EUROPEAN JOURNAL OF CANCER 47 (2011) 255–261

available at www.sciencedirect.com

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journal homepage: www.ejconline.com

False-positive Human Papillomavirus DNA tests in cervical screening: It is all in a definition

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ARTICLE INFO

Article history:
Received 27 May 2010
Received in revised form 10 August 2010
Accepted 11 August 2010

Keywords:
Cervical cancer
Cytology
HPV DNA probes
Early detection of cancer
Triage

ABSTRACT

Aim: Based on data from randomised controlled trials (RCT) on primary cervical screening, it has been reported that the problem of more frequent false-positive tests in Human Papillomavirus (HPV) DNA screening compared to cytology could be overcome. However, these reports predominantly operated with a narrow definition of a (false-)positive test. The aim of this paper was to illustrate how the narrow definition affected the measured adverse effects of HPV DNA screening compared with cytology screening.

Methods: In the European RCT data, we measured the impact of the narrow definition of a positive screening test on the published relative positive predictive values (PPV), an indicator of the relative frequency of false-positive screening tests.

Results: Using the trialists' definitions of positive screening tests, HPV screening combined with cytology triage had relative PPVs of 0.87 (95% confidence interval (CI): 0.60–1.26) for ⩾CIN3 based on Swedish RCT data, and 0.78 (0.52–1.16) for ⩾CIN2 in the Italian Phase 1 RCT (25–34 years). These PPVs changed to 0.44 (0.30–0.64) and 0.51 (0.33–0.79), respectively, when all positive HPV or cytology screening tests were accounted for. In the Finnish RCT data, HPV screening using the cut-off point of ⩾10 pg/ml had a relative PPV of 0.27 (0.15–0.50) for ⩾CIN3, which changed to 1.84 (0.99–3.41).

Conclusion: The relative PPV was incorrectly estimated in six out of seven studies. In three of those six studies, the relative PPV changed significantly after inclusion of the previously erroneously excluded false-positive HPV or cytology tests.

1. Introduction

The recently introduced Human Papillomavirus (HPV) vaccine represents a major step forward in control of cervical cancer, but as it is expected to prevent only around 70% of cervical cancers, screening will still be needed as a supplementary tool. For the currently sexually active women screening will furthermore remain the most important preventive strategy.

While observational studies have shown that cytological screening reduced both the incidence and mortality from cervical cancer,[1] one-third of all cervical cancer patients had previous negative cytology.[2] Randomised controlled trials (RCT) comparing cytology with HPV DNA testing in primary screening showed that the latter detects about 50% more high-grade cervical intraepithelial neoplasia (⩾CIN2).[3] An added benefit of the switch from cytology to HPV DNA screening is the possibility of widening the screening intervals.[4–6] As a consequence, several countries may in the near future switch from cervical screening with cytology to screening for HPV infection.

However, test-positive rates are up to three times higher with HPV DNA screening than with cytology.[3,6] Increased

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0959-8049/$ - see front matter
doi:10.1016/j.ejca.2010.08.010

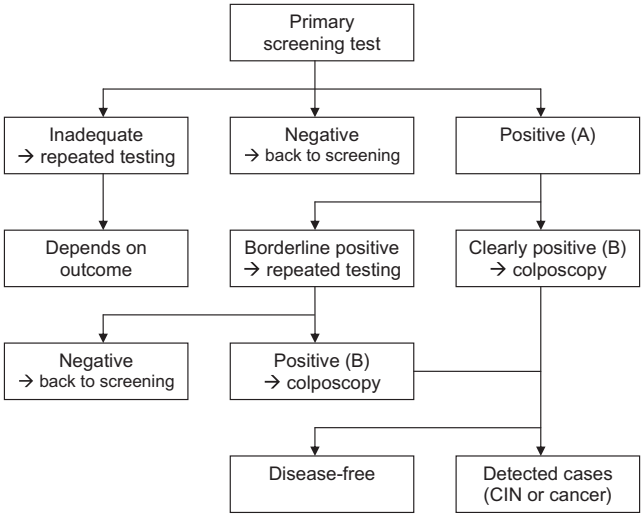

Fig. 1 – Definition of a positive screen in cervical cancer screening.

test-positive rates seem to persist over the course of subsequent screening rounds.[3,7] HPV DNA screening consequently causes more false-positive tests, i.e. positive screening tests without underlying CIN: about seven extra women above age 30 had a false-positive test for each additionally detected ⩾CIN2 compared with cytology screening in most European RCTs.[3] These false-positive tests, found predominantly in HPV DNA positive/cytology normal women, decrease the positive predictive value (PPV) and specificity, two standard indicators of adverse effects of screening.

