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## Clinical progression of high-grade cervical intraepithelial neoplasia: Estimating the time to preclinical cervical cancer from doubly censored national registry data

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## ABSTRACT

Little is known about the time span from high-grade cervical intraepithelial neoplasia (CIN2/3) to invasive cancer. Estimation of this duration from longitudinal studies is not permitted, as CIN2/3 should be treated when detected. Cross-sectional data on the age-specific incidence of detected CIN2/3 and cervical cancer cases are readily available in national registries, but these are difficult to interpret because neither the moment of lesion development nor the onset of invasive cancer is observed. The authors developed a statistical model for the duration between CIN2/3 and pre-clinical cancer using Dutch national registries over the years 2000-2005. Human papillomavirus (HPV) genotype data were projected on the CIN2/3 and cancer incidences to obtain separate estimates for HPV16-positive and -negative lesions. The median time from CIN2/3 to cancer was estimated to be 23.5 years (95% confidence interval: 20.8, 26.6) and 1.6% of the lesions progressed to cancer within 10 years. The median duration for HPV16-positive lesions was similar but within 10 years, 2.4% of the HPV16-positive lesions progressed to cancer compared to 0.6% for HPV16-negative lesions. The estimated durations to cancer are essential for the re-assessment of the optimal screening interval in light of vaccination and novel screening tests.

## INTRODUCTION

Infection with the sexually transmitted human papillomavirus (HPV) is a necessary cause for the development of cervical cancer, the second most common cancer among women worldwide.<sup>1</sup> The majority of the sexually active population will experience an HPV infection at some point in life, with estimates of the lifetime risk around 80% for any oncogenic type.<sup>2</sup> Less than 10% of these infections are persistent and only few persistent infections progress to cervical intraepithelial neoplasia grade 2 or 3 (CIN2/3).<sup>3</sup> CIN2/3 is considered a precursor of cervical cancer and is treated when detected, even though the possibility of regression to normal exists. Whereas CIN2/3 typically develops within a few years from infection with HPV,<sup>4,6</sup> progression to invasive carcinoma is generally thought to require much more time. The duration from CIN2/3 to cancer is, however, largely unknown. This time span strongly determines the eventual impact of screening programs on the cervical cancer incidence, and the time scale at which cervical cancer reductions will be realized in vaccinated cohorts.

Longitudinal studies on the development from precancerous cervical lesions to preclinical cervical cancer are not available with the exception of a study conducted in New Zealand in 1965 in which treatment was withheld from women with large CIN3 lesions.<sup>7</sup> In this study, 31.3% of the CIN3 lesions progressed to cancer within 30 years. However, these CIN3 lesions were more advanced than high-grade lesions typically found in screening programs<sup>8</sup> and the biopsy taken could have influenced the course of disease. The corresponding estimates of clinical progression may be positively biased despite the longitudinal nature of this study and under those assumptions, cervical cancer rates among young women should be much higher than those observed in regularly screened populations.<sup>9</sup>

A different approach is to infer the time span between onset of CIN2/3 to cancer from cross-sectional data on the occurrence of CIN2/3 and cervical cancer. These data are readily available in national screening databases and cancer registries, but they are difficult to interpret since neither the moment of development of CIN2/3 nor the onset of cancer is observed. These data are referred to as doubly censored current status data in the statistical literature.<sup>10</sup> Moreover, cross-sectional data can only be used to reliably estimate longitudinal parameters if the underlying dynamical system is in a state of equilibrium. Regarding the epidemiology of HPV in the Netherlands, this assumption likely holds for the decade between 2000 and 2009 when the age-adjusted incidence of high-grade cervical lesions and cervical cancer had stabilized after a 30 year period of decreasing cervical cancer rates.<sup>11</sup> Previous studies have used cross-sectional data to estimate the time from CIN2/3 to cancer but the variation in reported mean time spans is considerable; estimates range from 11.8 years to 24.3 years.<sup>12-15</sup> To our knowledge, no statistical models have been developed for estimating the time span from CIN2/3 to cervical cancer that explicitly incorporate the natural history from HPV infection to CIN2/3 to cancer. Van Oortmarsen<sup>13</sup> and Bos<sup>14</sup> developed a statistical model based on cytological and histological screening data, but they did not incorporate the age-specific incidence of HPV infection. This means that onset of CIN2/3 was determined without the use of viral data which is now abundantly available

via population-based screening trials,<sup>16</sup> affording a more precise estimate of the onset of CIN2/3. Others have used compartmental models to describe the natural history of HPV infection up to cervical cancer, but these require simultaneous estimation of numerous parameters and fitting procedures are not well defined for such complex models (see for example <sup>17, 18, 15</sup>).

In this paper, we develop a statistical model for the time span between CIN2/3 and cervical cancer, using data from national registries in the Netherlands. This model accounts for the age-specific incidence of HPV infection, the age-specific attendance of cervical screening, and for the sensitivity of screening by conventional Pap smear. We describe the time from CIN2/3 to cancer by a Gamma density the parameters of which are estimated using maximum likelihood. We also estimate separate Gamma distributions for HPV16-positive and HPV16-negative lesions.

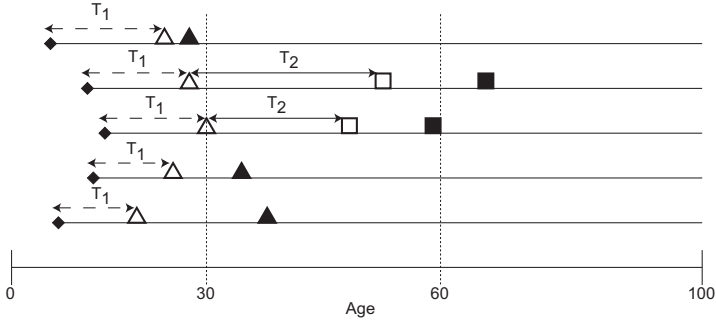
## MATERIALS AND METHODS

### Data

We used cross-sectional registry data of women with either CIN2/3 or cancer in the Netherlands over the years 2000-2005. For each woman we observed the disease status  $Y$  (0 if CIN2/3, 1 if cancer) and the categorized age of diagnosis  $A_d$  (1 if 14-18, 2 if 19-23, ..., 17 if 94-98). The CIN2/3 data were obtained from PALGA, the nationwide network and registry of histo- and cytopathology in the Netherlands.<sup>19</sup> PALGA registers all cytological and histological excerpts that are made in- and outside the national screening program (NSP). The NSP invites women aged 30-60 years once every five years to participate in cervical screening. Cervical cancer diagnoses were derived from the Netherlands Cancer Registry,<sup>20</sup> a nationwide registry that retrieves and confirms histological information from PALGA. The data are given in Appendix Table 1.

