy. Five programmes (Torino, Trento, Reggio Emilia, Firenze, and Molise) invited both women to HPV-based and cytology-based screening (the first 3 within a randomized pilot project), while the remaining 14 invited women just to HPV-based screening. Overall, 311,856 women aged 25-64 years were invited to HPV screening, representing 8.0% of all women invited for cervical screening in Italy in 2012 (9.5%, 4.0%, and 8.8% of those invited in northern, central, and southern Italy, respectively). The regions with the largest number of women invited to HPV were Veneto, where 6 programmes converted completely to HPV, and Abruzzo, where the entire region moved to HPV testing. In addition, the region of Liguria, where only a small area was previously covered by organized programmes, chose to extend coverage inviting to HPV testing. In 2012, 61% of women invited for cervical screening in Liguria were invited to HPV testing.

As the national guideline came out in 2013, all programmes active in 2012 were pilot projects. Among them, 12 programmes started inviting women to HPV testing at 25 years and 7 at 35. However, after publication of the national guidelines, many programmes have planned to shift age of first testing to 30 or 35 years. All programmes used clinically-validated DNA-HPV tests (mostly Digene Hybrid Capture2, and in few cases Roche's Cobas or the Abbott real-time PCR test) except one which used an mRNA test. This programme was excluded from further analyses.

In 2012, 41.5% of all women invited to HPV DNA-based screening complied. There was a strong variability between centres. The lowest values, below 20%, were in southern Italy and the highest, above 65%, in northern Italy, reproducing outcomes observed with all invitations[13] (figure 2, p.80). Results were very similar when restricted to women aged 35-64 years (mean 42.1%, data by centre not shown).

Process indicators with HPV

All programmes used stand-alone HPV as primary test and adopted cytological triage as recommended by national

Region	Number of programmes	Target age	Women invited	Women screened
Abruzzo	4	25-64	108,739	34,094
Emilia-Romagna	1	35-64	5,192	3,280
Lazio	2	25-64 e 35-64	36,052	13,068
Liguria	1	35-64	14,164	6,453
Lombardia	1	25-64	8,317	5,294
Molise	1	35-64	2,000	251
Piemonte	1	35-64	24,289	12,419
Toscana	1	35-64	40	29
Trento	1	35-64	2,865	1,134
Veneto	6	25-64	110,198	55,147
Northern Italy	**11**		**165,025**	**83,727**
Central Italy	**3**		**36,076**	**13,083**
Southern Italy	**5**		**110,739**	**34,345**
Italy	**19**		**311,840**	**131,155**

Table 1. Organized programmes that invited women to HPV-based screening in Italy. 2012 activity.

Tabella 1. Programmi organizzati che hanno invitato a uno screening basato sul test HPV in Italia. Attività 2012.

guidelines and reported in figure 1. One programme (Firenze) was excluded from calculations given the very low number of women screened in 2012.

Since HPV infection prevalence is age-dependent and age of start was different between programmes, we computed the proportion of women positive to the primary HPV test both for any age and restricted to age 35-64 years (figure 2). Overall, 7.9% (range 4.3%-13.9%) of screened women of any age and 6.6% (range 4.0%-12.4%) of those aged 35-64 years (excluding Roma G because data by age were not available) were HPV positive. Within programmes that invited women aged 25-34 years, the overall prevalence was 1.5%-2.7% higher than the prevalence in the same programmes restricted to women aged 35-64 years. The lowest value was observed in Trento (as was already the case in the NTCC study[14]). High values were observed in Abruzzo and Molise (southern Italy).

Overall, when including all ages, 34.8% of HPV-positive women were judged to have ASC-US or more severe cytology, with a very large variation, ranging from 11.1% in Trento and 19.4% in Torino to 59.3% in a programme in Veneto (figure 3). The proportion of HPV-positive women classified as ASC-US or AGC was 5.3% (range 0.0%-23.1%), that of women classified as L-SIL was 24.6%

