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Safety of extending screening intervals beyond five years in cervical screening programmes with testing for high risk human papillomavirus: 14 year follow-up of population based randomised cohort in the Netherlands

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ABSTRACT

OBJECTIVES

To provide an early risk assessment of extending screening intervals beyond five years for a human papillomavirus (HPV) based cervical screening programme in the Netherlands.

DESIGN

14 year follow-up of a population based randomised cohort from the POBASCAM randomised trial.

SETTING

Organised cervical screening in the Netherlands, based on a programme of three screening rounds (each round done every five years).

PARTICIPANTS

43 339 women aged 29-61 years with a negative HPV and/or negative cytology test participating in the POBASCAM trial.

INTERVENTIONS

Women randomly assigned to HPV and cytology co-testing (intervention) or cytology testing only (control), and managed accordingly.

MAIN OUTCOME MEASURES

Cumulative incidence of cervical cancer and cervical intraepithelial neoplasia (CIN) grade 3 or worse (CIN3+). Associations with age were expressed as incidence rate ratios. In HPV positive women, reductions in CIN3+ incidence after negative cytology, HPV type 16/18 genotyping, and/or repeat cytology were estimated.

RESULTS

The cumulative incidence of cervical cancer (0.09%) and CIN3+ (0.56%) among HPV negative women in the intervention group after three rounds of screening were similar to the cumulative among women with negative cytology in the control group after two rounds (0.09% and 0.69%, respectively). Cervical cancer and CIN3+ risk ratios were 0.97 (95% confidence interval 0.41 to 2.31, P=0.95) and 0.82 (0.62 to 1.09, P=0.17), respectively. CIN3+ incidence was 72.2% (95% confidence interval 61.6% to 79.9%, P<0.001) lower among HPV negative women aged at least 40 years than among younger women. No significant association between cervical cancer incidence and age could be demonstrated. CIN3+ incidence among HPV positive women with negative cytology, HPV 16/18 genotyping, and/or repeat cytology was 10.4 (95% confidence interval 5.9 to 18.4) times higher than among HPV negative women.

CONCLUSIONS

Long term incidences of cervical cancer and CIN3+ were low among HPV negative women in this study cohort, and supports an extension of the cervical screening interval beyond five years for women aged 40 years and older. HPV positive women with subsequent negative cytology, HPV16/18 genotyping, and/or repeat cytology have at least a fivefold higher risk of CIN3+ than HPV negative women, indicating that HPV based programmes with long intervals (>five years) should be implemented with risk stratification.

TRIAL REGISTRATION

POBASCAM trial number ISRCTN20781131.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Randomised controlled trials have shown that cervical screening with primary human papillomavirus (HPV) testing or combined HPV and cytology testing leads to earlier detection of cervical intraepithelial neoplasia (CIN) grade 3 than cytology screening and provides a better protection against cervical cancer

Evidence on the safety of screening intervals beyond five years is limited

For HPV negative women aged 40 years and older in the Netherlands, screening intervals in the HPV based screening programme will be increased from five years to 10 years in 2017

WHAT THIS STUDY ADDS

Cumulative incidence of cervical cancer and CIN3+ among HPV negative women after three screening rounds at five year intervals was similar to the corresponding cumulative incidence among cytology negative women after two screening rounds

HPV based programmes with long screening intervals (at least five years) should be implemented with risk stratification, because HPV positive women with subsequent negative cytology, genotyping for HPV 16/18 subtypes, and/or repeat cytology have at least a fivefold higher risk of CIN3+ than HPV negative women

Age dependent screening intervals are supported by CIN3+ risk estimates but data on cervical cancer risk are inconclusive

Introduction

Randomised controlled clinical trials have shown that screening for high risk human papillomavirus (HPV) leads to earlier detection of cervical intraepithelial neoplasia (CIN) grade 3 or worse (CIN3+) than cytology,[1-4] and provides better protection against cervical cancer.[5-10] Primary HPV testing shows positive results more often than primary cytology testing in the general screening population, and subsequent triage testing of HPV positive women (by use of cytology and of genotyping of HPV subtypes 16 and 18) has been recommended to avoid over-referral to colposcopy and overuse of biopsies.[8 11-15] The screening programme

could be further improved by reducing the number of screening rounds. Separately defined screening intervals have been suggested for women who are HPV negative and women initially HPV positive with negative triage tests, because they have substantially different risks of CIN3+.[1 16-18] However, stratification of screened women on the basis of their HPV (DNA) test result will add to the complexity of the programme and should be supported by evidence from longitudinal studies.