### Model

Figure 1 gives a schematic representation of the data that enter the model. A woman is infected with HPV at age  $A_{HPV}$  and develops a CIN2/3 lesion at age  $A_{CIN} = A_{HPV} + T_1$  (see Appendix). The inclusion of the HPV incidence together with an assumed duration from HPV to onset CIN2/3,  $T_1$ , allowed us to estimate the CIN2/3 incidence. This incidence cannot be retrieved from screening data only, as one observes prevalent instead of incident lesions. After CIN2/3 onset, the lesion may either be detected by screening after which it is treated, or it may progress to cervical cancer in  $T_2$  years at age  $A_{CA} = A_{CIN} + T_2$ . We are interested in the unknown probability distribution  $P(T_2 = t_2)$ , the time from CIN2/3 to cancer. This problem addresses a form of doubly censored current status data as we observe for each woman only  $(Y, A_d)$ , thus both  $A_{CIN}$  and  $A_{CA}$  are interval-censored (if  $Y=0$ :  $A_{HPV} < A_{CIN} < A_d < A_{CA}$  and if  $Y=1$ :  $A_{HPV} < A_{CIN} < A_{CA} < A_d$ ). We modeled the probability of detecting  $X_j$  CIN2/3 cases and  $Z_j$  cervical cancer cases in age group  $A_d=j$  ( $j=1, \dots, N$ ) given the total number of detected cases in this age group:  $X_j + Z_j$ . This probability depends on the unknown probability distribution of the time between CIN2/3 and cervical cancer, and on the probability of being detected by cervical screening. By conditioning on the age of detection, model adjustments for



**Figure 1.** Presentation of the high-grade lesions (CIN2/3) and cervical cancer data.  $\blacklozenge$  denotes  $A_{HPV}$ , the age of human papillomavirus (HPV) infection based on the age-specific HPV incidence in the Netherlands;  $\triangle$  is  $A_{CIN}$ , the age of CIN2/3 lesion development (unobserved);  $\blacktriangle$  gives the age of CIN2/3 lesion detection (from the nationwide histo- and cytopathology registry);  $\square$  is  $A_{CA}$ , the age of cervical cancer development (unobserved) and  $\blacksquare$  denotes the age of cervical cancer detection (Dutch cancer registry). Between the dotted lines, women are every five years invited to participate in the national screening program. A woman progresses from  $A_{HPV}$  to  $A_{CIN}$  in  $T_1$  years, and from  $A_{CIN}$  to  $A_{CA}$  in  $T_2$  years.

competing risks such as population mortality and hysterectomy will only influence parameter estimates via their effect on the ratio of detected CIN2/3 to detected cancer cases. This effect is likely to be negligible and therefore we did not adjust for competing risks in the model. Our model assumes that a woman with CIN2/3 either persists or progresses to cancer. However, lesions may also regress in particular CIN2.<sup>21-23</sup> Ignoring the competing risk of regression of CIN2/3 will lead to a downward bias in the duration from CIN2/3 to cancer. This bias depends on the duration of regression of the lesion and will be small if the mean regression time is substantially smaller than the mean progression time. This seems an acceptable assumption as longitudinal studies have shown that regression is likely to occur fast, with approximately 40% regression of undiagnosed CIN2 over 2 years.<sup>22</sup> The time from CIN2/3 to cancer,  $T_2$ , is modeled by a mixture of a proportion  $\omega$  with increasing hazard and a proportion  $1-\omega$  with zero hazard. The function with increasing hazard is assumed to follow a Gamma density:

$$f(t|\kappa, \theta) = \frac{1}{\Gamma(\kappa)\theta^\kappa} t^{\kappa-1} e^{-t/\theta},$$

with shape parameter  $\kappa$  and scale parameter  $\theta$ .

## Estimation method

We estimated the parameters  $\varphi = \{\omega, \kappa, \theta\}$  by maximizing the log-likelihood function

$$\ell(\varphi|X, Z) = \sum_{j=1}^N X_j \log [P_\varphi(Y = 0|A_d = j)] + Z_j \log [P_\varphi(Y = 1|A_d = j)],$$

with  $N$  the total number of age groups. We optimized the log-likelihood using the optim function of the statistical package R version 2.13.1 (R Foundation for Statistical Computing, Vienna, Austria). The

full derivations of the log-likelihood function can be found in the Appendix. Ninety-five percent confidence intervals (95% CI) were calculated using the non-parametric bootstrap method. The confidence bounds were corrected for bias by the BC<sub>a</sub> correction method.<sup>24</sup>

## Parameter assumptions

### *CIN2/3 incidence*

We calculated the probability distribution for the age of CIN2/3 development  $A_{CIN}$  as the sum of the incidence of HPV infection and the time from HPV infection to CIN2/3 (for complete derivations see the Appendix). The HPV incidence for the Netherlands was based on a large randomized screening trial, POBASCAM, in which 44,102 women were tested for HPV<sup>16</sup> and model estimates of the prevalence have been published before,<sup>25</sup> see Table 1 for incidence figures. The time from HPV infection to CIN2/3 development was assumed to follow an Exponential distribution and to be independent of age of infection. Its mean was also determined using the POBASCAM data and was estimated at 3.0 years (see Appendix).

**Table 1.** Age-specific HPV Incidence for the Netherlands

Age	HPV Incidence (Proportion per 5 years)
14-18 years	0.57
19-23 years	0.76
24-28 years	0.45
29-33 years	0.28
34-38 years	0.20
39-43 years	0.14
44-48 years	0.10
49-53 years	0.08
54-58 years	0.06
59-63 years	0.05

<sup>a</sup>Bogaards et al. (25)

HPV, human papillomavirus;

### *Screening*

We assumed that 90% of the women participates in the NSP<sup>26, 27</sup> and the remaining 10% only has a small probability of taking an opportunistic smear. The participants of the NSP have an age-specific rate of attendance which we calculated from PALGA-data. These rates are large at screen-eligible ages and small at other ages. All age-specific screening rates are given in Table 2.

**Table 2.** Rates of Screening Per Age Group in the Netherlands for Participants and Non Participants of the NSP

Age	Participants NSP <sup>a</sup>	Non Participants NSP
14-18 years	0.01	0.01
19-23 years	0.06	0.06
24-28 years	0.10	0.10
29-33 years	0.76	0.11
34-38 years	0.74	0.11
39-43 years	0.80	0.11
44-48 years	0.82	0.10
49-53 years	0.80	0.09
54-58 years	0.70	0.07
59-63 years	0.71	0.05
64-68 years	0.04	0.04
69-73 years	0.03	0.03
74-78 years	0.02	0.02
79-83 years	0.02	0.02
84-88 years	0.01	0.01
89-93 years	0.01	0.01
94-98 years	0.004	0.004

<sup>a</sup>We assumed that 90% of screen-eligible women participate in the NSP (van Ballegooijen et al. (26))  
NSP, national screening program

### ***Lesion detection***

The sensitivity of the Pap test for detection of CIN2/3 was set at 0.7<sup>28</sup> and treatment was assumed to be successful upon detection. For cervical cancer we assumed Pap test sensitivity of 1 at the first screen after onset of invasive disease, and detection within two screening rounds leading to a pre-clinical phase of cervical cancer with a mean of 5 years and a maximum of 10 years.