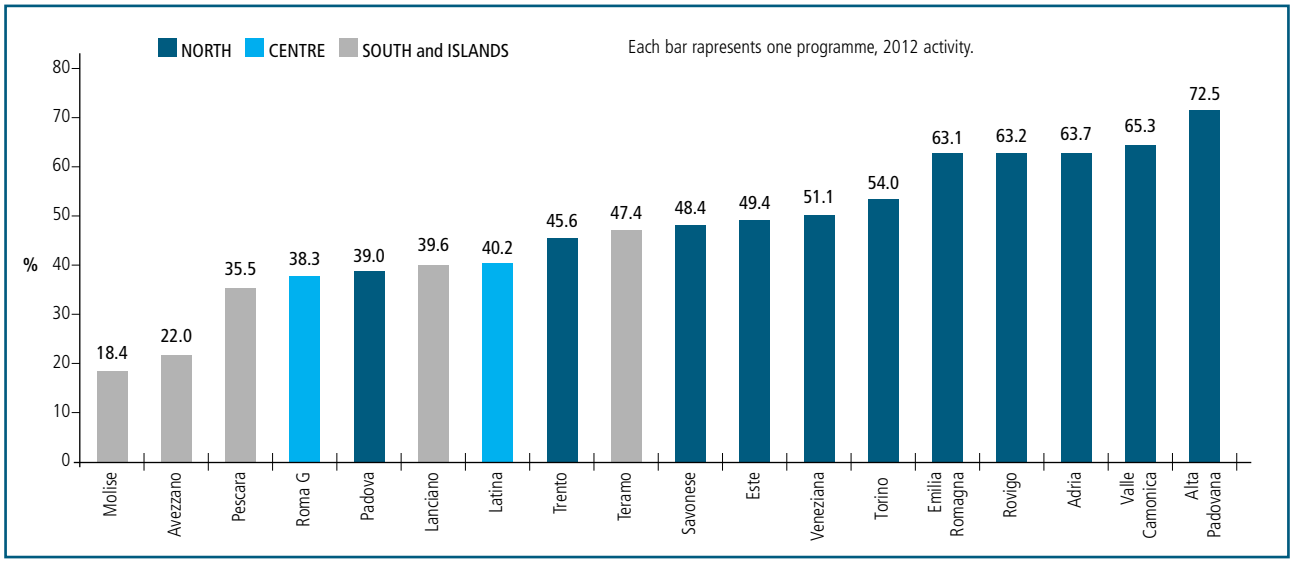


Figure 2. Compliance to invitation to HPV-based screening. All ages included. Italian organized programmes 2012 activity.
Figura 2. Compliance all'invito allo screening basato sul test HPV. Tutte le età incluse. Attività 2012 dei programmi organizzati.

