Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials

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Summary

Background In four randomised trials, human papillomavirus (HPV)-based screening for cervical cancer was compared with cytology-based cervical screening, and precursors of cancer were the endpoint in every trial. However, direct estimates are missing of the relative efficacy of HPV-based versus cytology-based screening for prevention of invasive cancer in women who undergo regular screening, of modifiers (eg, age) of this relative efficacy, and of the duration of protection. We did a follow-up study of the four randomised trials to investigate these outcomes.

Methods 176 464 women aged 20–64 years were randomly assigned to HPV-based (experimental arm) or cytology-based (control arm) screening in Sweden (Swedescreen), the Netherlands (POBASCAM), England (ARTISTIC), and Italy (NTCC). We followed up these women for a median of 6·5 years (1 214 415 person-years) and identified 107 invasive cervical carcinomas by linkage with screening, pathology, and cancer registries, by masked review of histological specimens, or from reports. Cumulative and study-adjusted rate ratios (experimental vs control) were calculated for incidence of invasive cervical carcinoma.

Findings The rate ratio for invasive cervical carcinoma among all women from recruitment to end of follow-up was 0·60 (95% CI 0·40–0·89), with no heterogeneity between studies (p=0·52). Detection of invasive cervical carcinoma was similar between screening methods during the first 2·5 years of follow-up (0·79, 0·46–1·36) but was significantly lower in the experimental arm thereafter (0·45, 0·25–0·81). In women with a negative screening test at entry, the rate ratio was 0·30 (0·15–0·60). The cumulative incidence of invasive cervical carcinoma in women with negative entry tests was 4·6 per 10⁵ (1·1–12·1) and 8·7 per 10⁵ (3·3–18·6) at 3·5 and 5·5 years, respectively, in the experimental arm, and 15·4 per 10⁵ (7·9–27·0) and 36·0 per 10⁵ (23·2–53·5), respectively, in the control arm. Rate ratios did not differ by cancer stage, but were lower for adenocarcinoma (0·31, 0·14–0·69) than for squamous-cell carcinoma (0·78, 0·49–1·25). The rate ratio was lowest in women aged 30–34 years (0·36, 0·14–0·94).

Interpretation HPV-based screening provides 60–70% greater protection against invasive cervical carcinomas compared with cytology. Data of large-scale randomised trials support initiation of HPV-based screening from age 30 years and extension of screening intervals to at least 5 years.

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Introduction Cervical screening aims to prevent invasive cervical carcinoma by detection and treatment of its precursors—cervical intraepithelial neoplasia grade 2 (CIN2) and, particularly, grade 3 (CIN3). In a cluster-randomised controlled trial from rural India,1 women who had received little or no previous cervical screening either underwent one round of human papillomavirus (HPV) testing or had no screening, cytological analysis, or visual inspection. Cumulative incidence of advanced cancer (stage ≥2), but not of stage 1 invasive cancer, was lower in women who had one HPV screening round compared with those who had no intervention.2 However, the effect of HPV testing—as an alternative to regular cytological screening—on incidence of invasive cancer has not been assessed adequately.

Four randomised controlled trials have been done—Swedescreen,3 POBASCAM,4 5 ARTISTIC,6 and NTCC7—in which women from industrialised countries were followed up for at least two rounds of cervical screening. A lower CIN3 incidence was recorded after HPV testing compared with cytology. Despite different screening protocols, the relative incidence of CIN3 or worse histological findings after the first screening round was similar in all studies: rate ratios (HPV vs cytology) were 0·53 (95% CI 0·29–0·98) in Swedescreen, 0·52 (0·28–0·97) in ARTISTIC, 0·34 (0·15–0·75) in NTCC (in women aged 35 years or older), and 0·39 (0·27–0·53) in POBASCAM, with no evidence of heterogeneity (p=0·68).1 These results show that HPV-based screening detects persistent high-grade CIN before cytology, thus increasing the probability of treatment before invasion.

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Furthermore, the effect was similar with the different screening protocols applied, which suggests that efficacy in cancer prevention is dependent primarily on the screening test and not on the exact protocol used, providing a strong rationale for joint analysis of trials.