### ***Type-specificity***

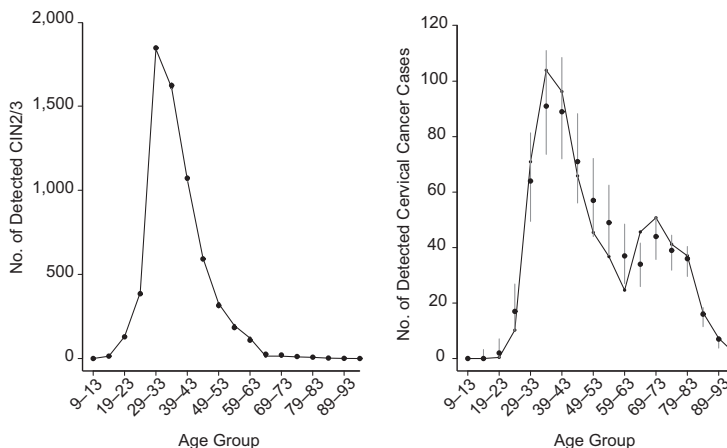
We used two Dutch studies in which CIN2/3 and cancer cases were evaluated with regard to HPV16 status.<sup>29,30</sup> We pooled the two studies and obtained a smooth estimator of the age-specific HPV16-positivity in CIN2/3 and in cervical cancer by performing a logistic regression analysis with a (fractional) polynomial function of age as explanatory variable (see Appendix Tables 2 and 3, and Appendix Figures 1 and 2). We projected the predicted age-specific proportions of HPV16-positive and HPV16-negative CIN2/3 and cancer cases on the registry data and estimated separate progression parameters for HPV16-positive and HPV16-negative lesions.

## Sensitivity analysis

We performed a sensitivity analysis to investigate the influence of parameter assumptions on the cumulative incidence of cancer development after onset of CIN2/3. The sensitivity of the Pap test was varied from 0.5 to 0.8. The proportion of women participating in the NSP was set at 0.8, 0.85, 0.9 (base-case), and 0.95. Recent research suggests the duration from HPV infection to CIN2/3 to be longer for HPV16-negative infections compared to HPV16-positive infections.<sup>31</sup> We set this duration at 2, 4, 6, 8 and 10 years, for both HPV16-positive and HPV16-negative infections.

## RESULTS

The model fit to the data is presented in Figure 2. The peak of observed CIN2/3 cases is at age 30 years, the starting age of organized screening in the Netherlands. The age distribution of cervical cancer detection has two peaks; one around age 35 years and a second one around age 70 years. The shape of this graph shows the effect of screening; at young age the fast progressing CIN2/3 develop to cancer and are detected by screening at age 30 to 35. After age 35, screening starts paying off leading to a reduction in the number of detected cancers. The preventive effect of screening will decline from age 60 (the upper-end of eligible screening age) leading to an increase in symptomatic cancers. Without screening, the peak of cancer cases would be at age 50, about 25 years after the peak of HPV infection. For HPV16-positive cervical cancers, the peak at older age is less pronounced compared to HPV16-negative cancers. Both for CIN2/3 and cervical cancer, the shape as well as the absolute height of the observed figures are fitted well by the model (see Appendix Figure 3).



**Figure 2.** Solid curves represent the expected number of detected high-grade lesions (CIN2/3, left panel) and cervical cancer cases (right panel) in the Netherlands. The large dots denote the observed number of CIN2/3 lesions and cervical cancer cases, the vertical lines reflect their 95% confidence intervals. The numbers are given per age group and are averaged over the years 2000-2005.

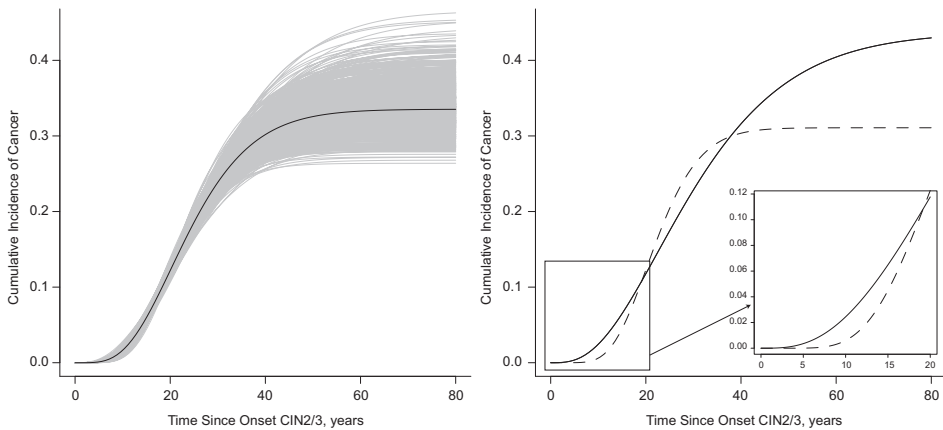


The parameter estimates together with their 95% bootstrapped confidence intervals are given in Table 3. The time to cancer in women with progressive CIN2/3, i.e. the CIN2/3 cases that have a positive hazard of developing cancer, follows a Gamma distribution with shape  $\kappa=5.1$  (95% CI: 1.7, 6.9) and scale  $\theta=4.9$  (95% CI: 3.3, 52). The median time from onset of these CIN2/3 to onset of cervical cancer is estimated at 23.5 years (95% CI: 20.8, 26.6). The cumulative cancer incidence is shown in Figure 3. Within 10 years, 1.6% of the CIN2/3 cases will develop into cervical cancer. Within 20 years, 12% will develop into cancer. The bootstrapped curves show there is considerable uncertainty about the cumulative cancer incidence after 20 years from onset of CIN2/3. We estimate that 60% (95% CI: 56%, 65%) of the cancers are found in NSP participants.

**Table 3.** Parameter Estimates of the Duration to Cancer Development for Progressive CIN2/3

	All lesions	95% CI	HPV-16-positive lesions	95% CI	HPV-16-negative lesions	95% CI
Parameter						
Shape parameter $\kappa$	5.13	1.66, 6.85	3.33	2.28, 5.06	9.14	5.91, 13.58
Scale parameter $\theta$	4.90	3.28, 52.03	9.67	4.74, 24.02	2.49	1.54, 3.95
Mixture weight $\omega$	0.34	0.28, 0.99	0.44	0.3, 0.99	0.31	0.26, 0.36

HPV, human papillomavirus; CIN2/3, cervical intraepithelial neoplasia grade 2 or 3; CI, (bootstrapped) confidence interval



**Figure 3.** Left panel: cumulative distribution function for cancer development for CIN2/3 (black line) together with 1000 bootstrapped cumulative incidence curves (gray lines). Right panel: cumulative distribution function for cancer development for HPV-16-positive CIN2/3 (solid line) compared to HPV-16-negative CIN2/3 (dashed line). We zoomed in on the progression within the first 20 years.

