Modeling the effects of cervical cancer prevention in the Netherlands

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3 | Primary human papillomavirus (HPV) DNA screening for cervical cancer prevention: Can the screening interval be safely extended?

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ABSTRACT

Cytological screening has substantially decreased the cervical cancer incidence, but even better protection may be achieved by primary high-risk human papillomavirus (hrHPV) screening. In the Netherlands, five-yearly cytological screening for women aged 30-60 years will be replaced by primary hrHPV screening in 2016. The new screening guidelines involve an extension of the screening interval from 5 to 10 years for hrHPV-negative women aged 40 or 50 years. We investigated the impact of this program change on the lifetime cancer risks in women without an hrHPV infection at age 30, 35, 40, 45, or 50 years. The time to cancer was estimated using 14-year follow-up data from a population-based screening intervention trial and the nationwide database of histopathology reports. The new screening guidelines are expected to lead to a reduced cervical cancer risk for all age groups. The average risk reduction was 34% and was smallest (25%) among women aged 35 years. The impact of hrHPV screening on the cancer risk was sensitive to the duration from cervical intraepithelial neoplasia grade 2/3 (CIN2/3) to cancer; a small increase in the cancer risk was estimated for women aged 35 or 40 years in case a substantial proportion of CIN2/3 showed fast progression to cancer. Our results indicate that primary hrHPV screening with a 10-yearly interval for hrHPV-negative women of age 40 and beyond will lead to a further reduction in lifetime cancer risk compared to 5-yearly cytology, provided that precancerous lesions progress slowly to cancer.

INTRODUCTION

Screening for cervical cancer has been implemented in many countries starting in the 1960's,[1] and has led to a large reduction in cervical cancer incidence since.[2-4] Most countries use a cytology-based screening instrument (the Pap test). The success of cervical screening is largely determined by the opportunity for timely detection and treatment of precancerous lesions and the accuracy of the screening instrument. The time spent in the screen-detectable, precancerous state is thought to be long enough to prevent the majority of cervical cancer cases,[5, 6] but the sensitivity of cytology for detection of cervical intraepithelial neoplasia grade 2 or 3 (CIN2/3) is only moderate and varies considerably between countries (see for example Cuzick et al.[7]). Repeated screening is therefore necessary to compensate for test inaccuracy.

Cervical cancer is caused by a persistent high-risk human papillomavirus (hrHPV) infection. HrHPV testing has been shown to have a higher sensitivity than cytology for detection of CIN2/3 (96% versus 53%[7]) at the cost of a 2.5 to 4% lower specificity.[7, 8] Moreover, hrHPV screening provides up to 70% better protection against CIN3 and cancer compared to cytology.[9, 10] Despite its lower specificity, organized screening by hrHPV testing in cervical smears is considered cost-effective on the basis of modeling studies[11-13] and several countries are considering implementation of the hrHPV DNA test as primary screening instrument, either used alone or in combination with cytology.

Currently, women in the Netherlands are invited every 5 years to cytological screening starting from age 30 to 60 years. The Netherlands have recently decided to adapt their organized screening program and to replace the Pap-test by the hrHPV DNA test as the primary screening instrument, starting in 2016.[14] In the new program, hrHPV testing is offered every 5 years from age 30 to 60 years. HrHPV-positive women will be triaged by cytology and referred for colposcopy in case of abnormal cytology. To limit the burden of screening and to control costs, the screening interval will be extended from 5 to 10 years for women who test hrHPV-negative at age 40 or 50 years. For hrHPV-positive women, the 5-year invitation scheme will be preserved. Such a risk-based screening approach, where the screening interval depends on the hrHPV DNA test result, is expected to provide a good balance between safety and screening burden.[14]

Although assessments based on simulation models have indicated that hrHPV screening will lower the cervical cancer incidence for the population as a whole, it is important to confirm such predictions with long-term follow-up data when available. Furthermore, it is not yet known whether the overall reduction comes with an increase in cancer risk for some age groups. The new program involves an interval extension to 10 years for women aged 40 years or older. An interval of 10 years is substantially longer than recommended in the current screening programs and it must be assessed whether women 30 years and older are at increased cancer risk under the new screening program. Cohort studies in which the preventive effect of hrHPV DNA testing is compared to that of cytology in a nationwide screening setting usually have primary end-point CIN3 or cancer (CIN3+).[15-18] However, control of CIN3+ incidence does not preclude an increase in the incidence of interval carcinomas once the screening interval has been extended. A recent

pooled study of European screening trials indicated that the cervical cancer incidence already decreases within 5 years after implementation of hrHPV-based screening.[10] This observation supports an interval extension under hrHPV screening but the length of the protective effect of hrHPV-screening remains to be determined.