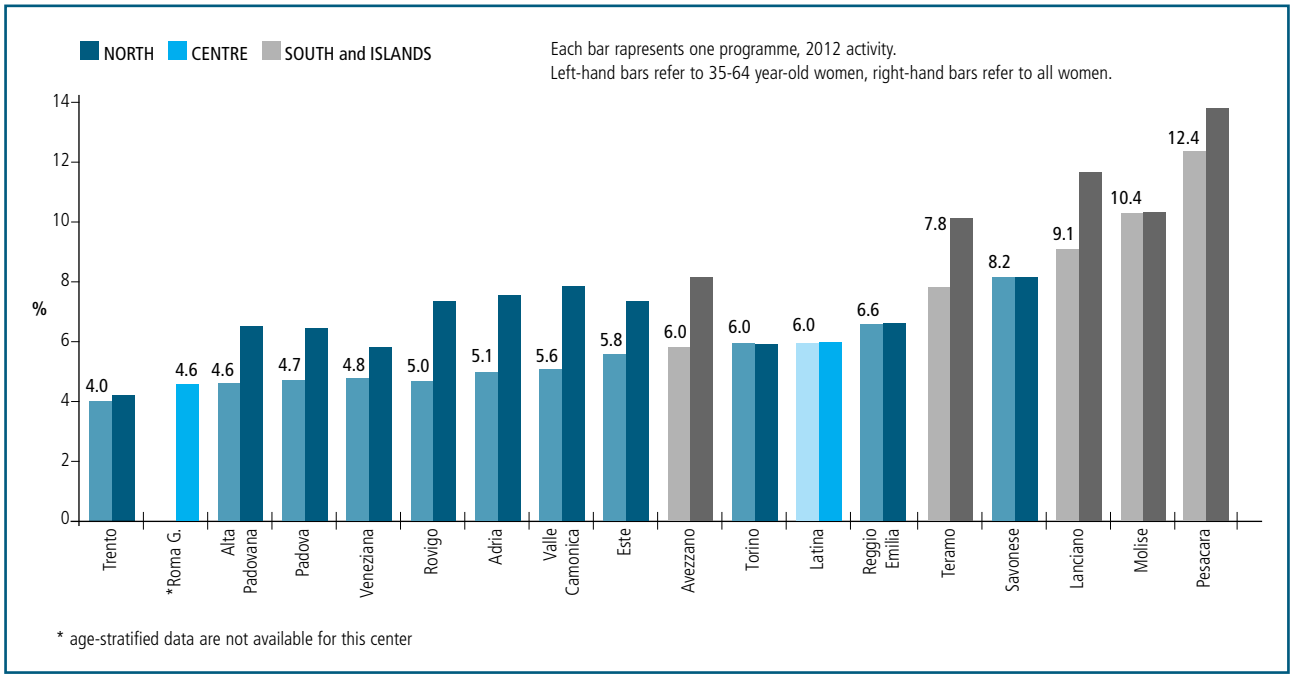


Figure 3. Proportion of HPV-positive women. Italian organized programmes 2012 activity.
Figura 3. Proporzione di donne HPV-positive. Attività 2012 dei programmi organizzati.

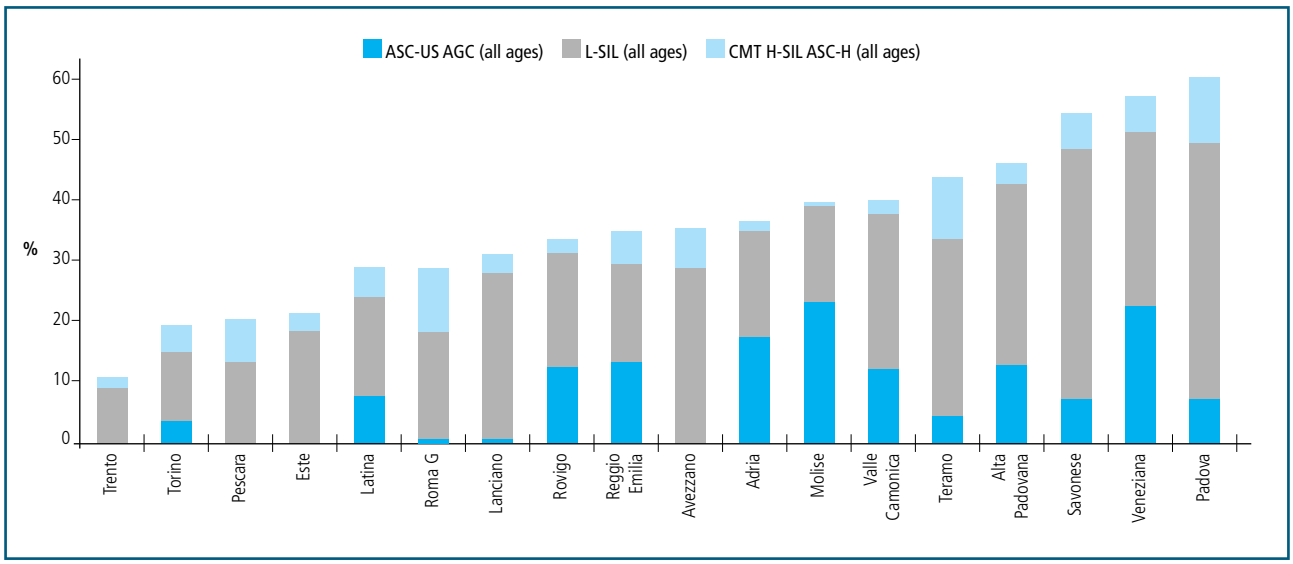


Figure 4. Proportion of HPV-positive women with abnormal cytology. Women of any age. Italian organized programmes 2012 activity.
Figura 4. Proporzione di donne HPV-positive con citologia anomala. Donne di ogni età. Attività 2012 dei programmi organizzati.

(range 9.8%-41.7%), and of women classified as H-SIL or ASC-H was 5.2% (range 1.7%-11.0%). Results were similar when restricted to women aged 35-64 years: 34.8% of HPV+ women were classified as ASC-US or higher.