## Type-specificity

The proportion of HPV16-positive lesions that have a positive hazard for progression to cancer, is estimated at 0.44 (95% CI: 0.3, 0.99) whereas this proportion is estimated at 0.31 (95% CI: 0.26, 0.36) for HPV16-negative lesions. The low shape parameter for HPV16-positive compared to HPV16-negative lesions (Table 3) indicates that the duration to cancer shows a much higher variability for HPV16-positive lesions than for HPV16-negative lesions. This is in line with the data: most cancers at young age are HPV16-positive but cancers in older women still have a moderate probability of being HPV16-positive as well (see Appendix Figure 2). This variance is also reflected in the median duration for progressive HPV16-positive versus progressive HPV16-negative CIN2/3 (29.0 years (95% CI: 22.0, 49.7) versus 21.9 years (95% CI: 19.8, 24.2) respectively). The cumulative incidence of cervical cancer is higher for HPV16-positive compared to HPV16-negative lesions in the first 20 years, see Figure 3. Although this seems to be a small difference, these fast progressing lesions are of importance when the length of the screening interval must be re-optimized (for instance when implementing HPV screening or when screening vaccinated women). This figure also shows the larger heterogeneity in progression of HPV16-positive CIN2/3, which may progress to cancer relatively fast as well as after 40 years. In comparison, the hazard becomes almost zero for HPV16-negative CIN2/3 after 40 years. Of the HPV16-positive cancers, 58% (95% CI: 49%, 65%) is found in participants of the NSP which is comparable to that of HPV16-negative cancers, 59% (95% CI: 54%, 64%).

## Sensitivity analysis

We performed a sensitivity analysis on the estimated cumulative incidence of cervical cancer with respect to the proportion of women participating in the NSP, the sensitivity of the Pap test (Appendix Figure 4), and the duration from HPV infection to CIN2/3 (Appendix Figure 5). For the first 15 years since onset of CIN2/3, the cumulative incidence of cancer was robust against a change in the proportion of women participating in the NSP. Thereafter, the cumulative incidence was positively associated with the proportion of women participating in the NSP. The cancer incidence was weakly related to the sensitivity of the Pap test with an increased sensitivity corresponding to a higher cumulative incidence of cervical cancer. The duration from HPV infection to CIN2/3 had a positive association with the cancer incidence, both for HPV16-positive and HPV16-negative infections. However, the median time from HPV infection to onset of cervical cancer remained fairly stable. For HPV16-positive infections, this median time was 32.2, 32.2, 33.0, 35.0 and 37.7 years for durations from HPV infection to CIN2/3 of 2, 4, 6, 8, and 10 years, respectively. For HPV16-negative infections, the corresponding estimates were 24.7, 25.1, 25.9, 27.1 and 28.5 years, respectively. Irrespective of the duration from HPV infection to CIN2/3, the cumulative cancer incidence of HPV16-positive lesions remained higher than the cumulative incidence of HPV16-negative lesions for the first 15 years after onset of CIN2/3.

## DISCUSSION

We developed a statistical model for the detected CIN2/3 and cervical cancer cases that accounted for age-specific attendance rates of cervical screening, and for the sensitivity of screening by the conventional Pap smear. With this model, we estimated a median time for progressive CIN2/3 to cancer development of 23.5. We further estimated that of all CIN2/3 (combined progressive and non-progressive), 1.6% will progress to cancer within 10 years after CIN2/3 onset. The 10 year progression risk was 2.4% for HPV16-positive CIN2/3 compared to 0.6% for HPV16-negative CIN2/3.

In our model, we were able to estimate the shape of the Gamma probability distribution for the time to cancer. This parameter was estimated at 5.13 indicating a strongly increasing cancer hazard since onset of CIN2/3. This is in line with the idea that the clinical significance of small, early CIN2/3 is still uncertain, but large CIN2/3 cases are likely to eventually progress to cancer.<sup>7</sup> <sup>8</sup> Most compartmental models used for assessing the effectiveness and cost-effectiveness of prevention programs, however, assume a direct link between disease compartments CIN3 and cancer (e.g. <sup>17, 32</sup>). Such models assume an exponentially distributed waiting time between CIN3 and cancer. The use of an exponential (i.e. a Gamma distribution with shape parameter 1) instead of a Gamma distribution may lead to an overestimation of the contribution of fast progressing lesions. Consequently, aggressive prevention programs with frequent screening may be recommended to prevent interval carcinomas, whereas a less aggressive program would also provide effective protection if the shape parameter had been markedly larger than 1, as indicated by our model.

Our model can be interpreted as a mover-stayer model with the movers (a proportion  $\omega$  of the CIN2/3 lesions) progressing to cancer following a gamma distribution. Similar work has been done using longitudinal data on colorectal cancer.<sup>33</sup> Our model facilitated describing the heterogeneity in the duration to cancer. However, for HPV16-positive CIN2/3, the cumulative incidence function still showed a large variability in duration compared to HPV16-negative CIN2/3. The large heterogeneity in duration resulted in a low shape parameter and a flat hazard function, leading to a larger median duration compared to HPV16-negative lesions.

Our estimate of the median time from CIN2/3 to cancer (23.5 years) is similar to the estimate of Insinga et al.<sup>15</sup> It is, however, clearly larger than earlier estimates,<sup>12-14</sup> which may be explained by the absence of HPV in the early models. We now know that most HPV infections happen early in life and hence the incidence of CIN2/3 may precede the detection of (prevalent) CIN2/3 by several years. In earlier studies, the onset of CIN2/3 was informed by screening data only and could therefore be strongly associated with screening characteristics. Estimation of the duration from CIN2/3 to cervical cancer depended on the assumed duration from HPV infection to onset of CIN2/3. The sensitivity analysis showed that estimates of the duration from HPV infection to CIN2/3 and from CIN2/3 to cancer were negatively correlated, but the total duration from HPV to cancer remained fairly stable.

We assumed successful treatment for the detected CIN2/3 cases, implying that women are detected only once with a lesion. However, lesions may recur which in our case would lead to an overrepresentation of the detected CIN2/3. We accounted for this by choosing the highest staged lesion per woman per calendar year from the PALGA database. As CIN2/3 lesions most often recur within 6 months,<sup>34</sup> we expect a negligible number of double counts.

The cancer data did not contain information on which cancer cases were detected in regular screening and which cancers were found due to symptoms. It is likely that symptomatic cancers are further in progression and hence older than screen-detected cancers. We did adjust for this heterogeneity as cancers could be missed in case of non-attendance to screening. These cancers were assumed to be detected in the subsequent screening round which means that the preclinical cancers in our model become clinical within 10 years with an average of 5 years, which corresponds to figures reported in the Netherlands.<sup>35,36</sup> In addition, our model estimate of the proportion of screen-detected cancers agrees well with a recent meta-analytic estimate by.<sup>37</sup>

In addition to our estimate of the median time to cancer, we provided estimates for the cumulative incidence of cancer after onset of CIN2/3. Whereas the median time may be sensitive to the tail of the distribution function of the duration to cancer, the cumulative cancer incidence appeared to be a robust measure for clinical progression for the first 25 years after onset of CIN2/3. It is useful for clinicians and other health professionals as accurate cumulative cancer risk estimates have not been widely available. These cumulative incidence rates, however, should be interpreted with caution and likely overestimate the absolute risk of a CIN2/3 lesion to progress since our model does not account for regression of CIN2/3. Just as for progression, relatively little is known about regression of CIN2/3 but it is thought to be fast.<sup>22</sup> For HPV16-positive CIN2/3 the cumulative incidence curve displayed in Figure 3 lies above the HPV16-negative CIN2/3 for the first 15 years, indicating that there is a difference in cumulative incidence rates. This difference will likely be larger for the absolute cancer risk as HPV16-positive lesions are thought to be less regressive than lesions caused by another HPV type.