In this study, we will evaluate the impact of the new screening program on the lifetime cervical cancer risk for women without an hrHPV infection at different ages. Our assessment uses 14 years of follow-up data from a large screening intervention trial (POpulation-BAsed SCreening AMsterdam; POBASCAM) to estimate the duration to CIN2/3.[19, 9] Projections of future cancer risk are provided by linking the POBASCAM analysis to a recently published analysis on the duration from CIN2/3 to cervical cancer estimated from nationwide histopathology registry data.[6]

MATERIALS AND METHODS

The change in lifetime cervical cancer risk was predicted from the time to cancer distribution. We estimated the time to cervical cancer by summing the estimated duration to CIN2/3 onset in women without an hrHPV infection and the duration from CIN2/3 onset to invasive cervical cancer. The latter duration was taken from a statistical model for doubly censored data fitted to the age-specific occurrence of CIN2/3 and cancer reported in the national registry of histopathology.[6] In order to accurately reflect the time from onset CIN2/3 to cancer (instead of the time from cytology-detected CIN2/3 to cancer), the progression time was linked to the age-dependent hrHPV incidence.[20, 21] In addition, we accounted for overdiagnosis of CIN2/3 by classifying the CIN2/3 cases into progressive CIN2/3 that will eventually progress to cancer if left untreated, and in non-progressive CIN2/3. The duration from onset of progressive CIN2/3 to cancer was accurately fitted by a Gamma distribution with shape 5.1 (95% confidence interval (CI) 1.7, 6.9) and scale 4.9 (95% CI 3.3, 52), with a corresponding mean duration of 25.0 years.

Estimating the time to CIN2/3 using POBASCAM

The time to CIN2/3 onset in women without an hrHPV infection was estimated from 14-year follow-up data of the Population-Based Screening Study Amsterdam (POBASCAM). The study design and results have been published before.[22, 19, 9] In short; 44,102 women aged 29-61 years were enrolled between January 1999 and September 2002 as part of the nationwide cervical screening program, and were randomly assigned to the intervention (n=21,996) and control group (n=22,106). In the baseline round, women in the intervention group were managed on the basis of cytological and hrHPV DNA test results and women assigned to the control group were managed on the basis of cytological results only. In the subsequent round, 5 years after baseline, women in the control and intervention group were both managed on the basis of cytological and hrHPV DNA test results. In the second and further follow-up rounds at least 10 years after baseline, women were managed on the basis of cytological results only. Details about the management of cytology and the hrHPV DNA co-test have been described previously.[22, 19, 9]

Cytology, hrHPV testing, and histology procedures in the POBASCAM study were as follows: conventional cytological smears were taken with a Cervex-Brush (Rovers, Oss, Netherlands) or a cytobrush. The brush was placed in a vial containing 5 mL phosphate-buffered saline for hrHPV testing. Cytology results were read according to the CISOE-A classification which can be roughly converted to the 2001 Bethesda system.[23] HrHPV testing was done by general primer (GP5+/6+) PCR enzyme immunoassay which detects 14 high-risk types (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68). Histological follow-up was obtained from four participating laboratories, and data were also tracked through the nationwide pathology database (PALGA).[24] Histology was examined locally and classified (in order of increasing severity) as no lesion found, CIN grade 1,2,3, or invasive cancer according to international criteria.[25] During the whole study period only 16 adenocarcinoma in situ cases were diagnosed versus 501 CIN3 and the mean age of detection was 36 years for both histological groups. Therefore, we decided to add the adenocarcinoma in situ cases to the CIN3 group. CIN2 or CIN3 histology was sufficient to treat women by a loop electrosurgical excision procedure.