The problem with many false-positive tests has been acknowledged by the authors of the RCTs, and some trialists suggested HPV DNA screening strategies appearing to have a positive predictive value (PPV) or specificity comparable to those of cytology screening.[8–14] For example, in the Swedish RCT primary HPV DNA screening with cytology triage and repeated testing after 1 year in HPV DNA positive/cytology normal women was found to give a PPV for ⩾CIN3 similar to that of conventional cytology screening, relative PPV 0.87 (95% confidence interval (CI) 0.60–1.26).[9] A similar HPV DNA screening strategy resulted in a relative PPV for ⩾CIN2 of 0.78 (0.52–1.16) for women aged 25–34 years in one of the Italian RCTs.[10]

While the numerator of the PPV for ⩾CIN2 or ⩾CIN3 was in all published reports defined as the number of women diagnosed with the relevant CIN lesions, the definition of the denominator, i.e. the number of women regarded as positive on the screening test, varied. One may define the denominator as the number of women with a screening test value above the threshold recommended for any type of follow-up (Fig. 1: definition A). However, some trialists used a narrower definition of a positive screening test by including only the number of women referred for colposcopy (Fig. 1: definition B).[4,8–13]

The difference between definitions A and B represents the women recommended for repeated testing and not later referred for colposcopy (Fig. 1). As no CIN is found in these women, they should be regarded as having had a false-positive screening test. Effectively, however, the narrower definition B shifts these women from the group with positive screening tests to the group with negative screening tests. As illustrated in Fig. 2, this makes both the PPV and the specificity appear more favourable. Assuming no disease in women not referred for colposcopy (denoted as X), which is reasonable for screening with high sensitivity, the use of definition A leads to $PPV_1 = A/(A + B)$ and $Specificity_1 = D/(B + D)$, while the use of definition B leads to $PPV_2 = A/(A + B - X)$ and $Specificity_2 = (D + X)/(B + D)$, with $PPV_2 > PPV_1$ and $Specificity_2 > Specificity_1$.

In most European RCTs, at least half of the women with positive HPV DNA screening tests were not later referred for colposcopy.[4,5,10,13,15] The aim of this paper was to illustrate how severely their inclusion among women with negative screening tests affected the measured adverse effects of HPV DNA screening as compared with cytology screening.

2. Material and methods

2.1. *Selection of RCTs*

We selected the RCTs undertaken in settings with well-established population-based, organized screening programmes.[16] Because the RCT in India was undertaken in women screened for the first time,[17] and the Canadian RCT recruited women if they sought screening,[18] we excluded these two RCTs from the present overview. The data were obtained by searching the PubMed database for articles published anytime until December 2009. The terms 'HPV' or 'Human Papillomavirus' and the names of the principle investigators were used as search terms.

Definition A	True disease	No disease	Total
Screen-positive	A	B	A+B
Screen-negative	C	D	C+D
Total	A+C	B+D	A+B+C+D

Definition B	True disease	No disease	Total
Screen-positive	A	B-X	A+B-X
Screen-negative	C	D+X	C+D+X
Total	A+C	B+D	A+B+C+D

X = women not referred for colposcopy.

Fig. 2 – Distribution of screening results.

2.2. Selection of HPV DNA screening strategies

The trialists had suggested one optimal HPV DNA screening strategy from the Swedish (SWEDESCREEN)[9] and the UK RCTs (ARTISTIC),[14] and two from the Italian (NTCC Phase 1[10,11] and Phase 2[12]) and the Finnish RCTs (Finnish Public Health Trial).[8,13] For the Dutch RCT (POBASCAM),[4] the authors presented a calculation of the efficiency of screening strategies, which can be interpreted as PPV. This was done for the HPV DNA screening strategy actually used in the RCT.