In the NTCC trial, the overall incidence of invasive cancers was reduced significantly with HPV screening compared with cytology, and in POBASCAM, incidence was diminished significantly at the second screening round. However, because none of the four randomised controlled trials was powered to show a reduction in cancer incidence, the numbers of cases in individual reports were small. Thus, precise direct estimates are absent for the relative efficacy of HPV-based versus cytology-based screening, of how efficacy changes according to age, cancer stage, and morphological features, and of the duration of protection against cancer. Such direct estimates are crucial to inform decisions about implementation of HPV-based screening as a routine activity and to define some important aspects of screening policies with HPV, such as the age at which to initiate screening and the optimum screening interval. Therefore, we pooled data from the four randomised trials and followed up the cohorts for analysis of invasive cervical carcinomas.

Methods

Study populations

Study populations and interventions used in the studies have been described elsewhere. Women recruited to all four trials had not had a hysterectomy and were attending for routine screening within organised population-based programmes. Participants in Swedescreen were recruited from five Swedish regions between May, 1997, and November, 2000; those in NTCC were recruited from nine areas of Italy during two preplanned phases, between March, 2002, and December, 2004; women in ARTISTIC were recruited from the Greater Manchester region of the UK between July, 2001, and September, 2003; and individuals in POBASCAM were recruited from the Netherlands between January, 1999, and September, 2002. Women were excluded from NTCC if they were pregnant or treated for CIN in the previous 5 years, and participants in POBASCAM were excluded if they had CIN2 or higher or abnormal cytology detected in the previous 2 years. No exclusion criteria were used at recruitment in Swedescreen and ARTISTIC; however, women diagnosed with CIN2 or higher were usually followed up in gynaecological clinics and they did not attend routine screening for many years. Ethics approval was obtained in every study, and all women provided informed consent.

Randomisation and masking

After enrolment, women were randomly assigned to either HPV-based or cytology-based screening in a 1:1 ratio, except in ARTISTIC (3:1 ratio). In POBASCAM, Swedescreen, ARTISTIC, and two centres of NTCC, central computers did the randomisation (not in blocks). In the remaining NTCC centres, sealed numbered envelopes containing the random allocation were prepared by the local coordinating centre and sent to every unit. The envelopes were opened according to the centrally provided sequence (done in blocks of eight in three centres, unblocked in the remaining). Women and clinical staff were not masked to randomisation, except in Swedescreen, in which participants and researchers were unaware of allocations during the first 6 years.

Interventions at first screening round

In the control arm had either liquid-based (ARTISTIC) or conventional (all other studies) cytological testing. Management essentially followed local routine guidelines. In most NTCC centres and in Stockholm (Swedescreen), women with a finding of ASC-US (atypical squamous cells of undetermined significance) or worse were referred directly for colposcopy, whereas in the other NTCC and Swedescreen centres, repeat cytology was an option. In POBASCAM and ARTISTIC, women with borderline or mild dyskaryosis—corresponding to ASC-US or low-grade squamous intraepithelial lesions in the Bethesda system—were referred for repeat cytology.

Women in the experimental arm had either HPV testing alone (in phase 2 of NTCC) or both HPV testing and cytology (all other studies). In ARTISTIC and NTCC, DNA testing of high-risk HPV types was done with the hybrid capture 2 assay (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68), using the 1 pg/μL (1 μg/L) recommended cutoff. In POBASCAM and Swedescreen, PCR was done with GP5+ and GP6+ general primers, followed by enzyme immunoassay targeting the same HPV types as with the hybrid capture 2 assay, plus HPV66. Interpretation of HPV testing and cytological analysis were masked reciprocally in all studies. In NTCC phase 1 (age 35–60 years) and phase 2 (any age), all HPV-positive women were referred directly for colposcopy. In the other studies, women were referred for immediate colposcopy on the basis of cytological findings, following the same rules as in the corresponding control arm. Cytology-negative HPV-positive women were referred for repeat HPV and then colposcopy if HPV infection persisted (we called this approach cytological triage). However, protocols differed slightly between studies with respect to retesting intervals, number of repeats, definition of persistence, and whether cytology was also repeated.