Several countries have decided or recommended to implement HPV screening as the primary screening test (Australia, Italy, Netherlands, New Zealand, Sweden, and the UK) or in combination with cytology (USA). In those countries screening women every two to three years, the interval will be extended to five or seven years. In the Netherlands, the screening interval for HPV negative women aged 40 years or more will be extended from five to 10 years; this extension is based on predictions from cost effectiveness models.[19 20] However, there remains a concern about an increase in the number of interval cancers;[21] hence, policy decisions should also be supported by estimated incidence of long term cervical cancer and precancer (CIN3+ risk) when available.

We assessed 14 year risks of histologically confirmed cervicalcancer and CIN3+ in women aged 29 years and older who participated in the POBASCAM (population based screening study Amsterdam) randomised controlled trial.[5] A follow-up of 14 years comprises three screens: at baseline, and after five and 10 years. Women were randomly assigned to receive both HPV and cytology testing (intervention), or cytology testing only (control). We aimed to compare cervicalcancer and CIN3+ incidence among HPV negative women in the intervention group and cytology negative women in the control group, and to evaluate the safety of extending the screening interval beyond five years in women who are HPV negative and in women who are HPV positive and triage negative.

Methods

Study population

The POBASCAM study design has been published previously.[1 5 15 22] In summary, women aged between 29 and 61 years were invited to participate in cervical screening from January 1999 to September 2002. They were randomised either to the intervention group (cytology and HPV co-testing) or the control group (cytology with blinded HPV testing). Of 44 938 women enrolled, 22 420 were randomised to the intervention group and 22 518 to the control group (fig 1).

In the intervention group, women who had negative results for both HPV and cytology co-testing (that is, double negative) were referred to routine screening every five years. Women with moderate dyskaryosis or worse cytology (comparable to cytology worse than atypical squamous cells of undetermined significance or low grade squamous intraepithelial lesions) were directly referred for colposcopy. HPV positive women with negative cytology and women with borderline or mild dyskaryosis cytology (comparable to atypical squamous cells of undetermined significance or low-grade squamous intraepithelial lesions) were advised to repeat both HPV and cytology testing at six and 18 months. These women were referred for colposcopy if they were HPV positive or if their cytology result showed moderate dyskaryosis or worse.

In the control group, women with negative cytology were referred to routine screening and women with moderate dyskaryosis or worse were immediately referred for colposcopy. Women with borderline or mild dyskaryosis cytology were advised to repeat cytology at six and 18 months, and were referred to colposcopy if their repeat cytology result showed borderline dyskaryosis or worse.

At the second screening round at five years, participants in both study groups were managed according to the protocol of the intervention group. At the third screening round at 10 years, participants in both study groups were managed according to the protocol of the control group.

A conventional cervical smear test was prepared on a glass slide after which the brush was placed in a vial for HPV testing (general primer 5+/6+ polymerase chain reaction enzyme immunoassay).[22 23] Cytology and HPV testing were performed without knowledge of the other test result. HPV positive samples were genotyped by a previously published reverse line blot assay.[24]

Study participants of the POBASCAM trial were enrolled by their general practitioner when attending the nationwide screening programme, and provided written informed consent. The general practitioners were invited to attend postgraduate medical education courses to best inform the study participants.

Histology

We tracked histological follow-up data through the nationwide network and registry of histopathology and cytopathology (PALGA).[25] Histology was examined locally and classified as no dysplasia; CIN grades 1, 2, or 3; or invasive cervical cancer according to international criteria.[26] We included adenocarcinoma in situ in the CIN3 group. Treatment by loop electrosurgical excision procedure was recommended after CIN2 or CIN3, whereas cervical cancer was treated depending on cancer stage and according to national guidelines.