2.3. Analysis

We extracted the reported measures of PPV for cytology screening and the selected HPV DNA-screening strategies as observed at the baseline screening rounds. As it was not systematically specified in all original reports which definition of a positive test had been used, we indirectly determined it by extracting additional data and study design information, if necessary from earlier publications,[15] so that we could reconstruct the reported PPV. For one of the proposed screening strategies from the Finnish RCT only specificity was reported,[8] and we calculated the PPV using the same definitions of positive tests as the trialists had used to calculate the specificity. For the strategy proposed from the UK RCT,[14] only the PPV of HPV DNA screening was reported, and we calculated the PPV of cytology screening using the same definition of the denominator. This corresponds to the definitions the same trialists used in an earlier publication using the data from the same RCT.[7] Where the PPV was reported only separately for HPV DNA and cytology screening, we calculated the relative PPV for HPV DNA versus cytology screening. Finally, we systematically calculated the relative PPV based on definition A of a positive test, i.e. accounting for all women eligible for any type of follow-up (Fig. 1). Whenever the numbers used for the calculation of the PPV were not directly reported in the original publications but were arrived at for instance by adding two numbers from the same reports, we annotated this by square brackets in line with the tradition used for e.g. the International Agency for Research on Cancer monographs. Inadequate quality tests were not considered positive tests and were thus not included in the definition A. Apart from varying the definition of positive screening tests, we sought to keep all other definitions the same as in the original reports. Thus, we used the focal endpoints from the original RCT publications: ⩾CIN2 for the UK and both Italian RCTs,[10–12,14] and ⩾CIN3 for other RCTs.[4,8,9,13] In line with the original reports, we did not stratify the calculated PPVs by age. 95% confidence intervals for the relative PPVs were calculated by assuming that the logarithms of relative PPVs were approximately normally distributed.

3. Results

The suggested optimal HPV DNA-screening strategies can be broadly classified into two groups: those that involve reacting to all positive HPV DNA screening tests, defined as such in RCTs using Polymerase Chain Reaction (PCR) GP5+/6+ testing or using the cut-off point of ⩾1 pg/ml in RCTs using Hybrid Capture 2 (HC2) testing (Table 1), and those setting a higher HC2 cut-off point (Table 2).

In the published calculations from Italy (for both tests), The Netherlands (for both tests), Sweden (for HPV DNA only) and Finland (for cytology only in one strategy,[8] and for both tests in another[13]), definition B was used to determine the number of women with a positive screening test, i.e. it included only the women referred for colposcopy. On the other hand, in the published calculations from Finland (for HPV DNA only in one strategy),[8] Sweden (for cytology only) and the UK definition A was used, i.e. it included all the women with screening tests at or above the threshold that made them eligible for any type of follow-up.

For strategies reacting to all positive HPV DNA-screening tests (defined as such in RCTs using PCR testing, and using the cut-off point of ⩾1 pg/ml in RCTs using HC2 testing), the published reports based predominantly on definition B from Sweden, Italy Phase 1 (25–34 years), The Netherlands and Finland showed the PPVs of HPV DNA screening to be similar to the PPVs of cytology screening (Table 1): relative PPVs were 0.87 (95% CI 0.60–1.26) for ⩾CIN3, 0.78 (0.52–1.16) for ⩾CIN2 and 1.02 (0.68–1.53) and 1.22 (0.78–1.92) for ⩾CIN3, respectively. However, when we calculated the relative PPVs based on our definition A of a positive test, the relative PPVs decreased to 0.44 (0.30–0.64), 0.51 (0.33–0.79), 0.82 (0.55–1.23) and 1.10 (0.70–1.73), respectively.

Using the trialists' definitions of positive screening tests, the strategy of reacting to HC2 HPV DNA tests at the ⩾2 pg/ml cut-off point had relative PPVs for ⩾CIN2 of 0.95 (0.83–1.09) in the UK, and of 0.85 (0.66–1.09) in the Italian (35–60 years) data (Table 2). While the UK relative PPV was already based on definition A of a positive screening test, the relative PPV in the Italian data changed to 1.07 (0.81–1.39) when definition A was used. The reported relative PPV for ⩾CIN3 from the Finnish RCT using the HC2 cut-off point ⩾10 pg/ml of 0.27 (0.15–0.50) changed to 1.84 (0.99–3.41) when we used definition A.