Women with CIN2 or more severe histological findings at colposcopy were referred for treatment. Almost all described interventions were concluded within 2·5 years of recruitment.

Interventions at subsequent screening rounds

After the first screening round was concluded, study participants were invited for further screening rounds...
within the organised programmes, at the routine interval (5 years in the Netherlands and 3 years in Italy, Sweden, and the UK). In NTCC and Swedescreen, women from both the control and experimental arms had cytology-based screening—ie, no further HPV testing was done. In POBASCAM, all individuals had HPV screening and conventional cytology at the second round, according to the procedure in the experimental arm at round one (47% of women were tested for HPV, with no difference recorded between control and experimental arms); thereafter, women underwent routine cytology-based screening. In ARTISTIC, at round two, women from each arm continued screening as in round one, and thereafter they had routine cytology-based screening.

Case ascertainment and validation

Our primary endpoint was invasive carcinoma of the cervix. We did not consider CIN, non-epithelial cervical cancers, and cancers at other sites. Potential cases of invasive cervical cancer arising during follow-up were identified in several ways, depending on the patient’s location (appendix pp 1–4). Cervical carcinomas were classified by morphological features—if possible, as squamous-cell carcinoma or adenocarcinoma (including adenosquamous)—and by FIGO (International Federation of Gynecology and Obstetrics) stage (IA vs >IA).

In Sweden (Swedescreen), cases were ascertained by linkage to the National Quality Registry for Cervical Screening, which contains a copy of cytology and histopathology reports from all laboratories in Sweden (both from organised screening and opportunistic testing), regional screening registries, and the National Cancer Registry. In the Netherlands (POBASCAM), cases of invasive cervical cancer were found by linkage to the PALGA archive, which contains a copy of all cytology and histopathology reports from organised screening and opportunistic testing. In Italy (NTCC), cases were identified from the computerised systems of participating screening centres and by linkage to local cancer and pathology registry databases. In the UK (ARTISTIC), cases of invasive cervical cancer were established by linkage to two local pathology units and the national cancer registration database.

In Swedescreen, original diagnostic slides and reports of potential cancer cases were reviewed by a pathologist who was unaware of the random allocation and HPV and cytology status. In NTCC, all histological slides from women with an original diagnosis of CIN1 or higher who were identified from screening registries were requested for review by a group of pathologists unaware of randomisation, HPV and cytology status, and the original histological diagnosis. In POBASCAM, all histological slides from women with an original diagnosis of CIN1 or more, who were identified from PALGA, were requested for review by a group of pathologists who were masked to randomisation, HPV status, and cytology result.

- **NTCC**
  - HPV-based
  - Cytology-based
  - Eligible, consented and randomly assigned: 47,369 (22,708 during phase 1 and 24,661 during phase 2)
  - Tested at baseline: 46,680 (68% incomplete or conventional management)
  - Tested between 2–5 years after recruitment and end of follow-up: 34,358 (73%)
  - Followed up and included in analysis: 47,369

- **POBASCAM**
  - HPV-based
  - Cytology-based
  - Eligible, consented and randomly assigned: 47,001 (22,466 during phase 1 and 24,535 during phase 2)
  - Tested at baseline: 46,149 (852 no testing or just unsatisfactory)
  - Tested between 2–5 years after recruitment and end of follow-up: 21,996 (201 had no valid sample for HPV testing and were excluded from follow-up)
  - Followed up and included in analysis: 47,001

- **Swedescreen**
  - HPV-based
  - Cytology-based
  - Eligible, consented and randomly assigned: 62,577
  - Tested at baseline: 62,388 completeds baseline testing
  - Tested between 2–5 years after recruitment and end of follow-up: 17,369 (78%)
  - Followed up and included in analysis: 62,571

- **ARTISTIC**
  - HPV-based
  - Cytology-based
  - Eligible, consented and randomly assigned: 18,816
  - Tested at baseline: 18,386
  - Tested between 2–5 years after recruitment and end of follow-up: 14,192 (75%) [13,691 for HPV]
  - Followed up and included in analysis: 18,386

Figure 1: Trial profiles

In ARTISTIC, all pathology reports—and slides from cases with an equivocal report—were reviewed.