Information on the proportion of women who participate in the NSP for several screening rounds was not available from our data but taken from another study.<sup>26</sup> In a sensitivity analysis, we showed that our estimates for the time to cancer were fairly robust against changes in this proportion. It may also be useful to compare the proportion of cancers detected in women participating in the NSP (60% in our study) to other retrospective studies. Bos et al. investigated the screening history of Dutch women with cancer detected between 1994-1997, a period in which the screening program was restructured.<sup>38</sup> In this study, 70% of all cancers were detected in women in the screening-eligible age cohort and 45% of these women had a screening history. Gök et al. investigated the screening history of cervical cancers detected between 2005 and 2007 and found that 74.5% of the cancer cases occurred in women with a screening history.<sup>39</sup> Our estimate lies in between these two Dutch studies and is similar to the proportion of cancers detected in screened women in a meta-analysis.<sup>37</sup> Note that our definition includes cancers detected in women who have been screened or who would have the intention to attend future screening rounds. The non-attenders have an increased risk of cancer development which is

explained by the poor attendance to screening. We did not assume an increased background risk for these women as screening is widely accepted and accessible in the Netherlands. This assumption is supported by data from a self-sampling study among non-attenders<sup>27</sup> showing that at 30 years of age HPV prevalence was comparable to those attending regular screening.

Including type-specificity improved the model fit and led to type-specific differences in estimates for the progression of CIN2/3, with a higher incidence of cervical cancer for HPV16-positive compared to HPV16-negative lesions. This finding is in line with previous research in the Netherlands that showed that 33% of HPV-positive women eligible for screening was infected with HPV16, whereas in women with a CIN2+ lesion this proportion was around 55%.<sup>40</sup> This increase suggests a more progressive nature of HPV16-positive lesions compared to other HPV-types (see also <sup>41, 28</sup>). The more aggressive nature of HPV16 was also studied by Wentzensen et al.<sup>31</sup> who showed that HPV16-positive lesions grew faster to CIN2 and CIN3; and by Khan et al.<sup>42</sup> and Kjær et al.<sup>43</sup> who showed that HPV16-positive women had the highest risk of CIN3 or worse.

Cost-effectiveness studies have suggested that the screening interval may be extended if cytology is replaced by the more sensitive HPV DNA test.<sup>44, 45</sup> Our results are helpful in determining the optimal screening interval as we have calculated the proportion of high-grade lesions progressing to cancer after a certain time since onset of CIN2/3. With the introduction of HPV vaccination against the oncogenic types HPV16 and HPV18, the current screening program must be reconsidered as well;<sup>46</sup> it is probably safe to offer vaccinated women fewer smears which lowers screening-related costs and harm. In addition, the results in this study indicate that HPV16-positive lesions progress faster to cancer than HPV16-negative lesions. This may have an additional impact on the expected decrease in the number lifetime screens per vaccinated woman, as our estimates indicate that interval cancers are more likely for HPV16-related lesions than for other lesions.

In summary, this paper provides parameter estimates for the waiting time distribution function from CIN2/3 lesions to preclinical cervical cancer. In our study, we include current insights of the natural history of cervical disease and use national registry data to obtain reliable estimates. To the best of our knowledge, this is the first study that models the natural history of CIN2/3 according to HPV type, and we found significant differences between HPV16-positive and -negative lesions. These results are essential in mathematical modeling studies that aim to predict the effect of HPV-based screening algorithms and vaccination strategies, and are also particularly interesting when studying type-specific referral strategies in organized screening.

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Conflict of interest:

MAV, JAB, FJvK, HEdM, CJLMM, JB: none declared.

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## APPENDIX

### Logistic regression analysis on the age-related proportion of HPV16 in CIN2/3 and cancer

We performed a logistic regression analysis on type-specific CIN2/3 and cervical cancer data from studies conducted in the Netherlands.<sup>1,2</sup> The predicted age-specific proportions of HPV16-positive and HPV16-negative CIN2/3 and cervical cancer were projected on the nation-wide registry data given in Appendix Table 1.

**Appendix Table 1.** The Number of CIN2/3 Lesions and Cervical Cancer Cases in The Netherlands per Age Group, Averaged Over the Years 2000-2005.

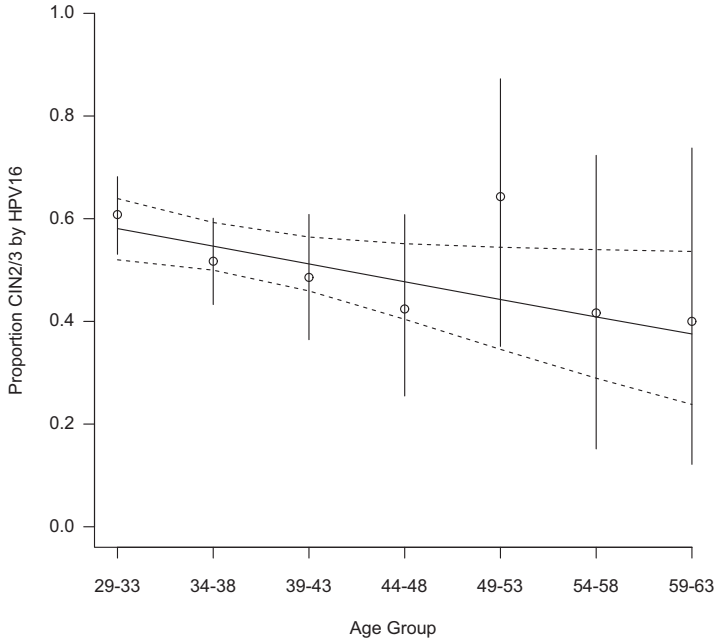
Age <sup>a</sup>	No. of CIN2/3 Lesions	No. of Cancer Cases
14-18 years	14	
19-23 years	129	2
24-28 years	385	17
29-33 years	1846	64
34-38 years	1623	91
39-43 years	1072	89
44-48 years	592	71
49-53 years	315	57
54-58 years	184	49
59-63 years	109	37
64-68 years	26	34
69-73 years	21	44
74-78 years	12	39
79-83 years	8	36
84-88 years	3	16
89-93 years	1	7
94-98 years		2
Total	6340	655

<sup>a</sup>Age of the woman is at the first of January of the year of lesion detection

**Appendix Table 2.** Parameter estimates of the logistic regression for HPV-16 in CIN2/3 lesions

	Estimate	Standard error	P-value
$\beta_0$	1.19	0.51	0.02
$\beta_1$	-0.03	0.013	0.038

For CIN2/3 we described the relationship between age (grouped into 5-year intervals) and HPV16 by a linear predictor. This led to the parameter estimates given in Appendix Table 2, the fit is presented in Appendix Figure 1.



**Appendix Figure 1.** Model fit (black line) of the logistic regression for the observed proportion of HPV-16 in CIN2/3 lesions (dots). Dashed lines denote the 95% confidence bound of the regression analysis, vertical bars denote the 95% confidence interval of the observed proportion HPV-16.