When considering all ages, 2.9% of screened women were referred to colposcopy on the basis of the primary HPV test and simultaneous cytology. Variability was still very high, ranging from 0.6% in Trento to 4.8% in Savona. Values were below 2% in 5 programmes and below 3% in 11 (figure 4). When restricting data to women aged 35-64 years, 2.0% of women were referred. Trento (0.5%) and Savona (4.8%) were again the programmes with the lowest and highest values. Within the centres that invited women from age 25, the referral rate including all women was 1.09 to 1.60 times the referral restricted to women aged 35-64 years.

DISCUSSION

In this first survey of HPV-based screening, only an incomplete set of performance indicators can be presented. Data dealing with the entire screening process on women screened in 2012 will be presented next year. Nevertheless, these are, to our knowledge, the first nationwide data on routine HPV screening based on a large population.

The shift to HPV-based screening is becoming relevant in Italy. In 2012, about 10% of women invited for primary screening by Italian organized programmes were invited to HPV testing. This proportion is expected to rapidly increase after the publication of the guidelines of the Ministry of Health in January 2013. To our knowledge, in May 2014, 7/21 regions had decided to implement HPV-based screening as the routine screening method to the entire female population in the recommended age range, although this implementation will be progressive (3 to 5 years) in most cases.[15] For example, the region of Toscana started by inviting the 55-64 age group in December 2012 and expects to complete accrual in three years by progressively inviting younger women. Conversely, the region of Piemonte plans to invite for HPV an increasing proportion of randomly defined women over a span of three years, and the entire target population starting from the fourth year.

One of the crucial issues with HPV-based screening is the application of appropriate protocols, in order to avoid negative effects for women and increased costs. Indeed, recommendations on stand-alone HPV testing and cytological triage were adopted by all centres. On the other hand, guidelines were delivered by the Ministry after the period of activity considered here. This explains the inclusion of younger women in the target population. Due to the same reason, screening intervals were still, officially, 3 years, but are now being changed.

Compliance to invitation was slightly higher than nationwide when considering compliance to all invitations (to HPV or cytology), which was 40.8% in 2012. Given the high variability between centres and ages, a comparison of this sort is not reliable, but at least suggests that invitation to HPV testing is not a barrier to participation. Indeed, an increased compliance to invitation to HPV when compared to historical controls was observed in the pilot programmes in Veneto[16,17] and Lazio.[18]

Variability in the proportion of women positive to HPV testing was substantial even when restricting data to women of the same age. However, it could well reflect true differences in screened populations. Substantial variability was also observed in the NTCC study, where prevalence was lowest in Trento.[14] High prevalence was also previously observed in Abruzzo.[19]

There was also a striking variability between programmes in the proportion of HPV-positive women classified as having abnormal cytology, resulting in strong variability of referral to colposcopy on the basis of cytological abnormalities.

