

## Nonattendance is still the main limitation for the effectiveness of screening for cervical cancer in the Netherlands

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Although mass screening for cervical cancer has been operational for more than 2 decades in the Netherlands, 700 women are still diagnosed with this cancer each year (9 per 100,000). We investigated these cases, in order to evaluate opportunities to further increase the effectiveness of the programme. We analyzed the screening history of women diagnosed with cervical cancer between 1994–1997 using the Dutch national pathology file that includes cervical cytology and histological results. More than half of the cases did not have previous preventive cervical smears, and another 30% had never been invited to the programme because of their age. In the future, we estimate that two thirds of all Dutch women with invasive cervical cancer will be unscreened or under-screened, based on current screening participation of more than 70%. We conclude that increasing screening participation has much more potential for further reducing cervical cancer incidence than reducing the screening interval, increasing the age range or having a screening test with higher sensitivity.

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**Key words:** invasive cervical cancer; screening history; coverage

In the Netherlands, screening for cervical cancer has been widespread since the early eighties. In the nineties more than 1,000,000 smears were taken yearly with roughly 3.5 million women in the target age group of the population.<sup>1</sup> The incidence of cervical cancer of 9 per 100,000 women is one of the lowest in the world. In 1996, the Dutch screening programme changed from a 3-yearly programme for women of 35–53 years of age, into a 5-yearly programme for women between 30 and 60 years of age. Both screening schedules reduce the incidence of cervical cancer. For the most recent schedule, we estimated that by responding to all 7 invitations the risk of dying from cervical cancer is reduced by 75%.<sup>2</sup> The percentage of women with any smear in the preceding 5 years in the Netherlands is estimated at over 80%.<sup>1</sup> The effect of screening on a population level, however, will be lower than expected based of these figures, since non participating women have a higher than average risk.<sup>3</sup>

Since 1993, at least 7 studies have described the screening histories of women with invasive cervical cancer.<sup>4–11</sup> The number of cases in these studies was between 46<sup>9</sup> and 481.<sup>4</sup> All studies concluded that the lack of a cervical smear history is the major reason why the disease still occurs. The percentage of women with invasive cervical cancer that had no screening history varied between 28% in Connecticut, USA,<sup>8</sup> and 54% for Maori women in New Zealand.<sup>9</sup> This percentage strongly depends on the population coverage of screening. With a 100% coverage, the percentage will only include young women diagnosed before the starting age of the programme.

For the Netherlands, which has a high screening coverage over a long period, we questioned why there are still about 720 cases of cervical cancer, which cause about 250 deaths yearly.<sup>12</sup> Were most of the women diagnosed with invasive cancer never invited for screening because of their age, were they missed by screening, or did they not or not regularly participate?

To answer this question, we analyzed the screening history of 3,175 women with invasive cervical cancer diagnosed in the years 1994–1997 in the Netherlands. The data were retrieved from the Dutch Network and National Database for Pathology (PALGA). We evaluated whether these women, according to their age at diagnosis, could have been invited for screening, whether they had cervical smears, whether they had abnormal results in the past,

and whether there was a delay in diagnosis after borderline or positive results. Based on this analysis, we explored the possibility of improving the current Dutch programme.

### Material and methods

In the PALGA, all cytological and histological examinations carried out in the Netherlands are registered.<sup>13</sup> This registration started in 1975, and coverage was at least 95% from 1990 onwards. We retrieved all cytological and histological examinations that concern the cervix uteri.<sup>13</sup>

We found 3,175 women diagnosed with histologically confirmed invasive cervical cancer in the years 1994–1997, with 787, 805, 790 and 793 women in the respective years. The numbers in the national cancer registry (which is not linked to the screening history) are about 10% lower: 715, 723, 718 and 721 cases, respectively.<sup>12</sup>

The identification code used in the PALGA consisted of the first 4 characters of the maiden name, gender and date of birth. Women whose names have common first characters can share the same code, leading to misclassification of screening histories. To avoid this influence, we excluded 0.5% of the most frequently registered first 4 characters of the maiden names.<sup>14</sup> This resulted in a reduction of number of cancer cases by 34.7% to 2,074.