Statistical analysis
We analysed individual data by intention to screen. Every woman contributed years of observation from recruitment to end of follow-up, cancer detection, death, or migration, whichever occurred first. Dates for migration and death were not available for POBASCAM. In the other studies, 1-6% of years of observation were censored for these reasons. Further analyses restricted to women with a negative test at entry were censored 2·5 years after detection of CIN2 or CIN3, if any.

We calculated the cumulative incidence of invasive cervical cancer in each study arm using the Kaplan-Meier method, for all randomised women from enrolment to end of observation and for women who were HPV-negative at entry in the HPV arm and who were cytology-negative at entry in the cytology arm. Because of the 3:1 randomisation ratio used in the ARTISTIC trial, but not in the other studies, the crude pooled Kaplan-Meier estimate could be biased. Therefore, in the Kaplan-Meier analysis, we multiplied the numbers of cancers and women at risk in the ARTISTIC trial by 0·5 in the HPV arm and 1·5 in the cytology arm. We adjusted Greenwood’s formula accordingly to calculate variance, and we calculated 95% CIs for a binomial proportion with the same value and variance. Curves are plotted until the 75th percentile of the distribution of observation times. All p values are two-sided.

We calculated the overall study-adjusted (unweighted) invasive cervical cancer detection rate ratio in the experimental arm versus the control arm, considering studies as fixed effects. We included all randomised women from enrolment to the end of observation and separately for the period from enrolment to 2·5 years thereafter (prevalence screen, roughly including the first primary test and related procedures, which could have led to detection of cancers prevalent at enrolment) and for the subsequent period. We also restricted analyses to women who were HPV-negative at entry in the experimental arm and those who were cytology-negative at entry in the control arm. When no invasive cervical cancer was recorded, 0·5 cases were added in the analysis. We assessed heterogeneity among studies with the χ² test and P statistic. We also calculated rate ratios for the entire observation period for all randomised women according to cancer morphology, stage, and age group (<30, 30–34, 35–49, and ≥50 years) at recruitment. Finally, we calculated the rate ratio of the proportion of women who had at least one biopsy procedure, as a measure of extent of diagnostic procedures.

Role of the funding source
The sponsor had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study, and GR had final responsibility for the decision to submit for publication.

Results
Figure 1 shows the trial profiles for the four randomised controlled trials, and table 1 summarises the main features of every study. Overall, 176 464 women were enrolled. Median age at recruitment was identical in both arms within every study (41 years for NTCC and

| Target age at recruitment (years) | 32–38 | 29–61 | 20–64 | 25–60 |
| Randomisation ratio (experimental vs control) | 1:1 | 1:1 | 3:1 | 1:1 |
| Primary test in the experimental arm | HPV (GP5+/GP6+ PCR) and conventional cytology | HPV (GP5+/GP6+ PCR) and conventional cytology | HPV (hybrid capture 2) and liquid-based cytology | Phase 1. HPV (hybrid capture 2) and liquid-based cytology |
| Primary test in the control arm | Conventional cytology | Conventional cytology | Liquid-based cytology | Conventional cytology |
| Tests in secondary and later screening rounds | In both arms: conventional cytology | At round 2 in both arms: HPV (GP5+/GP6+ PCR) and conventional cytology | At round 2 in both arms: conventional cytology with primary test | At round ≥3 in both arms: cytology |
| Management of HPV positive women | Cytological triage* | Cytological triage* | Cytological triage* | Colposcopy (in phase 2 and in women ≥25 years old in phase 1) Cytological triage* (in women aged 25–34 years in phase 1) |
| Screening interval for women with negative result (years) | 3 | 5 | 3 | 3 |

*If cytology was negative, HPV positive women were invited for repeat HPV testing, then colposcopy if infection persisted. If cytology was positive, women were referred immediately for colposcopy. This approach was denoted cytological triage.