Statistical analysis

We included women from the intervention and control group with a negative HPV test or negative cytology. Follow-up data were collected until July 2013, at which point all women had had the opportunity of three rounds of five year screening. Events occurring after 14 years were excluded because they are likely to be detected at the fourth screen after baseline. The censoring date was brought forward to the date when an interrupting event had occurred (eg, CIN2+ excision or uterus extirpation). If no screening test results had been reported at the third screen, the censoring date was brought forward to nine years after the study entry date. If no screening test results had been reported at the second or the third screen, the censoring date was brought

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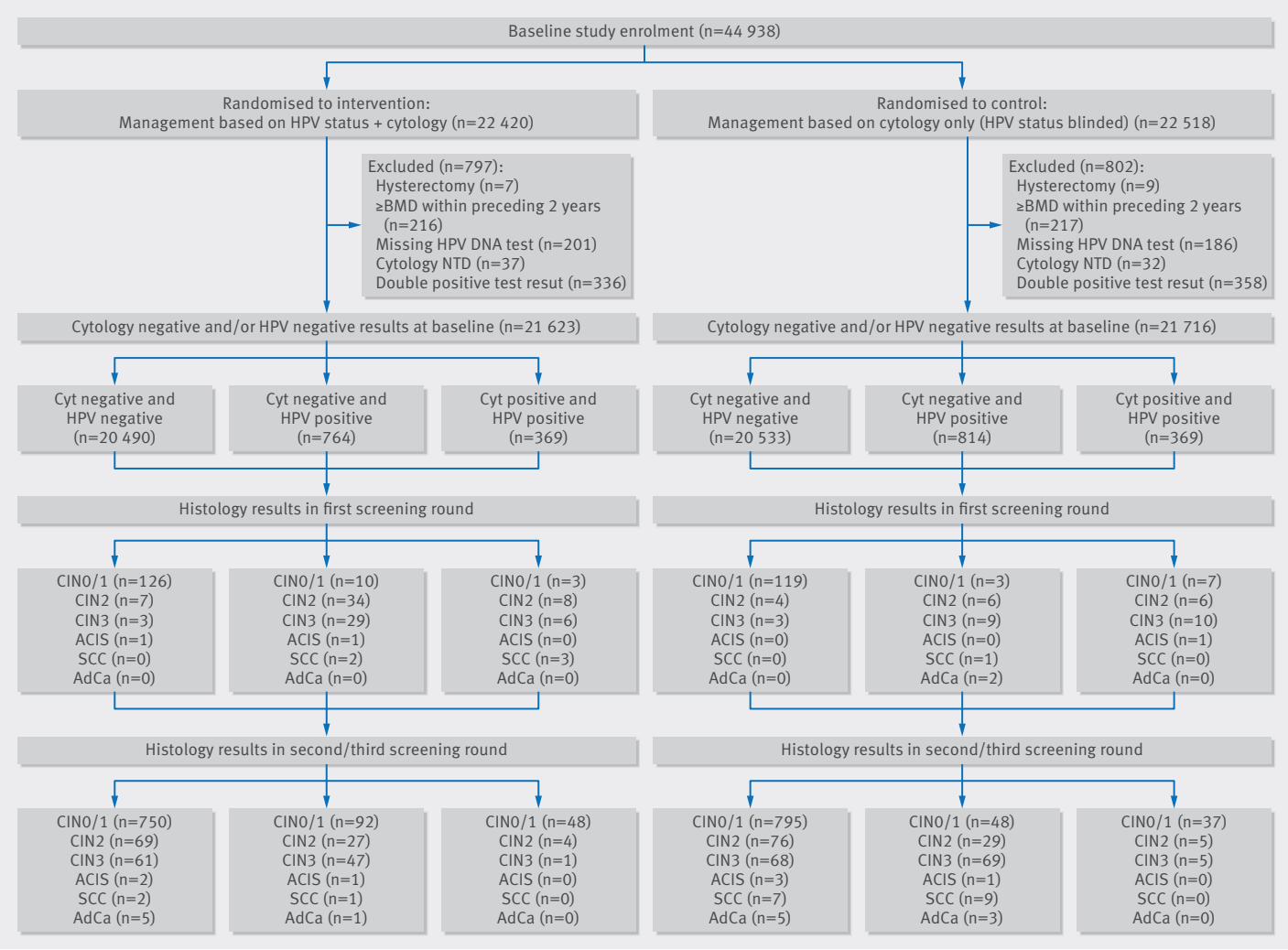