4. Discussion

While a shift from cytology to HPV DNA screening is expected to increase the sensitivity of cervical screening, the increased risk of false-positive tests and the associated unnecessary follow-up have been of concern. All seven published reports based on the European RCTs concluded that these adverse effects could be overcome, basing their conclusion on calculation of relative PPVs. However, these calculations predominantly operated with a narrow definition of a false-positive test. Only the UK reports defined all the tests recommended for any follow-up as positive, whereas the six other reports defined (entirely or partly) only the tests followed by colposcopy as positive. When we recalculated the original data and took into account all the tests recommended for any follow-up, three of the six reported relative estimates of the adverse effects of HPV DNA screening changed significantly. For two screening strategies using HPV DNA testing combined with cytology triage the originally reported adverse effects appeared to be similar to those of conventional cytology screening. In our recalculation, the adverse effects became significantly higher (Table 1). For

Table 1 – Relative positive predictive values (PPV) for ⩾CIN2 or ⩾CIN3 compared with cytology screening: suggested screening strategies reacting to all positive HPV DNA-screening tests (defined as such in RCTs using PCR testing, and using the cut-off point of ⩾1 pg/ml in RCTs using HC2 testing).

	Sweden[9]	Italy, Phase 1[e10]	The Netherlands[4]	Finland[13]
Analysis based on RCT data from	Intervention arm	Intervention and control arms	Intervention and control arms	Intervention and control arms
Age group (years)	32–38	25–34	29–56	25–⩾65
Control test	Conventional cytology	Conventional cytology	Conventional cytology	Conventional cytology
Referral for colposcopy in control group	⩾HSIL → colposcopy, ASCUS/ LSIL → colposcopy or repeated conventional cytology[c]	⩾LSIL → colposcopy, ASCUS → colposcopy or repeated conventional cytology with colposcopy if ⩾LSIL[f]	⩾HSIL → colposcopy, ASCUS/LSIL → repeated conventional cytology 6 or 18 months after initial screening with colposcopy if ⩾ASCUS	⩾LSIL → colposcopy, Papanicolaou class II → repeated cytology 12 months after initial screening with colposcopy if cytology Papanicolaou class II[i]
Reported definition of a positive cytology test	⩾ASCUS	⩾ASCUS and underwent colposcopy	Referred for colposcopy	Referred for colposcopy
Intervention tests	GP5+/6+ PCR HPV DNA screening with conventional cytology triage	HC2 HPV DNA ⩾1pg/ml screening with liquid-based cytology triage	Combined GP5+/6+ PCR HPV DNA and conventional cytology screening	HC2 HPV DNA ⩾1pg/ml screening with conventional cytology triage
Referral for colposcopy in intervention group given normal cytology[a]	Type-specific HPV DNA positive 1 year after initial screening	HPV DNA ⩾1pg/ml or cytology ⩾ASCUS 1 year after initial screening	HPV DNA positive or conventional cytology ⩾HSIL 6 or 18 months after initial screening	HPV DNA positive 12 months after initial screening[i]
Reported definition of a positive HPV DNA test	Referred for colposcopy[d]	Referred for and underwent colposcopy	Referred for colposcopy	Referred for colposcopy
Reported: relative PPV for ⩾CIN2 or ⩾CIN3[b] (95% CI)	0.87 (0.60–1.26) (48/218)/(37/146)	0.78 (0.52–1.16) [(54/448[g])/(33/213)]	[1.02 (0.68–1.53)] (66/201)/(37/115)	1.22 (0.78–1.92) ([42]/424)/([34]/420)
Definition A: relative PPV for ⩾CIN3 or ⩾CIN2[b] (95% CI)	0.44 (0.30–0.64) (48/433)/(37/146)	[0.51 (0.33–0.79) (54/836)/(33/261)]	[0.82 (0.55–1.23)] (66/[515])/(37/[238])[h]	[1.10 (0.70–1.73) (42/2795[j])/(34/2486[j])]

[ ] = calculated by the authors of the present overview. HC2 = hybrid capture 2. PCR = polymerase GP5+/6+ chain reaction.

[a] In these RCTs, women with concurrently abnormal cytology largely followed the standard referral procedures for cytology.

[b] ⩾CIN2 for the Italian Phase 1 RCT, and ⩾CIN3 for the data from the Swedish, Finnish and the Dutch RCT.

[c] The timing of repeated cytology and the procedure thereafter were not described. In case of a positive HPV test and no record of referral due to abnormal cytology the women in the intervention arm were offered a second round of HPV and Pap tests at least 12 months later, and were offered colposcopy if they continued to be infected with the same high-risk type of HPV.[5]

[d] Due to RCT study centre variation in follow-up recommendations for women with ASCUS or LSIL, the group may include some women with repeated testing instead of a referral for colposcopy.

[e] We did not include data from the Phase 2 RCT because no cytology triage was done in its experimental arm.