For cervical cancer we described the relationship between age and HPV16 by using a fractional polynomial of age. We used the polynomial  $\beta_0 + \beta_1 \text{age} + \beta_2 \text{age}^p$  with  $p$  restricted to the predefined set  $S = \{-2, -1, -0.5, 0, 0.5, 1, 2, 3\}$  with  $p=0$  indicating  $\log(\text{age})$ ,<sup>3</sup> and we preferred the model with the lowest Akaike Information Criterion (AIC). The parameter estimates are presented in Appendix Table 3, the fit is presented in Appendix Figure 2.

**Model for the detected CIN2/3 lesions and cervical cancer cases**

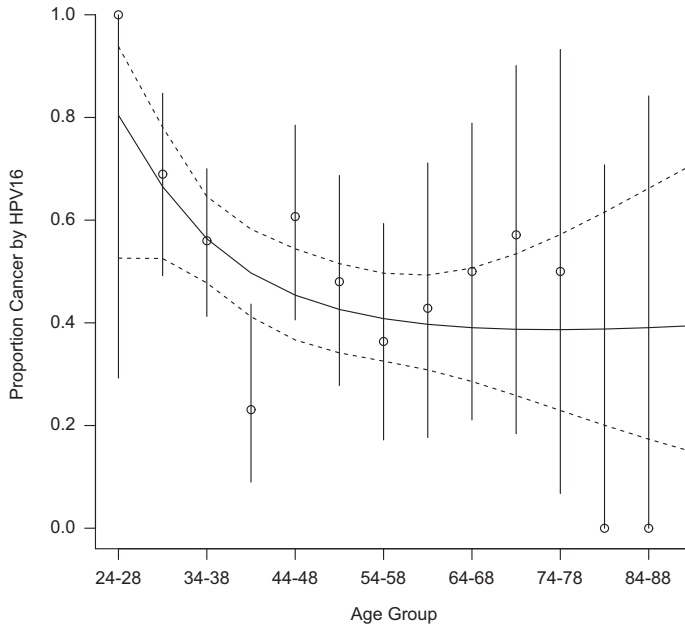
We developed a statistical model for the detection of CIN2/3 or cervical cancer, with the duration from high-grade lesions to cervical cancer as an unknown variable. A woman is infected with HPV at age  $A_{HPV}$  and develops a CIN2/3 lesion at age  $A_{CIN} = A_{HPV} + T_1$ .  $A_{HPV}$  follows the incidence of HPV infection in the Netherlands. Hence,

$$P(A_{CIN} = a_{CIN}) = \int_0^{a_{CIN}} P(T_1 = a_{CIN} - t) P(A_{HPV} = t) dt.$$

**Appendix Table 3.** Parameter estimates of the polynomial  $\beta_0 + \beta_1 \text{age} + \beta_2 \text{age}^2$  describing the proportion HPV-16 in cervical cancer ( $p \in \{-2, -1, -0.5, 0, 0.5, 1, 2, 3\}$ ).

$p$	$\beta_0$	SE	$\beta_1$	SE	$\beta_2$	SE	AIC
-2 <sup>a</sup>	-1.39	1.81	0.0083	0.02	$1.75 \times 10^3$	$1.19 \times 10^3$	310.5
-1	-3.06	3.43	0.017	0.04	98.2	78.7	311.2
-0.5	-6.34	6.72	0.025	0.05	34.3	30.6	311.5
0	10.55	9.5	0.04	0.07	-3.27	3.31	311.8
0.5	6.74	6.57	0.087	0.13	-1.6	1.9	312
1	1.19	0.5	-0.026	0.01	NA	NA	310.7
2	1.86	1.67	-0.054	0.07	$2.67 \times 10^{-4}$	$6.3 \times 10^{-4}$	312.6
3	1.35	1.16	-0.031	0.03	$5.65 \times 10^{-7}$	$3.8 \times 10^{-6}$	312.7

<sup>a</sup>The polynomial  $\text{age} + \text{age}^2$  provided the best model in terms of the AIC  
SE, standard error; AIC, akaikie information criterion



**Appendix Figure 2.** Model fit (black line) of the logistic regression for the observed proportion HPV-16 in cervical cancer (dots). Dashed lines denote the 95% confidence bound of the regression analysis, vertical bars denote the 95% confidence interval of the observed proportion HPV-16.

The time from HPV infection to CIN2/3 development,  $T_i$ , is assumed to be Exponentially distributed with mean  $\lambda$ . We calculated  $\lambda$  from the POBASCAM study.<sup>4</sup> In women with normal cytology at enrolment, 67% became HPV negative, 13% progressed to CIN2+ and 20% remained HPV positive after 5 years. This corresponds to a mean progression time  $\lambda$  of 3 years.

The CIN2/3 lesion may either be detected at screening and treated, or it may progress to cervical cancer (CA) in  $T_2$  years at age  $A_{CA} = A_{CIN} + T_2$ . We are interested in the unknown probability distribution of  $P(T_2 = t_2)$ , the time from CIN2/3 to cancer development.

For each woman we observed the vector  $(A_d, Y)$  with  $A_d$  the age of diagnosis and variable  $Y$  indicating whether cancer had developed before age  $A_d$  ( $Y=1$ ) or not ( $Y=0$ ). This problem addresses a form of doubly censored current status data as we observe for each woman only  $(Y, A_d)$  and both  $A_{CIN}$  and  $A_{CA}$  are interval-censored (if  $Y=1$ :  $A_{CIN} < A_{CA} < A_d$  and if  $Y=0$ :  $A_{HPV} < A_{CIN} < A_d < A_{CA}$ ). For each age group  $A_d=j$  the probability of detecting  $X_j$  CIN2/3 cases and  $Z_j$  cervical cancer cases can be determined, given the total number of detected cases in this age group:  $X_j + Z_j$ . This probability is described in terms of the unknown probability distribution of the time between high-grade lesions and cervical cancer, and the probability of detecting a lesion/cancer while accounting for age-specific screening rates due to cytological screening and the sensitivity of the Pap test. The time distribution from high-grade lesions to cancer,  $T_2$ , is given by a mixture distribution with an unknown proportion  $\omega$  with increasing hazard for ending in the state cancer, and a proportion  $(1-\omega)$  with zero hazard for ending in this state. The time in which the fraction  $\omega$  progress to cancer is assumed to follow a Gamma density with unknown shape parameter  $\kappa$  and scale parameter  $\theta$ . Thus

$$P(T_2 = t) = \omega f_1(t|\kappa, \theta) + (1 - \omega) f_2(t),$$

with,

$$f_1(t|\kappa, \theta) = \frac{1}{\Gamma(\kappa)\theta^\kappa} t^{\kappa-1} e^{-t/\theta}.$$

A proportion  $(1-\omega)$  of the CIN2/3 lesions has zero hazard for ending in the state cervical cancer, which corresponds with  $f_2(t)$  that applies to a length that exceeds life expectancy and is calculated by a uniform density from 110 to 120 years.

By taking the convolution of the distribution of the age of CIN2/3 lesion onset and of the time to cervical cancer, we obtain the distribution of the age of progression to cervical cancer  $A_{CA}$ :

$$P(A_{CA} = a_{CA}) = \int_0^{a_{CA}} P_\phi(T_2 = a_{CA} - t) P(A_{CIN} = t) dt.$$

The observations of CIN2/3 and cervical cancer detection are censored because of screening. Therefore we need to add characteristics of the age-dependent probability of screening due to the national screening program (NSP) and opportunistic smear taking, and of the sensitivity of the Pap test.