Fig 1 | **Overview of the POBASCAM study cohort with 14 year follow-up, including histology results in all three screening rounds. ACIS=adenocarcinoma in situ; AdCa=adenocarcinoma; ≥BMD=borderline or mild dyskaryosis or worse; CIN0/1=no dysplasia or cervical intraepithelial neoplasia grade 1; CIN2/3=cervical intraepithelial neoplasia grade 2 or 3; Cyt=cytology; HPV=human papillomavirus; cytology NTD=cytology results could not be determined; SCC=squamous cell carcinoma**

forward to four years. We did statistical analyses in SPSS Statistics for Windows version 20.0 and Stata Statistical Software release 11.

We used Kaplan-Meier methods to estimate the cumulative incidence of cervical cancer and CIN3+. Separate estimates were reported for HPV and cytology groups combined, from the intervention and control group. Cytology was labelled positive if the result was borderline dyskaryosis or worse (that is, atypical squamous cells of undetermined significance or low grade squamous intraepithelial lesions or worse), and labelled negative otherwise. Cervical cancer and CIN3+ incidence was also reported. We evaluated subgroup differences between cumulative incidence curves by log-rank testing and differences between incidences and between cumulative incidences at specific follow-up times by Wald testing. We constructed 95% confidence intervals using the normal approximation to the distribution of the logarithm of the incidence.

To determine the level of reassurance from a negative test result, we compared the cumulative incidences of cervical cancer and CIN3+ among HPV negative and double negative women from the intervention group with those among cytology negative women from the control group. Furthermore, because the new HPV based screening programme in the Netherlands involves an extension of the screening interval for women aged 40 years and older only, we studied the effect of age (≥40 *v* <40 years) on cervical cancer and CIN3+ incidence among HPV negative and double negative women. Because age specific incidence of cervical cancer and CIN3+ was similar in intervention and control groups (log rank test for the endpoints cancer and CIN3+, P>0.2), they were pooled over the two study groups.

Finally, in the intervention group, we compared the incidences of cervical cancer and CIN3+ among women with a negative HPV test with those among women with a HPV positive test and negative triage testing. We constructed four different triage algorithms by combining results for cytology at baseline, HPV 16/18 genotyping at baseline, and repeat cytology at six months. These

algorithms were identified in previous post hoc analyses and include the two time cytology triage algorithm (baseline and repeat cytology) that will be used in the new HPV based screening programme in the Netherlands.[13 15]

Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for recruitment, design, or implementation of the study. No patients were asked to advise on interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants or the relevant patient community. As described in the study protocol, women in the intervention group were informed about their HPV and cytology results. Women in the control group were only informed about their cytology results (regular screening).[22]

Results

The study included 43 339 women (fig 1). Of 21 623 women in the intervention group, 20 490 had double negative test results, 764 had negative cytology with a positive HPV result, and 369 had positive cytology with a negative HPV result. The control group included 21 716 women, of whom 20 533 had double negative test results, 814 had negative cytology with a positive HPV result, and 369 had positive cytology with a negative HPV result. The mean age was 42.8 years (range 29-61) in both study groups. Among women who were eligible for at least two screening rounds (based on their age), non-attendance in both the second and third screen after enrolment was 9.3% (1817/19 622) in the intervention group and 9.7% (1916/19 772) in the control group. Among women who participated at the second screen and were eligible for the third screen, non-attendance was 15.7% (2450/15 572) in the intervention group and 15.5% (2416/15 579) in the control group.

During 14 years of follow-up, 149 CIN2, 152 CIN3 (including five adenocarcinomas in situ), eight squamous cell carcinomas, and six adenocarcinomas were detected in the intervention group (fig 1). In the control group, 126 CIN2, 169 CIN3 (including five adenocarcinomas in situ), 17 squamous cell carcinomas, and 10 adenocarcinomas were detected. Table 1 shows incidence of cervical cancer and CIN3+ for the intervention and control groups, according to women with a negative cytology, negative HPV test result, or both at 14 year follow-up. Among women with negative cytology and a positive HPV test, the cancer incidence was significantly lower in the intervention group than the control group (rate ratio 0.29, 95% confidence interval 0.10 to 0.87, P=0.02). For the other cytology and HPV test groups, cancer incidence did not differ significantly between intervention and control group. CIN3+ incidence did not show a significant difference between the intervention and control group in any of the test groups.