Table 1: Main features of the four randomised controlled trials
POBASCAM, 39 years for ARTISTIC, and 35 years for Swedescreen). The proportion of women with further screening beyond 2.5 years after recruitment was similar in both arms within every study, ranging from 71% in NTCC to 95% in Swedescreen. Of women whose first cervical screening test was negative (and who were expected to follow the same protocol thereafter), the average number of subsequent tests was similar between arms in POBASCAM (1.13 in both) and ARTISTIC (1.20 in both), but it was slightly higher in the cytology arm in NTCC (1.05 vs 0.71) and Swedescreen (2.93 vs 2.81).

Women were followed up for a total of 1,214,415 person-years (median 6.5 years). In total, 107 invasive cervical carcinomas were detected (Table 2). In Swedescreen, of 20 potential cases reviewed, 12 were confirmed as invasive cervical carcinoma (appendix p 1). One case in the cancer registry with no diagnostic slide and two cases with diagnostic slides but not accepted as cases by the cancer registry were excluded. In NTCC, of 43 potential invasive

<table>
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<th>Invasive cell carcinomas (n)</th>
<th>Total person-years</th>
<th>Median follow-up (years)</th>
<th>Time from enrolment</th>
<th>Age at enrolment (years)</th>
<th>Women with a negative test at entry†</th>
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Data are number of cases/person-years, unless otherwise stated. AC=adenocarcinoma. CIN=cervical intraepithelial neoplasia. SCC=squamous-cell carcinoma. *In ARTISTIC, stage not available for four cases in HPV arm. †Observations are censored 2.5 years after CIN2 or CIN3, if any. ‡Women younger than 30 years at enrolment were excluded from the analysis. §Data not usable to compare arms because of different randomisation ratios in studies.

Table 2: Cases of invasive cervical carcinoma, number of person-years, and median duration of follow-up

![Figure 2: Cumulative detection of invasive cervical carcinoma](image-url)

*Observations are censored 2.5 years after CIN2 or CIN3 detection, if any.
cases initially identified, 23 had the original slide reviewed (17 confirmed); the original reports of the remaining 20 cases were obtained (13 confirmed). Three cases originally diagnosed as CIN were reclassified as invasive cervical cancer during masked review of slides (appendix p 2). In POBASCAM, of 40 potential cases of invasive cervical cancer, the slide was reviewed for 36 and the original report for four. One case was downgraded to CIN3, but one CIN3, seven in-situ adenocarcinomas, and one endometrioid carcinoma were reclassified as invasive carcinoma of the cervix (appendix p 3). In ARTISTIC, 18 potential invasive cases were identified. Slides were examined for four cases with equivocal reports. Overall, 14 were confirmed as invasive cervical cancer (appendix p 4).

When considering all randomised women, cumulative detection of invasive cervical carcinoma was similar in both arms up to about 2 years from enrolment, but diverged thereafter, reaching 46·7 per 10⁵ (95% CI 32·1–65·5) in the experimental arm and 93·6 per 10⁵ (70·5–121·8) in the control arm 8 years after enrolment (figure 2). The corresponding overall rate ratio was 0·60 (95% CI 0·40–0·89; table 3). No evidence of heterogeneity was noted between studies (p=0·52), and a random-effects model gave an almost identical estimate (0·61, 0·41–0·91). Detection of invasive cancers of the cervix did not differ significantly between the two arms during the prevalence screen up to 2·5 years from enrolment (0·79, 0·46–1·36), but was significantly lower in the experimental arm thereafter (0·45, 0·25–0·81; table 3). 11 of 19 cancers detected in the experimental arm during follow-up were HPV-positive at baseline. Within 2·5 years of recruitment, ten of them had not undergone biopsy and one biopsy showed CIN1.