[f] The timing of repeated cytology was not described.

[g] Women with immediate colposcopy, and women with colposcopy based on follow-up testing after 1 year.

[h] Excluding two ⩾CIN3 cases in the HPV DNA + cytology screening arm and three ⩾CIN3 cases in the cytology arm found by opportunistic screening, which the trialists included in the calculation of the relative detection rate. If these ⩾CIN3 were included, the relative PPV using the definition A would change to [0.79 (0.53–1.16)].

[i] Outcomes of repeated testing not reported.[13]

[j] Estimated from proportions reported by Leinonen and colleagues.[13]

one HPV-screening strategy using a cut-off point of ⩾10 pg/ml the adverse effects appeared to be higher than for conventional cytology screening using the original definitions. In our recalculation, the adverse effects became significantly lower (Table 2). In these three reports, the definitions of positive screening test were not adequately balanced. Whereas in the

Table 2 – Relative PPV for ⩾CIN2 or ⩾CIN3 compared with cytology screening: suggested screening strategies not reacting to all HPV DNA-screening tests with HC2 using the cut-off point of ⩾1 pg/ml.

	Italy, Phase 1 + Phase 2[11,12]	UK[14]	Finland[8]
Analysis based on RCT data from	Intervention and control arms	Intervention arm	Intervention and control arms
Age group (years)	35–60	20–64	30–60
Control test	Conventional cytology	Liquid-based cytology	Conventional cytology
Referral for colposcopy in control group	⩾LSIL → colposcopy, ASCUS → colposcopy or repeated conventional cytology with colposcopy if ⩾LSIL[c]	⩾HSIL → colposcopy, ASCUS/LSIL → repeated liquid-based cytology and HPV DNA testing 6 and 12 months after initial screening with colposcopy if ⩾ASCUS or HPV DNA ⩾1 pg/ml	⩾LSIL → colposcopy, Papanicolaou class II → repeated cytology 12 months after initial screening with colposcopy if cytology Papanicolaou class II[d]
Reported definition of a positive cytology test	⩾ASCUS and underwent colposcopy	⩾ASCUS	⩾LSIL
Intervention tests	HC2 HPV DNA ⩾2 pg/ml screening	HC2 HPV DNA ⩾2 pg/ml screening	HC2 HPV DNA ⩾10 pg/ml screening
Referral for colposcopy in intervention group	HPV DNA ⩾2 pg/ml → colposcopy	HPV DNA ⩾2 pg/ml and ⩾HSIL → colposcopy, HPV DNA ⩾2 pg/ml and ASCUS/LSIL → repeated liquid-based cytology and HPV DNA testing 6 and 12 months after initial screening with colposcopy if ⩾ASCUS or HPV DNA ⩾1 pg/ml	HPV DNA ⩾10 pg/ml and ⩾LSIL → colposcopy, other HPV DNA ⩾10 pg/ml → repeated testing 12 months after initial screening with colposcopy if HPV DNA positive[d]
Reported definition of a positive HPV DNA test	HPV DNA ⩾2 pg/ml and underwent colposcopy	HPV DNA ⩾2 pg/ml	HPV DNA ⩾10 pg/ml
Reported:[a] relative PPV for ⩾CIN3 or ⩾CIN2 (95% CI)[b]	0.85 (0.66–1.09) [(137/1583)/(87/851)]	As below	[0.27 (0.15–0.50)] (20/797)/(20/216)
Definition A: relative PPV for ⩾CIN3 or ⩾CIN2 (95% CI)[b]	[1.07 (0.81–1.39) (137/1697)/(87/1149)]	[0.95 (0.83–1.09)] (409/2403)/ ([421/2344])	[1.84 (0.99–3.41)] (20/797)/(20/[1463])

[ ] = calculated by the authors of the present overview. HC2 = hybrid capture 2.
[a] Or calculated using the same definition of a positive screening test as used for the reported estimate of specificity from the same RCT.
[b] ⩾CIN2 for the Italian Phase 1, Phase 2 and the UK RCT, and ⩾CIN3 for the Finnish RCT.
[c] The timing of repeated cytology not described.
[d] Outcomes of repeated testing not reported.

first two reports, a complete follow-up of cytology-positive women was compared with selective referral for colposcopy of HPV DNA positive women,[9,10] in the third selective referral for colposcopy in cytology-positive women was compared with complete follow-up of HPV DNA positive women.[8]

