HPV-based screening for the precursors of cervical cancer: the Italian HTA report

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Purposes of the report

- To identify, on the basis of the resulting efficacy and of undesired effects, the best screening policies with HPV-based screening
- To compare them to cytology-based screening;

- To evaluate
  - economic cost
  - feasibility
  - impact on the organisation of services
- To define their best conditions of application in the Italian situation

Relation with EU Guidelines

- The section on efficacy and undesired effects is based on a first version (October 2010) of the chapter on cervical screening based on HPV as primary test prepared by Guglielmo Ronco, Marc Arbyn, Chris Mejier, Peter Snijders and Jack Cuzick for a supplement to the "European Guidelines on quality assurance for cervical cancer screening".
- An update of the literature review is on-going. Publication of the final version is expected within 2012. At authors knowledge, despite some relevant paper was published in the meanwhile, these are not expected to change the main conclusions

Efficacy and undesidered effects

- There is clear scientific evidence that a screening based on validated tests for the DNA of oncogenic HPV as primary test and an appropriate protocol is more effective than screening based on cytology in preventing invasive cervical cancer.
- In addition, it entails a limited – if any – increase of the undesired effects both in terms of unneeded referral to diagnostic work-up and in terms of overdiagnosis and consequent overtreatment of spontaneously regressive lesions.

NUMBER OF CASES OF INVASIVE CERVICAL CANCER BY SCREENING GROUP AND ROUND

	HPV group	Cytology group	p value
All ages pooled			
Screening round one	**7**	**9**	**0.62**
Screening round two	**0**	**9 ***	**0.004**
Total over first two rounds	**7**	**18**	**0.028**

*** 5 squamous-cell carcinomas (1 stage T1A, 4 stage T1B)**
4 adenocarcinomas (2 stage T1A, 1 stage T1B, 1 TX)

Ronco et al. Lancet Oncol 2010

Crucial Protocol Elements

Management of HPV positive women

- HPV-positive women are not to be directly referred to colposcopy, but the use of triage systems is essential.
- The currently recommended method is based on the performance of cytology in HPV positive women.
- If the result of this test is abnormal, the woman is immediately referred to colposcopy
- If cytology is normal, the woman is invited to repeat a new HPV test after one year.
  - In case such a test is still positive, the woman is referred to colposcopy;
  - in case of negative result, the woman will be re-invited for a new screening round at standard interval

NTCC STUDY
WOMEN AGE 35-60

DETECTION OF CIN 2 or 3 or AIS BY STUDY PERIOD

	Women enrolled (invited to round 2)	screening round1 N (%)	screening round2 N (%)	Total over both rounds N (%)
HPV group	34430 (33363)	**206** (0.60%)	**16** (0.05%)	**222** (0.64%)
Cytology group	34405 (33979)	**101** (0.29%)	**32** (0.09%)	**133** (0.39%)
RR (95%CI)		**2.03** (1.60-2.57)	**0.51** (0.28-0.93)	**1.66** (1.34-2.06)
P heterogeneity between phases		**0.70**	**0.15**	**0.90**

Ronco et al. Lancet Oncol 2010 modif.

RCTs comparing HPV- to cytology-based screening

Study	Primary test experimental group	Management of HPV+ve women
Swedscreen	HPV and conv. Cytol.	Cytological triage
POBASCAM	HPV and conv. Cytol.	Cytological triage
ARTISTIC	HPV and LBC	Cytological triage
NTCC phase 1 35-60 yrs	HPV and LBC	Colposcopy
NTCC phase 2 35-60 yrs	HPV only	Colposcopy
Finland	HPV only	Cytological triage

Randomised controlled trials

Detection ratio of CIN3 or invasive cancer HPV vs. cytology groups in 2° screening round

Study	Women randomised	Detection ratio (95%CI)
Sweedscreen[1]	**12,527 (1:1)**	0.53 (0.38-0.98)
POBASCAM[2]	**18,403 (1:1)**	0.43 (0.28-0.66)
ARTISTIC[3]	**25,078 (3:1)**	0.53 (0.30-0.96)
NTCC 35-60yrs[4]	**68,835 (1:1)**	0.34 (0.16-0.75)

p heterogeneity: 0.79

1 Naucler et al 2007 2 Bulkmans et al. 2007 3 Kitchener et al 2009 4 Ronco et al. 2010 modif

Relative Positive Predictive Value of colposcopy referral (HPV vs. cytology)

- Stand-alone HPV plus "cytological triage" (Finnish trial[1]): 1.34 (1.04-1.72)
- Double testing with "cytological triage" (Swedscreen[2]): 0.90 (0.70-1.16)
- Stand alone HPV with direct referral (NTCC PHASE 2[3]): 0.80 (0.55-1.18)
- Combined testing with direct referral NTCC PHASE 1[4]): 0.34 (0.21-0.54)

1. Leinonen et al JNCI 2009 2.Naucler et al JNCI 2009 3. Ronco et al JNCI 2008 4.Ronco et al JNCI 2006

Crucial Protocol Elements
Screening intervals

- In organised population-based screening programmes, the interval after a negative primary HPV test should be at least 5 years.
- There is evidence that the 5-year cumulative risk of high-grade CIN after a negative HPV test is lower than the 3-year risk after a normal cytology
- The probability of unneeded colposcopies and treatments would plausibly be relevant with 3-year intervals after a negative HPV test

Crucial Protocol Elements

Starting age

- HPV-based screening should not start before 30-35 years.
- There is evidence that below 30 years HPV-based screening leads to an increased overdiagnosis of CIN2 that would regress spontaneously, with consequent overtreatment. Some overdiagnosis could be possible also between 30 and 34 years.
- Below such ages, cytological screening is the recommended test.