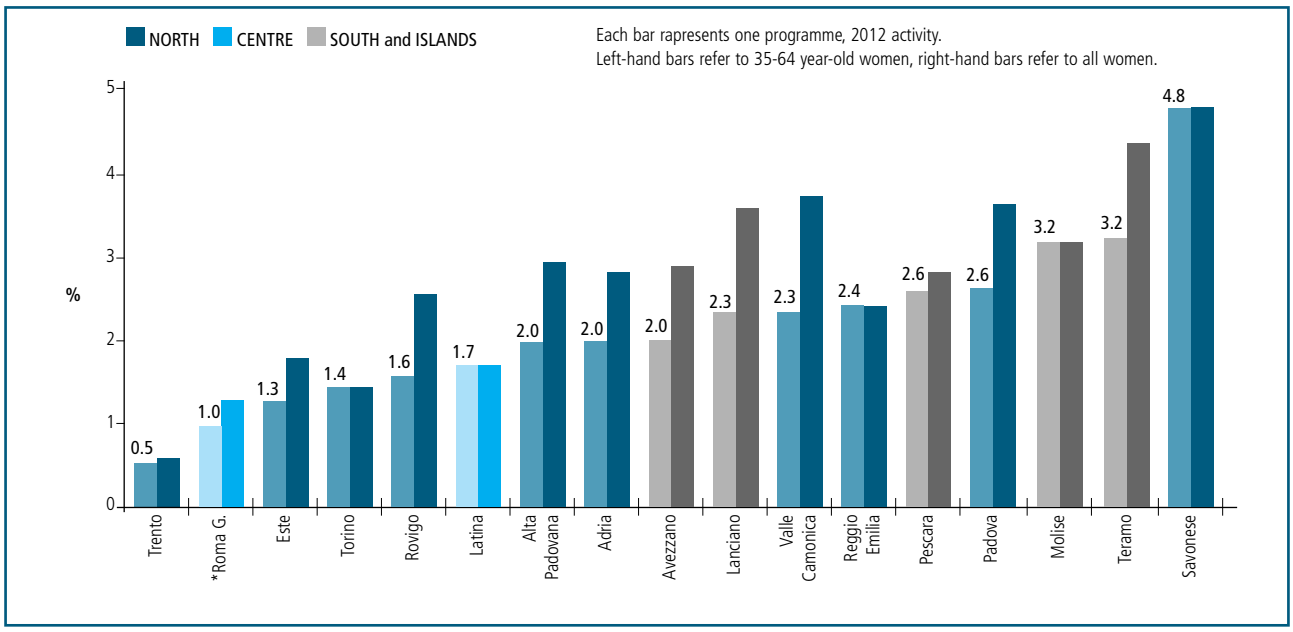


Figure 5. Proportion of women screened by HPV who are immediately referred to colposcopy because both HPV positive and judged to have abnormal cytology.
Figura 5. Proporzione di donne screenate per HPV che sono immediatamente inviate a colposcopia perché positive all'HPV e con citologia anomala.

The PPV of stand-alone HPV testing for high-grade CIN was actually quite stable (except for an inverse correlation to the previous screening activity) in different situations.[20] Therefore, variability between areas is expected to be lower than the variability in abnormal cytology in the entire population (which also reflects true variations in baseline risk). Thus, the observed variability in cytology triage plausibly reflects variability in the criteria of interpretation. Knowledge that slides came from HPV-positive women probably had a strong impact. Very high frequencies of cytological abnormalities were also observed in early reports of pilot projects.[16,18] These data clearly show the need to train cytologists and cytopathologists involved in the triage of HPV-positive women.

Conflicts of interests: One of the authors, Paolo Giorgi Rossi, as principal investigator in a study funded by the Italian Ministry of Health, is in charge of leading negotiations with Hologic, Roche Diagnostics, Qiagen, and Abbot in order to obtain reagents for free or at lower costs.

HPV screening survey working group:
Gruppo di lavoro per la survey sullo screening con HPV:

N. Segnan, A. Gillio Tos: CPO Piemonte
L. Bonelli: IRCCS AOU San Martino-IST, Genova
A. Franco, E. Venturino: ASL2 Savonese
L. Pasquale, G. Luciano: ASL Valle Camonica Sebino
E. Polla, P. Dalla Palma: Ospedale S. Chiara, Trento
M. Zorzi: Registro tumori Veneto
C. Fedato: Regione Veneto
F. Zago: ULSS 12 Venezia
A. Pupo: ULSS 15 Alta Padovana
I. Simoncello: ULSS 16 Padova
A. Ferro: ULSS 17 Este-Monselice
L. Gallo: ULSS 18 Rovigo
A. Del Sole: ULSS 19 Adria
L. Paterlini, C. Campari: AUSL Reggio Emilia
A. Iossa, M. Confortini: ISPO, Firenze
A. Barca: Regione Lazio
M.C. Tufi: ASL Roma G
P. Bellardini: ASL Latina
C. Fortunato: ASL Teramo
M. Minna: ASL Pescara
A. Macerola: ASL Av-Sulmona-L'Aquila
D. Caraceni: ASL Lanciano-Vasto-Chieti