Figure 2 shows cumulative incidence of cervical cancer and CIN3+ after two and three screens (corresponding to nine and 14 years after baseline, respectively). After the second and third screening round, cumulative cervical cancer incidence was 0.03% (95% confidence interval 0.01% to 0.06%) and 0.09% (0.04% to 0.18%) among HPV negative women from the intervention group, respectively. Corresponding values for the second and third rounds were 0.01% (95% confidence interval0.00% to 0.05%) and 0.07% (0.03% to 0.17%) among double negative women from the intervention group, and 0.09% (0.05% to 0.14%) and 0.19% (0.12% to 0.28%) among cytology negative women from the control group.

After the second and third screening rounds, cumulative CIN3+ incidence was 0.31% (95% confidence interval 0.24% to 0.41%) and 0.56% (0.45% to 0.70%) among HPV negative women from the intervention group, respectively. Corresponding values for the second and third rounds were 0.27% (95% confidence interval 0.20% to 0.36%) and 0.52% (0.41% to 0.66%) among double negative women from the intervention group, and 0.69% (0.58% to 0.82%) and 1.20% (1.01% to 1.37%), among cytology negative women from the control group.

After the third screening round, cervical cancer incidence among HPV negative and double negative women from the intervention group were similar to the cervical cancer incidence among cytology negative women from the control group after the second round (risk ratio 0.97 (95% confidence interval 0.41 to 2.31), P=0.95; 0.83 (0.32 to 2.15), P=0.69). This indicated that a negative HPV test provides longer reassurance against cervical cancer than negative cytology. After three

Table 1 | Incidence of cervical cancer and CIN3+ per study group, according to women with negative cytology or a negative HPV test result (or both) at 14 year follow-up*

	No of woman years		Count		Incidence per 100 000 woman years (95% CI)		Incidence ratio (95% CI; intervention *v* control)
	Intervention	Control	Intervention	Control	Intervention	Control	
Cancer							
Cytology negative/HPV negative	211 544	211 590	7	12	3.3 (1.6 to 6.9)	5.7 (3.2 to 10.0)	0.58 (0.23 to 1.48)
Cytology negative/HPV positive	7224	7859	4	15	55.4 (20.8 to 147.5)	190.9 (115.1 to 316.6)	0.29 (0.10 to 0.87)
Cytology positive/HPV negative	3764	3746	3	0	79.7 (25.7 to 247.1)	13.4† (0.8 to 213.4)	5.97† (0.30 to 119.22)
CIN3+							
Cytology negative/HPV negative	211 544	211 590	74	86	35.0 (27.9 to 43.9)	40.7 (32.9 to 50.2)	0.86 (0.63 to 1.17)
Cytology negative/HPV positive	7224	7859	82	94	1135.1 (914.2 to 1409.4)	1196.1 (977.2 to 1464.1)	0.95 (0.71 to 1.28)
Cytology positive/HPV negative	3764	3746	10	16	265.7 (143.0 to 493.8)	427.1 (261.7 to 697.2)	0.62 (0.28 to 1.37)

*Including only women with valid test results for both cytology and HPV testing.
†Cancer count 0 replaced by 0.5.