Crucial Protocol Elements

Use of validated tests

- Only test for the DNA of oncogenic HPV types validated as for sensitivity and specificity for high-grade lesions according to the European guidelines should be applied

Crucial Protocol Elements
Primary testing

- There is no evidence that double testing with cytology and HPV is more protective than stand-alone HPV as primary test, although it entails a small and not relevant increase in sensitivity *vs* stand-alone HPV.
- On the contrary, there is evidence that double testing causes a substantial increase in referral to colposcopy and a decrease in its PPV.
- For this reason, if HPV is used as primary screening test, it is recommended not to add cytology in parallel.

Impact on Organisation

- For reasons of quality and cost, both the interpretation of cytology and HPV testing require a centralisation. This need is particularly strong, in terms of costs, for HPV test execution. It is therefore recommended to perform the HPV test in a limited number of reference laboratories of large size. This also makes it easier to monitor and evaluate the spontaneous activity.
- HPV-based screening entails problems of organisation related to the need of triage, to complex protocols and to reconversion of the activities of cytological interpretation.

Social, ethical and legal impact

- The communication of the result of the HPV test to women, particularly if positive, is a further crucial aspect in order to reduce not only the emotional impact, but also the possible risks that women are inappropriately managed or lost to follow-up.
- Great efforts must be put in the education of healthcare professionals, involved in organised programmes or not, particularly private gynaecologists and general practitioners

Costo e valutazione economica

Si stima che, nell'attuale situazione italiana utilizzando il protocollo sopra descritto, i costi complessivi dello screening basato sul test HPV siano inferiori a quelli di uno screening citologico convenzionale con gli attuali intervalli, anche se il costo per singolo round di screening è superiore

Cost and economic evaluation

- It is estimated that in the current Italian situation, with the described protocol the overall costs of HPV-based screening are lower than those of conventional cytological screening with the current 3-year intervals, although the cost of each screening round is higher.

Estimated costs (treatment included)

	HPV based screening every 5 years	Cytology based Screening every 3 years
Cost of a screening round	**€ 53.2** (first round with HPV) **€ 47.5** (subsequent rounds)	**€ 38,4**
Cost of screening 34-64 yrs	**€ 337.9**	**€ 442.6**

At price of **€ 12.45** (VAT included) per HPV test

Estimated costs (treatment included)

	HPV based screening every 5 years	Cytology based Screening every 3 years
Cost of a screening round	**€ 46.3** (first round with HPV) **€ 40.7** (subsequent rounds)	**€ 38,4**
Cost of screening 34-64 yrs	**€ 290.3**	**€ 442.6**

At price of **€ 6** (VAT included) per HPV test

Conclusions

- In conclusion, the crucial requirement to introduce HPV-based screening programmes is the capacity to guarantee the application of appropriate screening protocols.
- If these protocols do not respect the criteria described above can cause relevant increase of undesired effects and costs compared to cytology-based screening; therefore they should be avoided, except in studies able to provide clear evidence about human and economic costs.

Raccomandations
Education and information

- Correct education and information both to healthcare professionals and to the population is essential

Organised screening and spontaneous activity

- In the Italian situation, the interaction between coexisting organised screening and relevant spontaneous activity is crucial. Actions directed to integrate and guarantee as more uniformity of interventions as possible are needed, in particular through the integration of registries, a through monitoring and a progressive homogenization of protocols

Monitoring and coordination

- In order to grant the safety of transition, it is needed that the HPV-based organised screening activities are strictly monitored and that coordination within the National Centre for Screening Monitoring (ONS) is ensured.

Perspectives

- Knowledge about HPV based screening is still rapidly evolving. It is therefore possible that currently on-going researches can suggest changes to the optimal protocols in the next few years, particularly as for the management of HPV positive women. In addition, studies on the validation of new assays were recently published and others are expected.

Controlled implementation and evaluation

- It is suggested to exploit the organised screening activity to create scientific evidences, in order to clarify the still uncertain aspects of optimal protocols.
- Different protocols in terms of screening intervals, age of application and management of HPV positive women should be studied in the frame of controlled implementation, through multicentre projects coordinated by ONS.

Update of recommendations

- It is suggested the creation of a National working group to promptly update the recommendations for screening and the list of assays to be considered as validated.
- On the bases of the results obtained in the first vaccinated cohorts reaching the screening age, for the future, it will be crucial to deliver specific recommendations to the population vaccinated against HPV during adolescence.

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