Cervical cancer screening in younger women

Study protocol

Background and rational

Cervical screening based on the DNA test for oncogenic types of papilloma virus (HPV) as the primary test, hereinafter referred to as "HPV test-based screening" is currently recommended by the Ministry of Health for women between 30 and 64 years[1] with 5-year intervals between negative tests. For women between the ages of 25 and 29, cytology-based screening is recommended.

A combined analysis of European randomized trials clearly demonstrated that in this range of age screening based on the HPV test can further reduce the risk of 60-70% invasive cervical cancer versus cytology-based screening [2]. The same studio[2] has demonstrated that the risk of invasive cervical cancer within 5.5 years after a negative HPV test it is about half the risk of invasive cervical cancer within 3.5 years after a cytology negative.

The Resolution of the Piedmont Regional Council of 23 April 2013, No 21-5705 indicated the introduction of the HPV test for women between the ages of 30 and 64.

The HPV test is not currently recommended for women under the age of 30 because one study[3] (but not others [4-5]) suggests greater overdiagnosis of cervical intraepithelial neoplasms than grade 3 (CIN3) and especially grade 2 (CIN2) with the HPV test at younger ages.

A relevant overdiagnosis is also present with cytological screening (about 30% of CIN3 progress to invasive Ca in 30 years[6]), especially at younger ages.

It is believed that the use of the HPV test as a "filter" to pre-select 25-year-old women who need screening for up to 30 years, which would subsequently undergo to cytology alone, does not imply an increase in overdiagnosis. The increase in overdiagnosis it is, in fact, related to positive but cytologically normal HPV lesions. Moreover, this approach, avoiding a cytological screening round, reduces the number of tests and colposcopies (therefore the disturbance for women and the costs) and plausibly also the overdiagnosis. On the other hand, given the very low incidence of invasive cancer between 25 and 29 years[7] and the very low risk of invasive cancer observed in HPV negative women within 5.5 years[2], the recall after 5 years of women HPV negative, as already occurs in older women, does not imply a reduction of protection compared to cytological screening currently in use. This approach would also have significant organizational advantages as it avoids withdrawals differentiated by age group. The "screening protocol based on the HPV test as primary test", Annex A of DGR 21-5705 / 2013 of which it is a substantial and integral part, provides for this experimental

management of women under the age of 30, entrusting the coordination to the Unit of Cancer Epidemiology, CPO Piemonte.

Aim

Evaluate whether, among women between the ages of 25 and 29, the use of the HPV test as a "filter" for preselect women aged 25 who need screening up to age 30 reduce the number of tests and colposcopies (therefore the costs) and the overdiagnosis compared to the three-year cytological screening.

Population, invitations participation and random assignment

Women born in 1990-1992 (unvaccinated birth cohorts) invited for the 1st screening, or the 2nd round if the first had been performed with cytology and no CIN2+ found, within the organized screening program' Prevenzione Serena', Piedmont Region-Italy will be eligible for the study.
The women will receive an information sheet together with the letter of invitation to the screening informing that they will be asked to participate in the study and providing relevant information.
At the time of presentation at the sampling units midwives, who will undergo specific training, will request written informed consent to participate in the study. Women who have given informed consent will be randomly assigned to one of the two arms of the study.
The random assignment will be carried out centrally by the computer of CSI Piemonte at time of indication of consent. Both women and midwives will be informed of which arm the woman has been assigned to. The women assigned to the experimental arm may at any time request to return to the conventional management.
It is expected to randomise about 20,000 women.

Procedure
A) Conventional arm
Women will be invited at 25 and 28 years and managed according to the current cytological protocol i.e .:
- a cytological slide will be prepared
- women with cytology ASC-US or more severe, will be referred for colposcopy
- women with cytology <ASC-US, recruited at the age of 25 will be invited for a new cytology at the age of 28. On such occasion they will be referred for colposcopy if cytology is ASC-US or more severe. Women recruited at age 28 if cytology <ASC-US will be sent to new round at 30 years.

B) Experimental arm

Women will have a sample of cervical cells taken and put in transport medium for liquid based cytology (LBC). All women will be tested for HPV by Hybrid Capture 2, which looks for presence of at least one of the 12 types classified as oncogenes (16,18,31,33,35,39,45,51,52, 56,58,59) and of type 68, classified as probably oncogenic[8]. Women with Relative Light Units (RLU) ≥1 will be considered as positive, as recommended by the manufacturer.