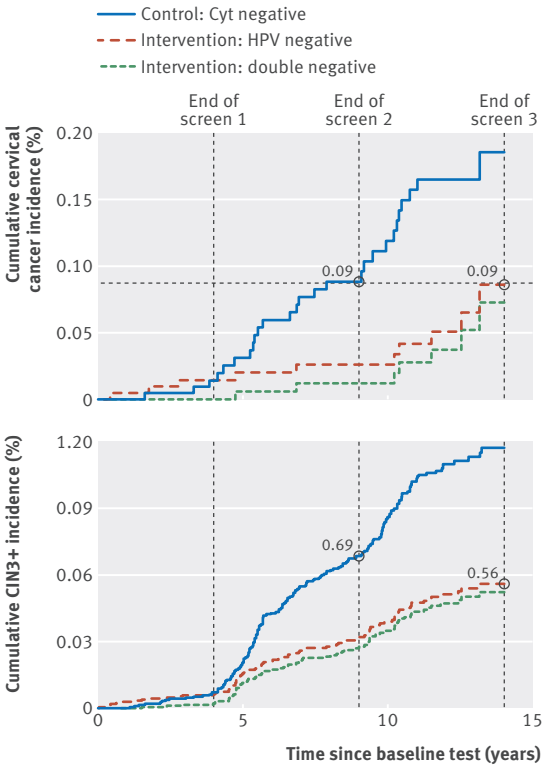

Fig 2 | Cumulative incidence of cervical cancer and CIN3+ per trial group and baseline screening result, after up to three screening rounds. Double negative=women who had negative results for both HPV and cytology testing; Cyt=cytology; HPV=human papillomavirus

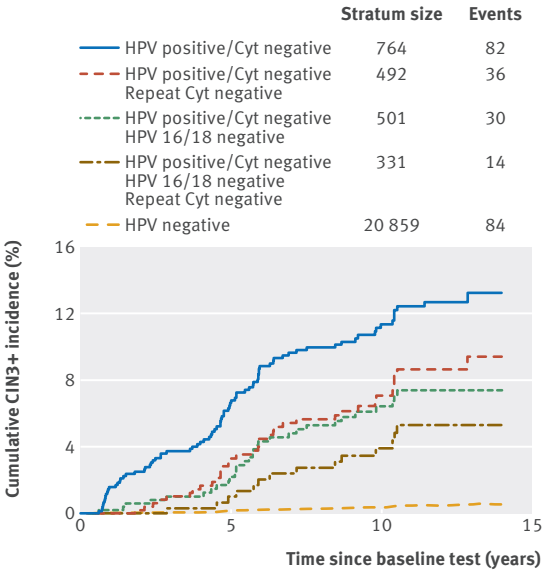

Fig 3 | Cumulative CIN3+ incidence following different triage strategies in the intervention group. Cyt=cytology; HPV=human papillomavirus

rounds of screening, CIN3+ incidence among HPV negative and double negative women from the intervention group was slightly lower than CIN3+ incidence among cytology negative women from the control group after the second round (risk ratio 0.82 (0.62 to 1.09), P=0.17; 0.76 (0.57 to 1.03), P=0.07).

Among women with double negative test results pooled over the intervention and control groups, cervical cancer incidence was 64.2% (95% confidence interval −37.6% to 332%) higher in women aged at least 40 years than in younger women, although this increase was not significant (P=0.32). The corresponding incidence of CIN3+ was 72.1% (60.5% to 80.4%) lower in women aged at least 40 years than in younger women (P<0.001). Similarly, among HPV negative women, cervical cancer incidence was 62.0% (−33.9% to 297%, P=0.29) higher in women aged at least 40 years than in younger women; CIN3+ incidence was 72.2% (61.6% to 79.9%, P<0.001) lower.

In the intervention group, cervical cancer incidence among HPV positive women with negative cytology triage was 11.9 (95% confidence interval3.7 to 38.1; P<0.001) times higher than among HPV negative women. When HPV 16/18 genotyping or repeat cytology was added as a triage test, only one cancer case was observed.

Cumulative CIN3+ incidence among HPV positive, triage negative women were substantially higher than among HPV negative women (P<0.001; fig 3). The fold increases in CIN3+ incidence, relative to the CIN3+ incidence after a negative HPV test, were 29.1 (95% confidence interval21.5 to 39.5) after a positive HPV and negative cytology test; 18.5 (12.5 to 27.3) after a positive HPV test and negative baseline and repeat cytology tests; 15.5 (10.2 to 23.5) after a positive HPV test and negative genotyping HPV 16/18 test; and 10.4 (5.9 to 18.4) after a positive HPV test, negative genotyping HPV 16/18 test, and negative baseline and repeat cytology tests.