From the intervention and control arm, we selected women with a negative hrHPV DNA test and negative cytology at baseline (double negative test, n = 40,981). Here we implicitly assume that the duration to CIN2/3 in women with a double negative test at baseline is similar to the duration in women without an hrHPV infection. For each woman we recorded the time of the last double negative test in follow-up and the time of CIN2/3 detection. Women without CIN2/3 were censored at the time of the last screening test or uterus extirpation. We estimated the time to CIN2/3 detection by Kaplan-Meier which provides an estimate of the cumulative incidence of CIN2/3. We rescaled the Kaplan-Meier curve such that it takes value 1 at 14 years after baseline. The scaled Kaplan-Meier curve represents the distribution of the time to detection of CIN2/3 for cases developed within 14 years after baseline. Note that our model does not require absolute CIN2/3 risks but only CIN2/3 risks conditional on the assumption that CIN2/3 develops within 14 years. To assess whether the time distribution for CIN2/3 cases developed within 14 years depends on age, separate analyses were carried out for women aged 29-35 years (n = 12,896) and >35 years at baseline (n = 28,085). The time from hrHPV-negative to CIN2/3 detection is larger than the time to CIN2/3 onset, and this needs to be accounted for. We used the time of the last double negative test as a lower bound of the moment of CIN2/3 onset, and the time of CIN2/3 detection as an upper bound. We assumed that the onset time of CIN2/3 is uniformly distributed on this interval. A uniform time distribution holds if the incidence of CIN2/3 in the general population of screen-eligible women is low and constant.[26] Furthermore, we assumed that the times of hrHPV infection and CIN2/3 onset coincide. This yields a conservative safety assessment of hrHPV screening as it ignores the possibility of the hrHPV DNA test to identify women at risk prior to CIN2/3 onset. It is important to realize that our analysis is based on CIN2/3 cases developed within 14 years after a double negative baseline test and does not evaluate CIN2/3 developed at a later time. Safety of a new screening program will be mainly associated with the ability to detect the fast progressing lesions, therefore we studied the influence of shorter follow-up lengths on the cancer risk in the sensitivity analysis.

Current and new screening guidelines

In the current screening program, 30- to 60-year-old women are invited every 5 years to cytological screening. If cytology is moderate dyskaryosis or worse, the woman is referred directly to the gynecologist for colposcopy. If the smear is borderline or mild dyskaryosis the woman is recalled after 6 and 18 months and referred for colposcopy if repeat cytology is abnormal. Treatment follows after histologically confirmed CIN2 or worse (CIN2+). The sensitivity of cytology for detecting CIN2+ (baseline plus triage) is 0.64 (95% CI: 0.58-0.70).[27, 28]

In the new screening program, women will be invited at age 30, 35, 40, 50 and 60 years for a hrHPV DNA test. HrHPV-positive women are triaged by cytology at baseline and after 6 months, and are referred for colposcopy in case of abnormal cytology. If a woman does not have a negative hrHPV DNA test at age 40, 50 or 60 years, she will be re-invited after 5 years. The sensitivity for detecting CIN2+ (baseline plus triage) is 0.82 (95% CI: 0.78-0.86).[27, 29, 28]

Effect of screening on the cervical cancer risk

Per 5-year age cohort, we estimated the number of cancers averted under the old and new screening program. The estimates are obtained by the Monte Carlo method, simulating 1,000,000 women and comparing for each simulated woman the time to cancer with the time to treatment of CIN2/3; if the time to treatment of CIN2/3 exceeds the time to cancer, then cancer has not been prevented by screening. The prevented cancers were weighted by the age-specific mortality rates due to other causes. We only considered women who have the intention to participate in organized screening (90% in the Netherlands), and for those women assumed a per-round screening attendance rate of 80%.[30] The success rate of CIN2/3 treatment was set at 100%. Ninety-percent non-parametric bootstrap confidence intervals[31] were calculated for the relative change in cancer risk in order to reflect uncertainty in the Gamma distribution for the time from CIN2/3 to cancer and in the screening test sensitivities.