For all women with cervical cancer, we assessed whether they could have been invited for mass screening. After a build up period, a 3-yearly mass screening programme for women 35–53 years of age covered 84% of all districts in 1990 in the Netherlands.<sup>15</sup> Women received an invitation to the programme but were not sent reminders. Outside of the programme, spontaneous smears were taken on the initiative of the woman or her physician. Women born before 1925 were over 53 years of age in 1978 and were categorized as being never invited ('too old'). All women born after 1925 were considered as invited at least once. The guidelines for mass screening for cervical cancer changed into a 5-yearly programme for women of 30–60 years of age in 1996 (and since then the geographic coverage of the programme has been 100%, and reminders have been sent systematically). Therefore, for women diagnosed in 1996 and 1997, we included women of 30 years of age (years of birth 1966 and 1967) in the invited group.

For each woman, we distinguished different episodes. An episode starts with a primary (not follow-up) cytological or histological examination. If the primary examination is negative, the episode ends where it started. If positive, the subsequent examinations are considered as follow-up examinations in the same episode. This episode ends when 2 consecutive negative follow-up smears are registered or when there is no examination during 4 consecutive years (Fig. 1).

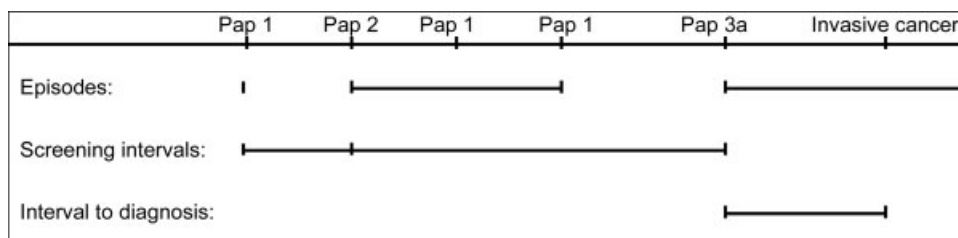
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**FIGURE 1** – Overview of the definitions of our study using 1 exemplary screening history with 3 episodes, 2 screening intervals and the interval to diagnosis.



**TABLE I** – WOMEN DIAGNOSED WITH INVASIVE CERVICAL CANCER IN THE PERIOD 1994–1997, CLASSIFIED TO WHETHER EVER INVITED FOR CERVICAL CANCER SCREENING, PALGA

	Women with cervical cancer	
	Number	Percentage (%)
Never invited for mass screening (too young)	256	12
Invited for mass screening	1458	70
Never invited for mass screening (too old)	360	17
<i>Total</i>	2074	100

**TABLE II** – SCREENING HISTORY OF WOMEN WITH CERVICAL CANCER 1994–1997 AND EVER INVITED FOR MASS SCREENING, PALGA

Screening history	Women with cervical cancer	
	Numbers	Percentage (%)
Diagnosed at first screening invitation (age 30 or 35) <sup>1</sup>	210	14
No preceding smears	797	55
Age < 60 years, screening interval < 6 years	284	19
Age < 60 years, screening interval > 6 years	108	7
Age over 60 years	59	4
<i>Total</i>	1458	100

<sup>1</sup>Screening at age 30 or 35, depending on year of diagnosis (see Material and methods).

We categorized the cases by their age on 31 December of the year of diagnosis. A case was considered to be detected at first screening when the primary examination of the episode in which the cancer was diagnosed was performed at age 35 (or at age 30 in the years 1996 and 1997). For the screening-interval, we used the interval between the primary examination of the episode in which the invasive cancer was diagnosed, and the last preceding primary smear.

According to the guidelines, women should have an additional smear after 6 weeks to 12 months after a smear diagnosed as unqualified, light or moderate dysplasia or negative without endocervical cells. In these cases, we accepted a time until diagnosis of 1.5 year as “in time.” In women with a severely dysplastic smear, an invasive cancer diagnosis within 6 months was classified as “in time.” Women who did not have a diagnosis “in time,” were considered as having “a delay in diagnosis.” The interval to diagnosis is the time between the primary examination of the episode in which the cancer is diagnosed and the actual diagnosis of invasive cervical cancer (Fig. 1).