Discussion

Principal findings

This study reports on 14 year follow-up data of a large population based screening cohort from the Dutch POBASCAM trial, with a five year screening interval, in which participants were managed on the basis of both cytology and HPV test results. Our findings on the long term protective effect of a HPV negative test are consistent with previously reported data.[4-6 8-10 16-18 27 28] Together, these publications indicate that HPV based screening provides significantly better protection against CIN3 than cytology based screening. Furthermore, compared with primary HPV testing, the value of primary HPV and cytology co-testing is limited. Our data also provide a long term confirmation of the protective effect against invasive cervical carcinomas, as previously described by Ronco and colleagues.[8]

Strengths and limitations of study

The major strengths of the current study are its large size, long follow-up, and wide age range of participants (29-61 years). The study was nested within a population based screening programme, indicating that results should be scalable to the country level.

A limitation to our study was that the presented incidence estimates of cervical cancer and CIN3+ were tracked through the nationwide histopathology and

cytopathology registry PALGA, which does not contain information on gynaecological procedures. Therefore, we were not able to assess how many cases were missed because women did not comply with the colposcopy advice.

The histological diagnoses were performed by local pathologists, which could have led to misclassification, resulting in a dilution of true differences between study groups. However, in earlier publications, we showed that interobserver reliability of CIN3+ was very high (absolute agreement 0.97).[5 22] The absolute cumulative CIN3 incidences presented in our study might also be influenced by the screening protocol, because the third screen after study entry uses cytology only, and thus women with newly developed CIN3 could have been missed.

Another limitation related to the time of cancer diagnosis. In order to compare cervical cancer risk after a negative HPV test in the intervention group at the third screening round with the risk after a negative cytology test in the control group at the second round, we included all cancers detected up to 14 and nine years after enrolment, respectively. These follow-up times are greater than the targeted screening times at 10 and five years, respectively, because of variation in the month of invitation, variation in the time between invitation and screening appointment, and conservative management of positive screening results. Regarding the management of positive screening results, only women with moderate or severe dyskaryosis cytology were immediately referred for colposcopy. Other women are reinvited for a cervical smear after six and 18 months. The adopted approach implicitly assumes that cervical cancers are present at the beginning of the screening round, but that some are detected with delay. However, a proportion of these cancers could have progressed during the screening round. To evaluate whether this altered our conclusions, we compared the cervical cancer risk after a negative HPV test in the intervention group at 10.5 years after baseline with the corresponding risk after a negative cytology test in the control group at 5.5 years after baseline. The estimates were 0.05% for both subgroups with a risk ratio of 0.94 (95% confidence interval 0.37 to 2.43, P=0.91), and are in accordance with our findings.

Comparison with other studies

Several other studies have also recommended extending the interval after a negative HPV test. Recently, Elfström and colleagues[18] reported on the potential of extending the screening interval with primary HPV based screening and recommended, based on CIN3+ risks, an extension of three to five years for Sweden. A similar analysis was provided after a six year follow-up of the ARTISTIC screening trial in the UK, which supported an extension of the interval from three to six years after a negative HPV test.[27] Ronco and colleagues[8] pooled data from four screening trials and recommended an extension of the screening interval to five years after negative HPV testing, replacing a cytological screening programme done every three years. In the USA, Katki and colleagues[17] recommended extending a screening interval from one year after negative cytology to three years after a negative HPV test and up to five years after a negative co-test. Both studies based their recommendations on estimated cancer risks. To summarise, recommendations are consistent in the different studies. Extensions to 10 years (as done in our analysis) have not yet been studied, because other countries used cytological based screening intervals of one to three years as a benchmark in their analyses.

Another conclusion that can be drawn from our data is that a long interval of 10 years is supported for only HPV negative women and not for HPV positive, triage negative women. The risks of cervical cancer and CIN3+ among HPV positive, triage negative women were at least five times higher than those among HPV negative women for all four triage strategies. Triaging distinguishes HPV positive women with and without underlying CIN3+,[13 15] but apparently does not offer additional reassurance against future CIN3 or cervical cancer over a longer period of follow-up. Another Dutch screening study, in which women were followed for five years, reached a similar conclusion.[29] In a US study evaluating the value of co-testing done every three years to identify women at high risk of CIN3+, researchers also concluded that HPV positive women with negative cytology accrued a substantial risk of CIN3+ over five years, and thus needed follow-up.[17]

Conclusions and policy implications

The current cytological based screening in the Netherlands has a five year interval that provides a cumulative five year risk of CIN3+ after a negative screen below 1%.[30] A screening interval of 10 years for HPV negative women aged at least 40 years will be incorporated in the new, primary, HPV based screening programme that will start in 2017.[21] Our data indicate that good safety for both cervical cancer and CIN3+ risk is provided by extending the interval from five to 10 years, because the risks after three screening rounds after a negative HPV test are similar to the risks after two rounds after negative cytology.