We estimated the parameters  $\varphi = \{\omega, \kappa, \theta\}$  by maximizing the log-likelihood function

$$\ell(\phi|X, Z) = \sum_{j=1}^N X_j \log [P_\phi(Y = 0|A_d = j)] + Z_j \log [P_\phi(Y = 1|A_d = j)], \quad (1)$$

with  $N$  the total number of age groups.

Note that for  $Y=0$  it holds  $a_{CIN} \leq a_d < a_{CA}$  and for  $Y=1$  we have  $a_{CIN} < a_{CA} \leq a_d$ .

For  $Y=0$  and  $Y=1$  we can determine the contribution to the likelihood function.

Note that,

$$P_\phi(Y = 0|A_d = j) = \frac{P_\phi(Y = 0, A_d = j)}{P_\phi(Y = 0, A_d = j) + P_\phi(Y = 1, A_d = j)},$$

$$P_\phi(Y = 1|A_d = j) = \frac{P_\phi(Y = 1, A_d = j)}{P_\phi(Y = 0, A_d = j) + P_\phi(Y = 1, A_d = j)}.$$

For the response CIN2/3 detection:  $Y=0$

$$P_\phi(A_d = a_d, Y = 0) = P_\phi(A_d = a_d|Y = 0)P_\phi(Y = 0)$$

$$= \int_0^\infty \int_0^\infty P_\phi(A_d = a_d, A_{CIN} = a_{CIN}, A_{CA} = a_{CA}|Y = 0)P_\phi(Y = 0)da_{CA}da_{CIN}.$$

We assume that CIN2/3 lesions can only be detected in women who participate in the NSP ( $r=1$ ). Besides, participation in the NSP is independent of the unknown parameters  $\phi = \{\omega, \kappa, \theta\}$ . Thus:

$$P_\phi(Y = 0) = P_\phi(Y = 0|r = 0)P(r = 0) + P_\phi(Y = 0|r = 1)P(r = 1),$$

with

$$P_\phi(Y = 0|r = 0) = 0.$$

Hence,

$$\int_0^\infty \int_0^\infty P_\phi(A_d = a_d, A_{CIN} = a_{CIN}, A_{CA} = a_{CA}|Y = 0)P_\phi(Y = 0|r = 1)P(r = 1)da_{CA}da_{CIN}$$

$$= P(r = 1) \int_0^\infty \int_0^\infty P_\phi(A_d = a_d, A_{CIN} = a_{CIN}, A_{CA} = a_{CA}|Y = 0)P_\phi(Y = 0|r = 1)da_{CA}da_{CIN}$$

$$= P(r = 1) \int_0^\infty \int_0^\infty P_\phi(A_d = a_d, A_{CIN} = a_{CIN}, A_{CA} = a_{CA}|Y = 0)I_{a_0 \leq a_d \leq a_{CA}} da_{CA}da_{CIN}$$

$$= P(r = 1) \int_0^{a_d} \int_{a_d}^\infty P_\phi(A_d = a_d, A_{CIN} = a_{CIN}, A_{CA} = a_{CA}|Y = 0) \times$$

$$P_\phi(A_{CA} = a_{CA}|A_{CIN} = a_{CIN}, Y = 0)P(A_{CIN} = a_{CIN}|Y = 0)da_{CA}da_{CIN}$$

$$= P(r = 1) \int_0^{a_d} \int_{a_d}^\infty p_{scr,r=1}(a_d)p_{det} \prod_{l=a_0}^{a_d-1} (1 - p_{scr,r=1}(l)p_{det})P_\phi(T_2 = a_{CA} - a_{CIN}) \times$$

$$P(A_{CIN} = a_{CIN})da_{CA}da_{CIN}$$

$$= P(r = 1) \int_0^{a_d} p_{scr,r=1}(a_d)p_{det} \prod_{l=a_0}^{a_d-1} (1 - p_{scr,r=1}(l)p_{det})P_\phi(T_2 > a_{CA} - a_{CIN}) \times$$

$$P(A_{CIN} = a_{CIN})da_{CIN}. \quad (1)$$

Here,  $p_{scr,r=1}(a)$  is the probability of screening at age  $a$  for participants in the screening program and  $p_{det}$  is the sensitivity of the screening instrument. Note that  $P(A_d=a_d|A_{CIN}=a_{CIN},A_{CA}=a_{CA},Y=0)$ ,  $P(A_{CIN}=a_{CIN}|Y=0)$  and  $P(r=1)$  are independent of  $\varphi=\{\omega,\kappa,\theta\}$ .

For the response CA detection:  $Y=1$

$$\begin{aligned}
 P_\phi(A_d = a_d, Y = 1) &= P_\phi(A_d = a_d | Y = 1) P_\phi(Y = 1) \\
 &= \int_0^\infty \int_0^\infty P_\phi(A_d, A_{CIN} = a_{CIN}, A_{CA} = a_{CA} | Y = 1) P_\phi(Y = 1) da_{CIN} da_{CA} \\
 &= \int_0^\infty \int_0^\infty P_\phi(A_d, A_{CIN} = a_{CIN}, A_{CA} = a_{CA} | Y = 1) \times \\
 &\quad [P_\phi(Y = 1 | r = 1) P(r = 1) + P_\phi(Y = 1 | r = 0) P(r = 0)] da_{CIN} da_{CA} \\
 &= \int_0^\infty \int_0^\infty P_\phi(A_d, A_{CIN} = a_{CIN}, A_{CA} = a_{CA} | Y = 1) I_{a_{CIN} < a_{CA} \leq a_d, r=1} + \\
 &\quad P(r = 0) P_\phi(A_d = a_d, A_{CIN} = a_{CIN}, A_{CA} = a_{CA} | Y = 1) I_{a_{CIN} < a_{CA} \leq a_d, r=0} da_{CIN} da_{CA}.
 \end{aligned}$$