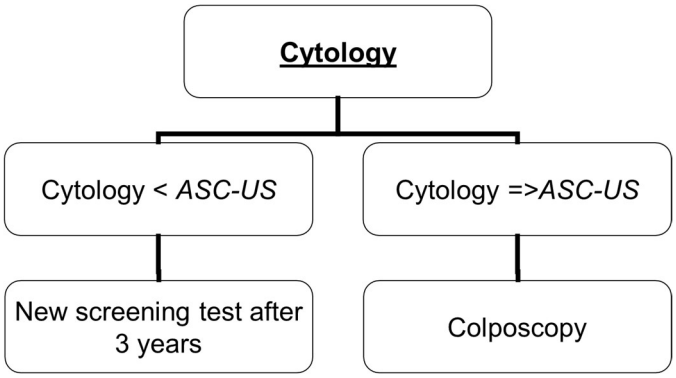
Only HC2 positive women will have cytology prepared and interpreted. These women will be managed only on the basis of cytology as women in the conventional arm. No HPV test repeat for HPV positive, cytology negative women (like at older ages) will be performed. Women with HPV positive test but normal cytology will be invited for a new cytology at age 28 years. On such occasion they will be referred to colposcopy if cytology is ASC-US or more severe. Women recruited at age 28 with positive HPV test but normal will be invited for a new round at age 30.

If the analysis conducted after the first year of enrolment will not show a significant reduction of the detection rate of CIN2 or more severe (CIN2+) histology in the experimental vs. conventional arm then HPV negative women will be referred to a new screening round after 5 years.

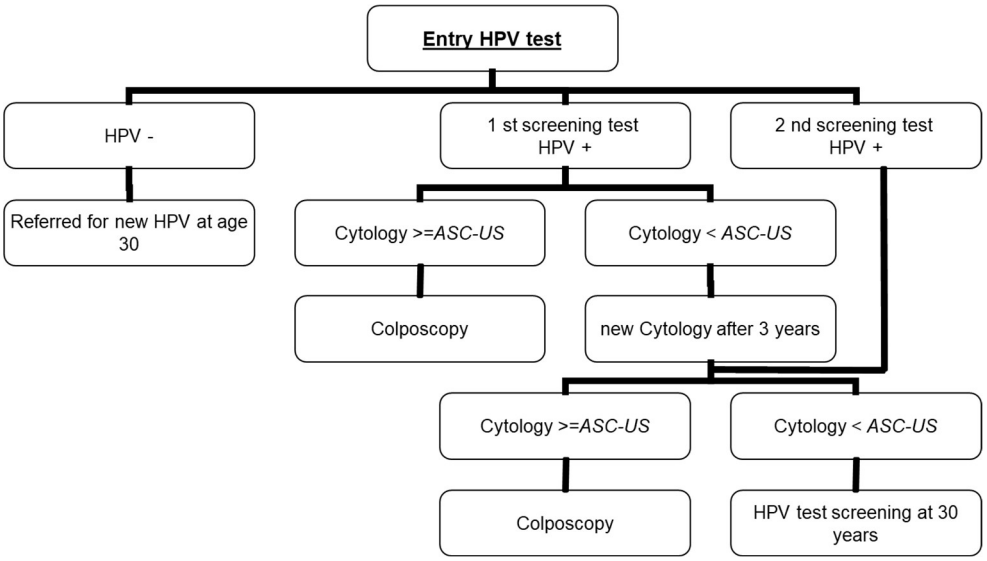
At the age of 30 years all women from both arms will be invited to screening with HPV according to Italian recommendations for women aged 30-64 years (i.e., HPV positive but cytology-negative women will be re-invited for new HPV test after 1 year).

Flow chart

Conventional arm



Experimental arm



Data collection

Comprehensive data on test results and related recommendations, second level tests done, their result and related recommendations and about treatments performed in the organized program are regularly registered and will be retrieved and used for the analysis.

Methodology and statistical analysis

The two study arms will be compared for indicators shown below. For each indicator the power with the size is specified indicated above (20,000 women).

a) CIN2 + detection, histologically determined at the entry screening round. If it will not be lower in the experimental arm, the safety of the same will be demonstrated (power> 80% to detect a 20% difference assuming a 0.6% detection in the conventional arm).

b) CIN2 + detection, histologically determined at 30 years. If it will not be higher in the experimental arm this will confirm its safety.

c) cumulative referral for colposcopy from recruitment to 30 years (including screening at 28 years if done). Power> 90% to detect a 20% reduction in the experimental arm assuming a 9% cumulative referral in the conventional arm.

d) CIN2 + cumulative detection, from recruitment to 30 years. A reduction in the experimental arm would show a reduced overdiagnosis (80% power to detect a 30% difference assuming 1.5% cumulative detection in the conventional arm).

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