The study-adjusted rate ratio after a negative test on entry (cytology-negative in the control arm and HPV-negative in the experimental arm) was 0·30 (0·15–0·60; table 3). No heterogeneity was noted between studies (p=0·23), and the random-effects model estimate was almost identical (0·34, 0·14–0·86). Cumulative incidence of invasive cervical cancer was 15·4 per 10⁵ (95% CI 7·9–27·0) and 36·0 per 10⁵ (23·2–53·5), respectively, 3·5 and 5·5 years after a negative cytology test on entry versus 4·6 per 10⁵ (1·1–12·1) and 8·7 per 10⁵ (3·3–18·6), respectively, 3·5 and 5·5 years after a negative HPV test on entry (figure 2).

The proportion of adenocarcinomas fell by age: 40% in women younger than 30 years, 35% in those aged 30–34 years, 30% in women age 35–49 years, and 23% in those 50 years or older. When we pooled data for women in the overall study period, we recorded a lower study-adjusted rate ratio for adenocarcinoma than for squamous-cell carcinoma, whereas rate ratios were similar for cancers of all stages (table 4). Considering age at enrolment, the lowest rate ratio (0·36, 95% CI 0·14–0·94) was noted in women aged 30–34 years.
Identification of invasive cervical cancers was based on linkage with population-based registries, to also include symptomatic invasive cancers of the cervix and those detected by opportunistic screening. Reports and, in most cases, histological specimens were reviewed by pathologists who were unaware of the random allocation and screening test status. The intensity of screening could have affected cancer prevention in women with a negative screening result at entry, but subsequent testing was most intense in the control arm. In POBASCAM, all women were invited for HPV-based screening at the second round, and almost half attended, so a reduced difference between arms was expected thereafter. Indeed, nine of ten invasive cervical cancers diagnosed over 6 years after recruitment had not been tested for HPV at round two.

We studied all women recruited in the four population-based randomised controlled trials for whom information was available from at least two screening rounds. The studies used different screening protocols, in particular for directly referring HPV-positive women to colposcopy.

**Discussion**

Our pooled analysis of four randomised controlled trials of HPV-based cervical screening versus conventional cytology showed a significant reduction in invasive cervical cancers in women who had HPV-based screening. When all randomised women and all cancers diagnosed from enrolment—including cases already present (prevalent)—were considered, detection of invasive cervical carcinomas was significantly lower with HPV-based testing. Data obtained at enrolment are essential to prove that HPV-based screening provides greater protection for prevention of cervical carcinoma. A reduction in the number of invasive cancers at second or later screens could simply be attributable to earlier diagnosis of invasive cervical cancer by HPV testing at the first (prevalence) screen (panel). In such a case, we would expect cancer detection to be higher in the experimental arm in the first 2–5 years, because this period mainly includes prevalent cases. In our analysis, however, rates noted in the first 2.5 years were similar in the experimental and control arms. Therefore, the best estimate for the gain in reducing incidence of invasive cervical cancers—ie, the true gain in efficacy—by HPV-based screening is provided by the rate ratio recorded after 2–5 years (0.45), particularly among women with a negative screening test at baseline (0–30), which essentially excludes prevalent cases.

Asymptomatic prevalent cancers were identified by different tests in the two arms. However, because cancer detection at the first (prevalence) screen was similar in the two arms, this factor could not have affected our estimate of the true gain with HPV screening. If anything, a non-significant, slightly lower rate of detection of prevalent cancers was recorded in the experimental arm, which could have underestimated the true reduction in incidence with HPV screening. Moreover, the gain could be larger in settings in which the quality of cytology is lower.

A similar gain in efficacy was recorded with HPV testing for prevention of microinvasive and frankly invasive cancers, which have worse prognosis and greater effect on quality of life. The larger gain noted for adenocarcinoma compared with squamous-cell carcinoma accords with the known lower efficacy for detection of adenocarcinoma by cytological screening.22,23
or triaging them by cytology and for using stand-alone HPV or cotesting (HPV and cytology). The pooled efficacy of HPV-based screening that we report represents an average (weighted by precision) of the effects of such procedures. We previously noted that such procedures resulted in a reduction of CIN3 or higher grades at the second screening round in women undergoing HPV-based screening compared with cytology, which was similar in all four trials, suggesting comparable lead-time gain. Therefore, we had strong reason to expect comparable efficacy. We recorded no differences in efficacy between studies, with consistently lower overall detection rates of invasive cervical cancer in the experimental arm. These findings suggest that the gain over cytology of using or not using primary HPV testing is much larger than the variability in efficacy, if any, between different HPV-based screening protocols.