References/Bibliografia

1. Naucler P, Ryd W, Tornberg S et al. Human papillomavirus and Papanicolau tests to screen for cervical cancer. *New Engl J Med* 2007;357:1589-97.
2. Rijkaart DC, Berkhof J, Rozendaal L et al. Human papillomavirus testing for the detection of high-grade cervical intraepithelial neoplasia and cancer: final results of the POBASCAM randomised controlled trial. *Lancet Oncol* 2012;13(1):78-88.
3. Kitchener HC, Almonte M, Thomson C et al. HPV testing in combination with liquid-based cytology in primary cervical screening (ARTISTIC): a randomised controlled trial. *Lancet Oncol* 2009;10:672-82.
4. Ronco G, Giorgi-Rossi P, Carozzi F et al., and the New Technologies for Cervical Cancer screening (NTCC) Working group. Efficacy of human papillomavirus testing for the detection of invasive cervical cancers and cervical intraepithelial neoplasia: a randomised controlled trial. *Lancet Oncol* 2010;11:249-57.
5. Sankaranarayanan R, Nene BM, Shastri SS et al. HPV screening for cervical cancer in rural India. *New Engl J Med* 2009;360:1385-94.
6. Leinonen MK, Nieminen P, Lönnberg S et al. Detection rates of precancerous and cancerous cervical lesions within one screening round of primary human papillomavirus DNA testing: prospective randomised trial in Finland. *BMJ* 2012;345:e7789.
7. Mayrand MH, Duarte-Franco E, Rodrigues I et al., and the Canadian Cervical Cancer Screening Trial Study Group. Human papillomavirus DNA versus Papanicolaou screening tests for cervical cancer. *New Engl J Med* 2007;357:1579-88.
8. Ogilvie GS, Krajden M, van Niekerk DJ et al. Primary cervical cancer screening with HPV testing compared with liquid-based cytology: results of round 1 of a randomised controlled trial – the HPV FOCAL Study. *Br J Cancer* 2012;107:1917-24.
9. Ronco G, Dillner J, Elfström M et al. Efficacy of HPV-based screening for preventing invasive cervical cancer: follow-up of European randomised controlled trials. *Lancet* 2014;383:524-32.
10. Ronco G, Biggeri A, Confortini M et al. HPV DNA based primary screening for cervical camcer precursors. *Epidemiol Prev* 2012;3-4(Suppl 1):e1-72.
11. Meijer CJ, Berkhof J, Castle PE et al. Guidelines for human papillomavirus DNA test requirements for primary cervical cancer screening in women 30 years and older. *Int J Cancer* 2009; 124:516-20.
12. Ministero della salute. Piano nazionale della prevenzione 2010-2012. *Azione centrale prioritaria concernente la definizione di documenti tecnici di sintesi delle evidenze scientifiche a supporto della programmazione, monitoraggio e valutazione degli interventi di prevenzione oncologica nella popolazione a rischio. Documento di indirizzo sull'utilizzo dell'HPV-DNA come test primario per lo screening del cancro del collo dell'utero*. [www.osservatorionazionalescreening.it/sites/default/files/allegati/Screening.pdf]
13. Ronco G, Giubilato P, Carozzi F et al. and the Cancer Screening Survey working group. Extension of organized cervical cancer screening programmes in Italy and their process indicators, 2011-2012 activity. *Epidemiol Prev* 2015;3(Suppl 1):61-76.
14. Baussano I, Franceschi S, Gillio-Tos A et al. Difference in overall and age-specific prevalence of high-risk human papilloma virus infection in Italy: evidence from NTCC trial. *BMC Infect Dis* 2013; 13:238.
15. Giorgi Rossi P and the Middir Working Group. MIDDIR - Methods for investments/disinvestments and distribution of health technologies in Italian Regions. 11th HTAi annual meeting, Washington DC, 16-18 June 2014.
16. Zorzi M, Del Mistro A, Farruggio A et al. Use of high-risk human papillomavirus DNA test as the primary test in a cervical cancer screening programme: a population-based cohort study. *BJOG* 2013;120:1260-67.
17. Del Mistro A, Frayle H, Ferro A et al. Cervical cancer screening by high risk HPV testing in routine practice: results at one year recall of high risk HPV-positive and cytology-negative women. *J Med Screen* 2014;21:30-37.
18. Confortini M, Giorgi-Rossi P, Barbarino P et al. Screening for cervical cancer with the human papilloma virus test in an area of central Italy with no previous active cytological screening programme. *J Med Screen* 2010;17:79-86.
19. Giorgi Rossi P, Bisanzi S, Paganini I et al. Prevalence of HPV high and low risk types in cervical samples from the Italian general population: a population based study. *BMC Infect Dis* 2010; 10:214.
20. Giorgi-Rossi P, Franceschi S, Ronco G. HPV prevalence and accuracy of HPV testing to detect cervical intraepithelial neoplasia. *Int J Cancer* 2012;130:1387-94.