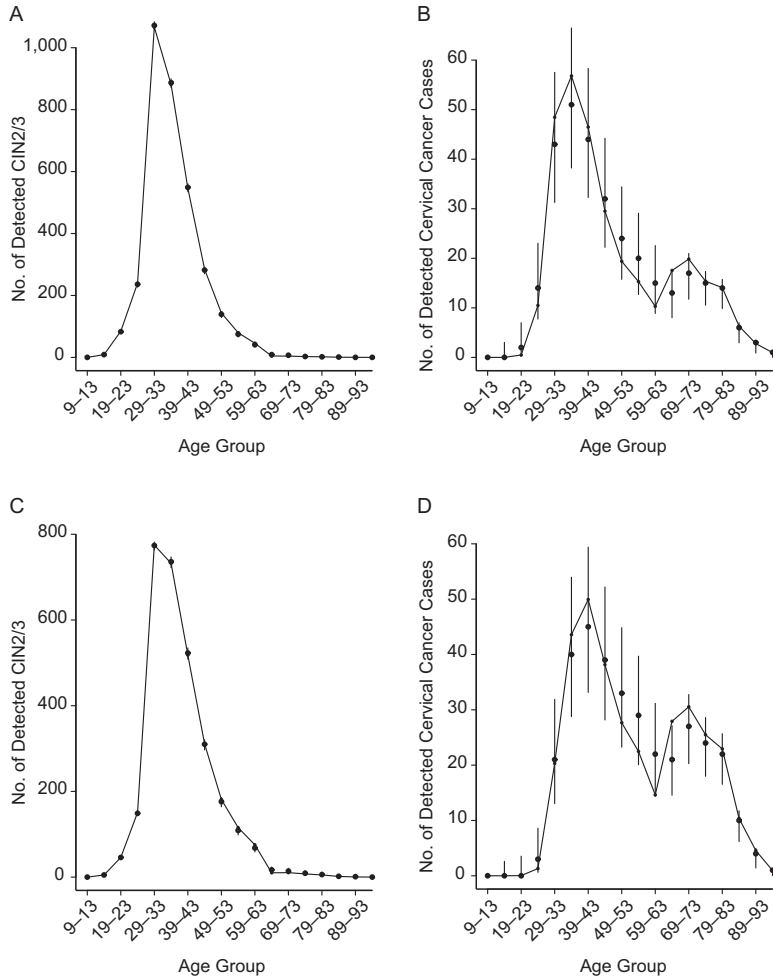
We assume the carcinoma has developed either in the round of detection or in the previous round. Hence,

$$\begin{aligned}
 P_\phi(A_d = a_d, Y = 1) &= \\
 &\int_0^{a_d-1} P(r = 1) p_{scr,r=1}(a_d) \prod_{l=a_{CIN}}^{a_d-1} (1 - p_{scr,r=1}(l) p_{det}) P_\phi(T_2 = a_d - a_{CIN}) P(A_{CIN} = a_{CIN}) + \\
 &\quad P(r = 0) p_{scr,r=0}(a_d) P_\phi(T_2 = a_d - a_{CIN}) P(A_{CIN} = a_{CIN}) da_{CIN} + \\
 &\int_0^{a_d-2} P(r = 1) (1 - p_{scr,r=1}(a_d - 1)) \prod_{l=a_{CIN}}^{a_d-2} (1 - p_{scr,r=1}(l) p_{det}) P_\phi(T_2 = a_d - 1 - a_{CIN}) P(A_{CIN} = a_{CIN}) + \\
 &\quad (r = 0) (1 - p_{scr,r=0}(a_d - 1)) P_\phi(T_2 = a_d - 1 - a_{CIN}) P(A_{CIN} = a_{CIN}) da_{CIN}. \quad (3)
 \end{aligned}$$

Here,  $p_{scr,r=0}(a)$  is the probability of screening at age  $a$  for women who do not participate in the NSP. In Table 2, the screening probabilities per age group are given for respectively the participants of the NSP and the non-participants.

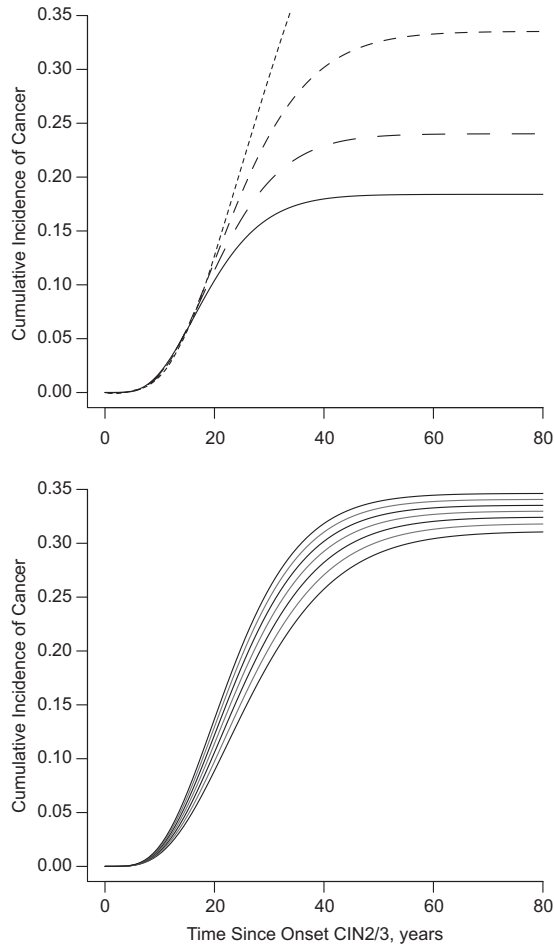
We used equations 2 and 3 in the likelihood function as formulated in equation 1. We maximized the log likelihood using the optim function with the BFGS method (quasi Newton method). All analyses were done using the statistical software package R 2.13.1. The model fit to the data is presented in Figure 2, the fits for HPV16-positive and -negative CIN2/3 and cancer are given in Appendix Figure 3.

Sensitivity analyses were performed to investigate the influence of the proportion of women participating in the NSP, the sensitivity of the Pap test, and of the duration from HPV-infection to CIN2/3 development. The results are presented in Appendix Figure 4 and Appendix Figure 5.

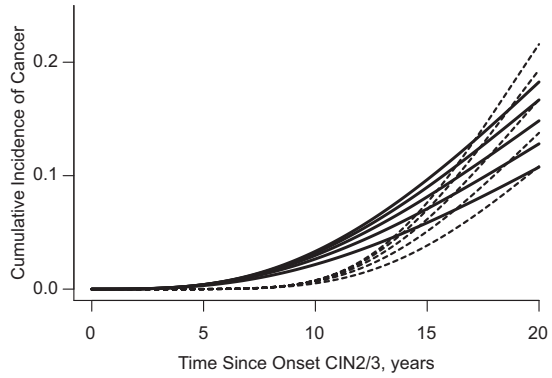


**Appendix Figure 3.** Solid curves represent the expected number of detected high-grade lesions (CIN2/3, sections A and C) and cervical cancer cases (sections B and D) in the Netherlands. The large dots denote the observed number of CIN2/3 lesions and cervical cancer cases, the vertical lines reflect their 95% confidence intervals. The top panel represents HPV-16-positive CIN2/3 and cervical cancer, and the bottom panel is for HPV-16-negative CIN2/3 and cervical cancer. The numbers are given per age group and are averaged over the years 2000-2005.





**Appendix Figure 4.** Sensitivity analysis of the proportion of participants in the NSP (top panel) and the sensitivity of the Pap test (bottom panel) on the cumulative incidence of cancer in absence of screening. The proportion of participants in the NSP varied from 80% (solid), 85% (dashed), 90% (small dashed) to 95% (dotted). The sensitivity of the Pap test was set at 0.5 (bottom), 0.55, 0.6, 0.65, 0.7, 0.75 and 0.8 (top).



**Appendix Figure 5.** Sensitivity analysis of the time from HPV infection to CIN2/3 development on the cumulative incidence of cervical cancer for HPV-16-positive (solid curves) and HPV-16-negative lesions (dotted curves). The mean duration was set at 2 (bottom), 4, 6, 8 and 10 (top) years, for both solid and dotted curves.

## APPENDIX REFERENCES

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