The dissimilar protocols resulted, however, in very different costs. In particular, in the studies that used cytological triage, the biopsy rate was not increased in the experimental arm whereas it was doubled with direct referral of all HPV-positive women for colposcopy (in NTCC). This finding supports the use of triage. Because cotesting leads to many unnecessary colposcopy referrals of all HPV-positive women for colposcopy (in NTCC). This finding supports the use of triage. Because cotesting leads to many unnecessary colposcopy procedures, stand-alone HPV testing also seems recommendable.

Findings of a randomised controlled trial from Finland showed no reduction in detection of invasive cervical cancer in the experimental arm during the first screening round. The researchers suggested that their follow-up period (average 3–6 years when 5-year screening intervals were used) might have been too short, because many invasive cancers of the cervix are screen-detected at subsequent rounds, which was indeed the case in our study. Since the Finnish study had augmented detection rates for CIN3 and higher grades with HPV testing versus cytology in the first screening round, similar to other studies, a comparable effect on cancer incidence with long-term follow-up is expected.

Our results show that at age 30–34 years, the gain in efficacy with HPV testing is at least similar to, and possibly larger than, that achieved in older women. Possible explanations for this finding are the increased proportion of adenocarcinomas in younger age groups in our pooled data or faster progression to cancer from CIN undetectable by cytology in younger women compared with older women. Moreover, low efficacy of cytology has been noted in young women. Data from NTCC suggested overdiagnosis of regressive CIN with HPV screening at age 25–34 years, implying that we should be cautious when screening young women in this way. Overdiagnosis was not noted in POBASCAM at age 30–33 years. Independent of the reasons for such a discrepancy, our pooled data suggest a relevant gain in efficacy with HPV testing, starting from age 30 years (data at younger ages are too sparse to draw conclusions).

The recorded cumulative incidence of cervical cancer was lower 5–5 years after a negative HPV test than 3–5 years after a negative cytology result, indicating that 5-year intervals for HPV screening are safer than 3-year intervals for cytology. With HPV testing, short screening intervals are expected to result in low specificity, because recently acquired infections are mostly transient, and possibly in overdiagnosis of regressive CIN. These situations can be avoided by extending the interval between screens. HPV screening every 5 years could reduce the number of unnecessary colposcopy and biopsy procedures compared with more frequent cytology, possibly also cutting costs.

In conclusion, data from follow-up analysis of four large randomised cohorts show that HPV-based cervical screening provides 60–70% greater protection against invasive cancer compared with cytology-based screening. Prevention of cancer in young women is a priority; our findings support HPV-based screening with triage at prolonged intervals, starting at age 30 years.

**Contributors**

GR, JD, JP, JB, CJLMM, and PG-R had the idea for and designed the study. KME, CG, JB, and ST updated follow-up data and provided them in a standardised format. ST did statistical analyses under the guidance of GR, JP, JD, and JB. GR, CJLMM, JD, PJFS, JB, HK, MA, NS, PG-R, and JP contributed to interpretation of data. GR and JD wrote the report. All authors critically revised the report.

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**Conflicts of interest**

CJLMM has been a member of the scientific advisory board of Qiagen, has received speaker’s fees from GlaxoSmithKline, Merck, and Roche, and is a shareholder of Self-Screen, a spin-off company from the VU University Medical Centre. His institution has received consultancy fees from Qiagen. PJFS has been an advisory board member for Gen-Probe, Roche, and GlaxoSmithKline and is a shareholder of Self-Screen. JB has received speaker’s fees from Qiagen and has received an advisory fee from GlaxoSmithKline. All other authors declare that they have no conflicts of interest.