Sensitivity analyses

We examined the robustness of the cervical cancer risk reductions with regard to the duration from CIN2/3 to cancer by extrapolating the parameters of the Gamma distribution beyond the 95% confidence bounds (a lower shape parameter implies a larger proportion of fast progressing lesions). We lowered the shape parameter from 5 (base-case) to 3 and 1, and the mean duration from 25 (base-case) to 20, 15, and 10 years. Furthermore, we studied the influence of the follow-up length in the POBASCAM trial on the cervical cancer risk reduction. In the base-case, we considered CIN2/3 cases that were detected within 14 years. We lowered the time to CIN2/3 by excluding CIN2/3 cases that were detected after 10 years of follow-up. Finally, we evaluated the impact of screening attendance on the cervical cancer risk reductions by varying the per-round attendance from 70% to 90% for hrHPV screening while keeping the attendance rate for cytological screening at 80%.

RESULTS

For the 40,981 women in the POBASCAM study with a double negative test at baseline, the total follow-up was 315,252 woman-years and 297 women were diagnosed with CIN2/3 within 14 years. Figure 1 shows cumulative incidence functions of time to CIN2/3 detection, normalized to 1, for women aged 29-35 years versus 35 years or older at baseline. The incidence curves are similar implying that for CIN2/3 cases detected within 14 years after baseline, the time to detection was equal for women <35 years and women >35 years. For the remainder of our analyses we assume that the time to detection of CIN2/3 is independent of age.

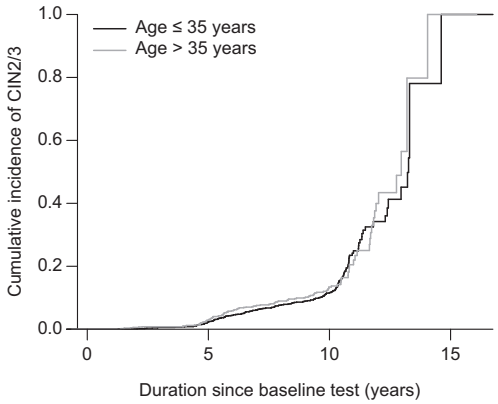

Figure 1. Empirical 14-year cumulative risk of CIN2/3 detection for women hrHPV-negative and cytological normal at baseline in the POBASCAM trial. The data is divided into two age groups (age 29-35 years and older than 35 years at baseline).

For women without an hrHPV infection at age 30, 35, 40, 45, and 50 years, we calculated the proportional change in lifetime cancer risk when replacing the old screening program by the new screening program. Figure 2 shows the changes in cancer risk together with 90% confidence intervals. For all age groups, hrHPV screening provides better protection against cervical cancer compared to cytology-based screening. The relative reduction is largest for women aged 45 years (43%) and smallest for women aged 35 years (25%). The average relative reduction in cancer risk over the five age groups is 34%.

Sensitivity analyses

Figure 3 presents the effect of the duration from CIN2/3 to cervical cancer on the relative change in cancer risk following implementation of the new screening guidelines. The relative benefit of hrHPV screening increases with the shape parameter of the time to cancer distribution as well as with the mean duration from CIN2/3 to cancer. Notably, both the shape parameter and the mean duration from CIN2/3 to cancer are negatively related to the risk of fast progression of CIN2/3 to

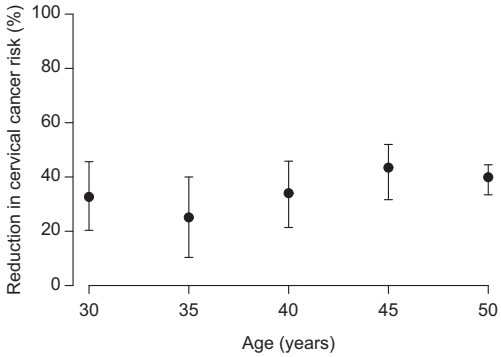

Figure 2. Reduction in cervical cancer risk when replacing cytology-based screening by hrHPV screening. The dot presents the median and the bars are 90% non-parametric bootstrap intervals obtained when varying the duration from CIN2/3 to cancer and the screening test sensitivities.

cancer. In some settings for the shape and mean duration of CIN2/3 to cancer, the new screening program leads to an increased cancer risk, in particular among women aged 35 years (maximum increase 10%) and among women aged 40 years (maximum increase 8%). An increase in cancer risk was only observed if at least 30% of cancers developed within 10 years since onset of CIN2/3.