In the new HPV based screening programme in the Netherlands, the screening interval will only be extended among women aged at least 40 years. This age specific recommendation is partly supported by our data—the CIN3+ risk in women aged at least 40 years was estimated to be 72% lower than in younger women, but cervical cancer risks did not decrease with age. Despite our analyses, the risk of an increase in interval cancers remains a point of concern. Controlling both cervical cancer and CIN3+ risks is reassuring but an increase in the cancer risk cannot be ruled out completely as long as the interval has not actually been extended. Therefore, it remains important to closely monitor the number of interval cancers observed under the new HPV based screening programme.

The use of the HPV test result and age to define the year of next screen is a first step towards risk based screening. Tailoring screening to individual risks could improve screening efficiency and eventually provide

optimal prevention for all women. However, risk stratification also adds to the complexity of the programme, and it could become challenging to maintain a high quality screening programme.

An important prerequisite for a risk based programme is the availability of a linked digitalised screening registry and invitation system. Such a system is not yet in place in every country with an organised programme. However, linking of screening and invitation systems is recommendable,[31] since the benefits of risk based screening are expected to become even larger in the future. Individual cancer risks can then be based on information from multiple HPV screening rounds and vaccination status, yielding individual risk assessments that will strongly deviate from average risks. This will offer substantial room for further improvement of resource allocation in the healthcare system.

In summary, our results indicate that primary HPV screening provides better long term protection against cervical cancer than cytology testing. HPV negative women have a very low risk of CIN3+ in the long term, indicating that extension of the current screening interval in the Netherlands to 10 years seems justifiable. For HPV positive, triage negative women, the long term risk of CIN3+ was too high to support an extension of the screening interval beyond five years for any of the used triage strategies.

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Contributors: MGD and MvZ contributed equally to the paper and their names are in alphabetical order. CJLMM is principal investigator of the POBASCAM study, and CJLMM and JB led this follow-up study. MGD, LR, FJvK, TJMH, PJFS, and CJLMM were involved in data collection. MvZ and LR collected the clinical follow-up data. MvZ and JB analysed the data. LR managed the database. MGD, MvZ, CJLMM, and JB drafted the paper. All authors critically reviewed the paper and approved the final version. All authors had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. JB is the guarantor of the study.

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Competing interests: All authors have completed the ICMJE uniform disclosure at www.icmje.org/coi_disclosure.pdf and declare: PJFS has been on the speakers' bureau of Roche, Gen-Probe, Abbott, Qiagen, and Seegene, and has been a consultant for Crucell BV; CJLMM has been on the speakers' bureau of GlaxoSmithKline, Qiagen, Merck/SPMSD, Roche, Menarini, and Seegene, has served occasionally on the scientific advisory boards of GlaxoSmithKline, Qiagen, Merck/SPMSD, Roche, and Genticel, and has occasionally been consultant for Qiagen; JB has received speaker fees from Qiagen and consultancy fees from Roche, DDL Diagnostic Laboratory, GlaxoSmithKline, and Merck/SPMSD, and fees were collected by his employer; CJLMM was formerly a minority shareholder of Delphi Biosciences, which bankrupted in 2014, and was a minority shareholder of Diassay BV until March 2016; CJLMM and PJFS are minority shareholders of Self-Screen BV, a spin-off company of the VU University Medical Centre; Self-Screen BV holds a patent on the HPV risk test; the remaining authors declare no interests.

Ethical approval: The POBASCAM trial was approved by the medical ethics committees of the VU University Medical Centre (no 96/103A) and the Ministry of Public Health (VWS no 328 650).

Data sharing: no additional data available.

The lead author (the manuscript's guarantor) and affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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