**Results**

Twelve percent of all women with invasive cervical cancer were never invited for mass screening because they were below the starting age of the programme at the time of the cancer diagnosis (Table I). Seventeen percent of the women were not invited because they were over 53 years of age when the programme was introduced.

**TABLE III** – DISEASE HISTORY: THE HIGHEST CYTOLOGICAL OR HISTOLOGICAL DIAGNOSIS EVER BEFORE THE EPISODE IN WHICH THE CERVICAL CANCER WAS DIAGNOSED IN THE PERIOD 1994–1997, FOR WOMEN FROM 35–60 YEARS OF AGE WITH A SCREENING LESS THAN 6 YEARS PREVIOUSLY, PALGA

Highest diagnosis in the screening history	Women with cervical cancer	
	Numbers	Percentage (%)
Negative	183	64
ASCUS and light dysplasia	87	31
Moderate or severe dysplasia	14	5
<i>Total</i>	284	100

The group of women with cervical cancer that was invited for mass screening was broken down according to the individual screening history (Table II). Fourteen percent were diagnosed at the time of the first invitation (around first age at which they are eligible for screening). Most women (55%) had no smear previous to the episode in which the cancer was diagnosed. In 7% of the women, the screening interval was longer than 6 years. Four percent of the women were over 60 years of age, which means that their last “mass screening” smear was taken at least 6 years ago. Most of these women (51 of the 59 cases) had no cervical smear taken around age 53 (the last age of invitation for the screening programme during the period studied). Finally, 19% of the women had a smear taken in the last 6 years preceding the cancer diagnosis.

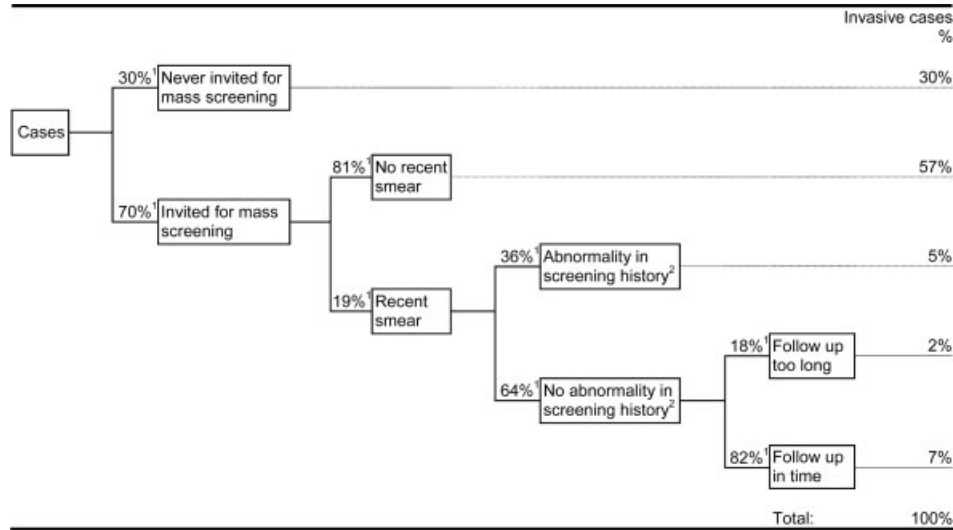
Of this latter group, consisting of the missed cases that were not picked up by screening, we retrieved the highest cytological or histological diagnosis ever in the past, which was before the episode in which the cervical cancer was found (Table III). We found that 31% of these women had a diagnosis of light dysplasia and 5% of at least moderate dysplasia.

For the remaining 64% of the women with only negative results in their previous screening history, we evaluated the time between the primary examination and the diagnosis of invasive cancer. Of all these latter 183 women, 18% had a delay in the diagnosis (see Material and Methods for the definitions).

Combining Tables I–III, we found (see Fig. 2) that among all women diagnosed with cervical cancer between 1994 and 1997, 30% were never invited for mass screening because of their age, 57% did not have a smear in the preceding 6 years, 5% had an abnormal test result in an earlier episode and 2% had a delay in the diagnosis of cancer. Seven percent of the women with cervical cancer did not fall into any of these categories: they had a negative smear within 6 years previously, a “clean” history and no delay in diagnosis.