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References

Embracing a new era in cervical cancer screening

Despite its low sensitivity, conventional cytology for cervical cancer (the Papanicolaou test) is one of the most successful cancer screening tests of all time. In countries with high-quality and broad-coverage screening programmes using this test, invasive cervical cancer incidence and mortality rates have plummeted. Why change a good thing?

After human papillomavirus (HPV) was identified as a cause of invasive cervical cancer, HPV DNA testing was developed to screen for the disease. Molecular techniques are better than cervical cytology with respect to diagnostic sensitivity and reproducibility to detect cervical intraepithelial neoplasia grade 2 (CIN2) or grade 3 (CIN3)—the high-grade lesion precursors of invasive cervical cancer.1 However, to be better at detecting these intermediate endpoints is not enough. Treatment of screen-detected lesions by ablative or excisional procedures must also stop the natural history of invasive cervical cancer and reduce incidence of and mortality from the disease.

Findings of randomised controlled trials need to show that HPV testing is more efficacious than cytology-based testing for prevention of subsequent invasive cervical cancer and related death. Up to now, such proof of the value of HPV testing has only been recorded in a population in rural India that did not benefit from routine high-quality screening.2 Moreover, most randomised controlled trials of cervical screening have taken place in developed countries, where cytological screening has long been practised and invasive cervical cancer morbidity and mortality are low. As a result, detection of CIN2 and CIN3 is mainly reported as the predefined study endpoint.3 Since most CIN2 and CIN3 lesions never become invasive or lead to death from cervical cancer, further evidence is needed about these vitally important, longitudinal outcomes before updated recommendations can be made about HPV-based screening.3,4

In The Lancet, Guglielmo Ronco and colleagues5 pool individual-level data from four European randomised trials comparing HPV-based with cytology-based cervical cancer screening. In Swedescreen,6 POBASCAM,7,8 ARTISTIC,9 and NTCC10 more than 175 000 women were randomised in total and accrued second-round screening outcomes. Linkage to screening, pathology, and cancer registries permitted Ronco and colleagues to extend follow-up of these enrolled women. HPV-based screening resulted in a 60–70% reduction in invasive cervical cancer incidence, compared with cytology-based screening. The decrease in incidence of invasive cervical cancer with HPV testing was not significant within 2·5 years of enrolment (rate ratio 0·79, 95% CI 0·46–1·36) but the effect became decisive with longer follow-up (0·45, 0·25–0·81).

These findings highlight the opportunity that HPV testing affords to permit enhanced detection of CIN2 and CIN3 in screened women, therefore enabling early treatment and reduction of invasive cervical cancer risk. However, the most important property of HPV-based screening is the safety it brings to most women who have a negative HPV test. Ronco and colleagues showed that the observed cumulative incidence of invasive cervical cancer was lower 5·5 years after a negative HPV test than 3·5 years after a negative cytology test, indicating that 5-year screen intervals with HPV-based testing are safer than 3-year intervals with conventional cytology.

Despite various differences in study features among the four randomised controlled trials, particularly with respect to management protocols triggered by test results, Ronco and colleagues noted very little heterogeneity between trials, with consistently lower overall detection of invasive cervical cancer in HPV-screened groups. This finding seems to indicate that the effect of HPV-based screening on invasive cervical cancer incidence is much larger than any potential effect
of differing management protocols from the trials. As shown by this work, sound meta-analytical pooling of data can provide more insightful, powerful, and precise estimates of an effect of interest than can be otherwise obtained, to inform future policy and practice.

The future of cervical cancer screening in high-resource settings will most probably incorporate primary HPV testing, a science-driven change in strategy that particularly befits the post-HPV vaccination era. With economies of scale that come with broad implementation of primary HPV testing (which will foster competition among various HPV tests) and the lengthening of screen intervals, cervical cancer screening might end up costing countries less money while providing greater safety than with conventional cervical cytology. To reap the benefits of this implementation, however, nations will need to consider important logistical challenges, including: settling on the type of HPV screening test to be used; ascertaining appropriate screening ages and intervals; defining triage and management policies for HPV-positive women; and ensuring quality of and adherence to revised policies.

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