Lowering the follow-up length of the POBASCAM study only had a weak effect on the cervical cancer risk reduction. The cervical cancer risk reductions varied between 18% and 48% across the different age groups after excluding CIN2/3 cases that were detected after 10 years of follow-up, compared to 25% - 43% in our base-case model.

Finally, the relative change in cancer risk was inversely related to the per-round screening attendance of hrHPV screening. The estimated reduction in cancer risk decreased to on average 18% if the hrHPV screening attendance was only 70%, but a cancer risk reduction was still predicted for all age cohorts (Figure 4).

DISCUSSION

In this study, we investigated the effect of replacing cytological screening by primary hrHPV screening on the lifetime cervical cancer risk. In the new screening program, the screening interval will be extended from 5 to 10 years for 40- and 50-year-old hrHPV-negative women which might put them at increased risk of cancer. Our analyses suggest that the screening interval can be safely extended for women without hrHPV infection at age 30, 35, 40, 45, or 50 years, and that hrHPV screening will lead to a further reduction in cancer risk, provided that CIN2/3 progresses slowly to cancer.

Our objective was to evaluate the impact of the new screening program in the Netherlands. This program involves risk stratification based on the screening outcomes and age. More complex risk stratification strategies, where strata depend not only on the screening outcomes in the

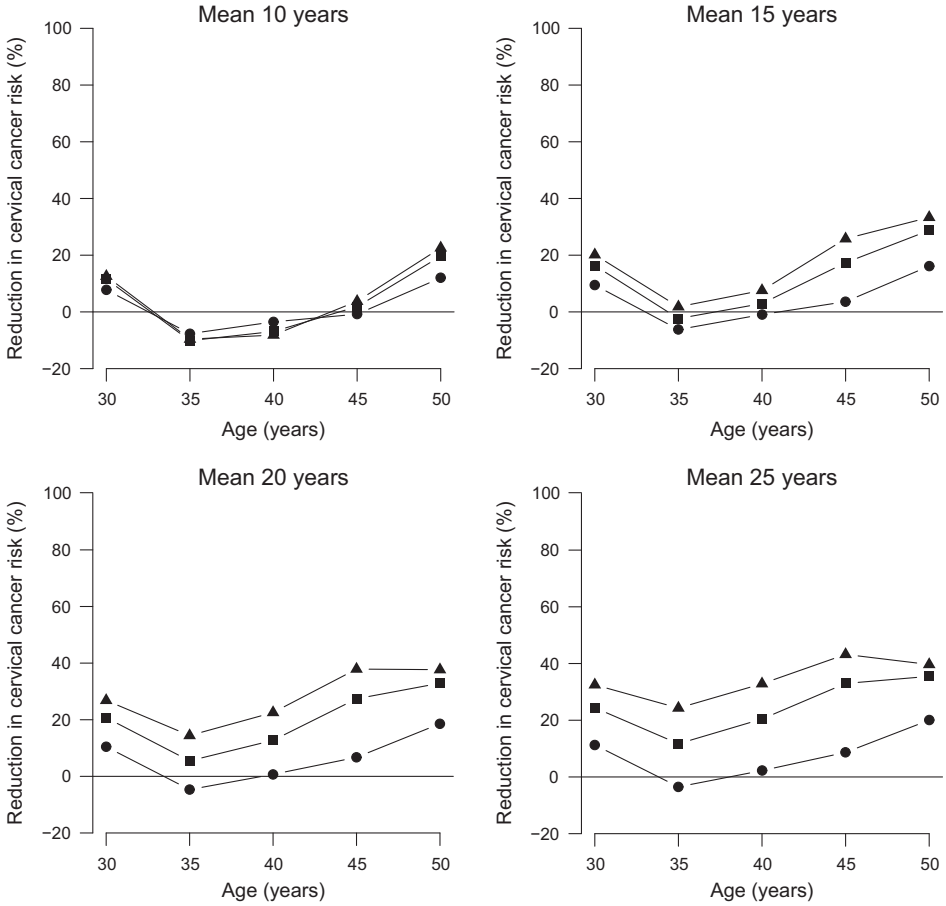

Figure 3. Sensitivity analysis: influence of the duration from CIN2/3 to cervical cancer for different mean values (mean duration 10, 15, 20 and 25 years) and different shape parameters (shape 1 (●), shape 3 (■) or shape 5 (▲)).