It may be somewhat surprising that despite originally using the definition B of positive screening tests, the Finnish and Dutch relative PPVs for HPV DNA screening with cytology triage/double testing changed only slightly when the definition A was used instead (Table 1). However, in Finland conventional cytology screening had an abnormality rate virtually equal to that of HPV DNA screening (definition A), and a virtually equal number of women were referred for colposcopy (definition B). Thus, a complete follow-up of all women using a cut-off point of ⩾1 pg/ml on the HPV test (8.0%)[15] did in Finland not represent a significantly more intensive screening strategy than the currently recommended follow-up of all women with Pap class II cytology (6.8%).[15] It is to be noted, however, that the Finnish relative PPV may again increase somewhat when follow-up data for women with repeated testing become available. In The Netherlands, HPV DNA testing increased both the referral for colposcopy (definition B) and the screening test-positivity rates (definition A). Both increases were, however, balanced by an increase in the detection of ⩾CIN3.[4] Therefore, HPV DNA screening combined with cytology appeared to have had a somewhat more favourable balance of positive and adverse effects in The Netherlands than elsewhere.

In Europe, the burden of HPV infection and the outcomes of cervical screening vary greatly by country.[19,20] It appears

that some aspects of this variation will remain if HPV testing will replace cytology. For example, it appears from our analysis that the degree to which the use of cytology triage in HPV DNA screening can resolve the problem of false-positive tests may vary depending on the RCT's context. The findings from one RCT may not be easily generalised across countries.

The focus on the women referred for colposcopy presumably originates from the practice adopted in earlier non-randomised studies comparing HPV DNA and cytology in primary screening.[21,22] In those studies, the women were tested with both screening tests simultaneously. Not yet having established evidence regarding the basic properties relative to cytology, the women tended to be referred for colposcopy if any of the two screening tests was positive. When this is the case, the use of definition B of a positive screening test is equal to using definition A. The aim of European RCTs, i.e. the next generation of studies investigating the use of HPV DNA testing in primary screening, was on the other hand to investigate the use in everyday screening practice in Europe. The RCTs thus differed from the preceding non-randomised studies in that the virtually complete referral for colposcopy of women with positive screening tests was replaced by a more conservative follow-up. Therefore, the standard methodology of describing adverse effects in non-randomised studies by focusing on women referred for colposcopy ceased to be appropriate. When the narrower definition B was used instead of definition A in the evaluation of the given RCTs, the resulting relative PPVs did not anymore include the total amount of adverse effects caused by the two compared screening tests. It should have more correctly been interpreted as a measure of triage to colposcopy.

For women, a referral for colposcopy has important psychosocial sequelae.[23–26] However, the psychosocial sequelae of repeated testing do not appear to be considerably weaker.[23,25–28] The women advised to undergo repeated testing remain in follow-up for several years before they are discharged to normal screening rounds.[29,30] Each repeated test generates anxiety,[25,31] which is coupled with the women's prolonged uncertainty regarding their future health.[28,31,32] On the population level, these extra tests and uncertainty will lead to a decrement in the gain of quality-adjusted life years (QALY) from preventing cervical cancer. Furthermore, repeated testing will increase the related health service workload and financial costs of screening.

In conclusion, six out of seven published reports exploring solutions to minimising false-positive HPV DNA-screening tests relative to cytology entirely or partly ignored the women with false-positive tests not referred for colposcopy. In those cases, the published relative PPVs were incorrectly estimated. In our re-analysis of the trialists' data, inclusion of the erroneously excluded false-positive HPV DNA or cytology tests changed the relative PPV substantially in three out of six published reports.

Sources of funding

Olga and Esper Boels Fund, Aase og Ejnar Danielsens Fond, Augustinus Fonden, Fabrikant Mads Clausens Fond, Familien Hede Nielsens Fond, Else og Mogens Wedell-Wedelsborgs Fond, Carl og Ellen Hertz' Legat til Dansk Læge- og Naturvidenskab and Købmand Sven Hansen og hustru Ina Hansens Fond. None of these sources of funding had any role in the study design, the collection of data, the analysis, the interpretation of the data, the writing of the paper and in the decision to submit the paper for publication.

Conflict of interest statement

The authors declare that they have no conflict of interest.

Acknowledgements

The authors would like to thank Sisse Helle Njor for statistical advice. We are indebted to Guglielmo Ronco for providing information on the Italian randomised controlled trials.

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