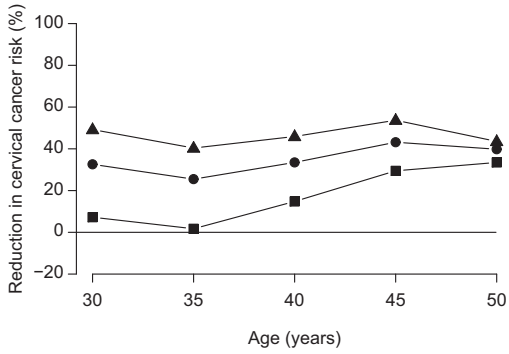

Figure 4. Sensitivity analysis: reduction in lifetime cervical cancer risk for different attendance rates in the hrHPV screening program compared to cytology-based screening with 80% attendance. Investigated scenarios: attendance rate in hrHPV screening of 70% (■), 80% (●, base-case), and 90% (▲).

current round but also on previous outcomes, might have been defined. However, the health authorities have chosen for a relatively simple program in order to evade logistic problems at the screening organizations. In addition, we have focused on women without an hrHPV infection at baseline for different age cohorts, but a complete evaluation would also involve a comparison of the current and new screening program for women with an underlying hrHPV infection at baseline. For the latter group, infection by hrHPV and progression to cancer does not take place in between to screens (no interval cancer), and it is sufficient to assess that the sensitivity of a single hrHPV test in ten years is at least as good as the sensitivity of two cytological tests in ten years (i.e., once every five years). This is supported by two Dutch screening trials[27, 32] and hence we expect the new screening program to be safe.

One of the reasons for implementing primary hrHPV screening is the better sensitivity of the hrHPV test as compared to cytology for detecting CIN2+.[7] We assumed that the screening test sensitivities were constant but in reality, the sensitivities may depend on the size of the lesion, and may be positively biased for incident lesions. To check this, we estimated the crude sensitivity (i.e., not adjusted for verification bias) of cytology and hrHPV test for detecting CIN2+ in the baseline round of the POBASCAM study and in the subsequent round 5 years later. For cytology, the sensitivities were 0.73 (95% CI: 0.67-0.78) and 0.66 (95% CI: 0.55-0.76) respectively, and for hrHPV, sensitivities were 0.91 (95% CI: 0.86-0.94) and 0.83 (95% CI: 0.72-0.90) respectively. For both cytology and the hrHPV test, the data suggest a trend towards lower sensitivities in the subsequent screening round, but the effect is weak and not different for cytology and hrHPV testing.

Our analyses indicated that in the base-case setting of our model, the new screening guidelines are not expected to increase the cancer risk in any particular age group, but that the benefits that accrue from hrHPV testing are not equally distributed across age. The relative benefit was smallest in the age range 35-40 years. At age 30, extra protection is obtained by 5-yearly hrHPV testing up to age 40 which compensates for the screening interval extension. Women aged 45 years and older will have a large relative benefit of a sensitive exit test at age 60 years.

Extension of the screening interval has been proposed by others, based on a comparison of the cumulative incidence rate of CIN3+ over multiple screening rounds for women who tested cytological normal and hrHPV-negative at baseline.[19, 15-18] Note however, that screen-negative women with CIN3+ detected at following screening round(s) received treatment. Therefore, these studies do not guarantee that control of CIN3+ incidence will also lead to control of cancer incidence once the screening interval has been extended. The use of the end-point cancer instead of CIN3+ in the pooled European screening trials study does not solve this problem as women included in this pooled study were screened at 3-5 yearly intervals and treated upon detection of CIN2/3.[10] As a consequence, the reported cancer risks may underestimate the risks that would have been observed under larger screening intervals. Note in this regard that our estimate of the average relative reduction in cancer risk was 34% (90% CI: 24-45%) and substantially smaller than the 70% (95% CI: 40-85%) reduction reported in the pooled study. In conclusion, we think that enlarging the time window for progression to cancer by leaving hrHPV-negative women unscreened and

untreated for 10 years demands evaluation of the effects based on the estimated time to cancer distribution.

The duration of progressing to cervical cancer has a strong influence on the expected effect of hrHPV screening. When estimating the duration from HPV-negative to CIN2/3 and from CIN2/3 to cervical cancer, one should correct for treatment of precancerous lesions that would or would not progress to cancer if left untreated. The estimated duration from HPV-negative to CIN2/3 may be biased because of discontinuation of the natural history via treatment of CIN1. However, according to the Dutch guidelines, CIN1 should not be treated immediately after detection but only after progression to CIN2/3.[33] Although progression of CIN1 may also be interrupted by a punch biopsy, we think that this only has a limited influence on the time to CIN2/3 distribution and hence on our safety assessments. Notably, as in our data 30 percent of the CIN1 cases progressed to CIN2+, there is no indication that the natural history is markedly disturbed by detection of CIN1. For the duration from onset CIN2/3 to cervical cancer, we used the results from a statistical model fitted to national registry data.[6] This model explicitly accounted for the probability that some detected CIN2/3 lesions would not have progressed to cervical cancer if left untreated. In this paper, it was estimated that 34% of the detected CIN2/3 lesions would progress to cervical cancer and that these lesions would on average progress within 25 years after onset CIN2/3.

In the literature, there is lack of consensus on the duration from onset CIN2/3 to cervical cancer. Modeling studies used to evaluate screening strategies, assume durations varying from 10 to 25 years[34-36] but evidence from data is limited and therefore we carried out a thorough sensitivity analysis. The increase in cancer risk was largest when the duration to cancer was short: if an exponential distribution with mean 10 years was used for the duration, we observed an increase in cancer risk for age cohorts 35 and 40 years of maximum 10%. We also compared our distribution of the time to cancer with the observed progression duration from a historic longitudinal analysis in New Zealand,[5] one of the few studies available that presents empirical data on this topic. We approximated their Kaplan-Meier curve (Figure 3 McCredie et al.) by a gamma distribution. The Kaplan-Meier curve was accurately fitted by an exponential distribution (i.e. a gamma distribution with shape parameter 1) with mean 10 years. This distribution has been covered by our sensitivity analysis. Nonetheless, the estimated duration to cancer in the New Zealand study and our base-case model are substantially different and this deserves closer inspection. An important reason for the difference in durations is that we use the time from onset CIN2/3 to cancer instead of the time from detected CIN2/3 to cancer. In our model, the mean time between onset and detection of CIN2/3 was around 5 years (not shown). This partly explains the difference in durations. In addition, the difference between onset and detection of CIN2/3 may be larger than 5 years in the New Zealand study. Note in this regard that the time of CIN2/3 detection is influenced by the coverage and intensity of screening which are expected to be different for an opportunistic program (New Zealand between 1965-74) and a well-organized program (the Netherlands 1998-2003).

The predicted impact of hrHPV screening on cancer risk was fairly robust against the screening attendance rate. This is expected because it is embedded in the design of the new screening

program. The screening interval is extended to 10 years only for hrHPV-negative women; non-attending women will be re-invited after 5 years. If the interval had been extended for all women, regardless whether screening is attended or not, screening attendance rates will have a large impact on the cervical cancer risk.

Due to the introduction of HPV vaccination and the fast development of novel screening instruments, cervical cancer screening is subject to continuous review. The Netherlands will take the first step from a cytology-based screening program with one fixed interval towards a risk-based strategy where both age (younger versus older than 40 years) and screening test result (hrHPV-positive versus hrHPV-negative) is used to determine the age of the next screen. With the availability of genotyping and vaccination, it is likely that the risk-based screening algorithm will undergo several changes in the future. Along with the implementation of risk-based screening strategies comes the need for quantitative methods to assess these new programs. Studies that merely focus on the population as a whole are not sufficient for evaluating programs that might be less beneficial for some subgroups. We have shown that the benefit of the new screening program may not be equal across age. Nonetheless, the main conclusion is that less intense screening of hrHPV-negative women aged 40 and 50 years will not lead to an increased cervical cancer risk provided that precancerous lesions progress slowly to cancer, which is an important message for policy makers and physicians to convey.

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