**Discussion**

In our study, 30% of the women were never invited for cervical cancer screening. In future, this proportion will be reduced. First, the starting age of the programme has been decreased from 35 to 30 years of age. As a consequence, the observed 12% of the women diagnosed with cervical cancer below the starting age of the programme will decrease to ~5% (the cancer incidence below age 30 years). Secondly, the 17% of cases born too early to have ever been invited for screening will eventually die out. Consequently, in the long run the remaining categories of Tables II and III will increase. Therefore, we expect that 10–15% of all women



**FIGURE 2** – Overview of screening history categories under which invasive cervical cancer cases occurred in the Netherlands. <sup>1</sup>The percentages for the categories are combinations of the percentages in Table I–III. *Never invited for screening*: 30% (17% + 12% of Table I), remaining 70% invited; *No recent smear*: 81% (14% + 55% + 7% + 4% of Table II), remaining 19% with a recent smear; *Abnormality in screening history*: 36% (31% + 5% of Table III), remaining 64% without abnormality; *Follow-up too long*: 18% who had a delay, as described in the Results, remaining 82% without a delay. <sup>2</sup>Abnormality (cytological or histological) detected prior to the episode in which the cancer is diagnosed (see Material and methods).

with invasive cervical cancer will be detected at first screening, 15–20% of cancers will be detected in women who followed the guidelines of the programme, 50–55% of all cancer will be detected in women who were not screened or were underscreened and 5–10% of the cancers will be detected in women over 65 years of age. This last percentage is uncertain, because we have no data for women over 75 years of age who have been through a screening program like the one we now offer. Eventually all birth cohorts will have the opportunity to fully participate in the screening program, and we also expect a decrease in the total incidence due to the enlargement of the screening target age-range. So, an increase in a percentage of one of the categories described above may well correspond with a decrease in number of cases.

We analyzed the reasons for the missed cases based on the guidelines for the organized screening programme. However, in the Netherlands, spontaneous screening outside the programme was common. For all categories, opportunistic smears have been included in the analyses. Only for the categorization of “women detected at first screening (age 30 or 35)” opportunistic screening was not included; these women may have had opportunistic smears before the starting age of the programme. This may have decreased the number of women detected at first screening. Because opportunistic screening has been reduced recently in the Netherlands, particularly under the starting age of the programme, its influence will be shown in the coming years.

What are the possibilities to further prevent cervical cancer in the Netherlands? To enlarge the age-range even further, to shorten the screening interval in order to increase programme sensitivity, to improve the test-sensitivity and to decrease the delay in following the guidelines would only affect participants. Adding screening in young ages would decrease incidence by (5 + 10) 15% at most. For adding screening in older ages this would be 5–10%, for increasing sensitivity 15–20% and only a small proportion of cases with delayed follow-up. Therefore, any increase in sensitivity will

have to be accomplished at very low extra costs and no loss in specificity to be cost-effective. Shortening the interval to increase programme sensitivity certainly does not meet these criteria.<sup>14,16</sup>

As far as decreasing nonparticipation is concerned, the question is to what extent the behavior of nonparticipants can be influenced nowadays. In a Dutch study, 72% of all nonparticipants declared they would participate the “next” time, suggesting that they do not have a negative attitude towards screening.<sup>17</sup> This issue needs further investigation.

In other countries the percentage of women with invasive cervical cancer who had not been screened has been reported to be 53%<sup>6</sup> up to 77%.<sup>10</sup> Our study, with 57%, is on the lower end of this range. However, this percentage depends strongly on the screening participation rate. A higher participation rate will lower the fraction of un(der)screened cancer cases. And the participation rate depends partly on the proportion of women invited for the screening programme, and thus also on the number of decades the programme is running.

Our data gives no information on the stage of the cervical cancers. The microinvasive cancers, which have a very good prognosis, presumably, are discovered by screening and especially at first screening. In the latter cases, women have no screening history but have benefited from screening. Therefore, we expect that under-screening will explain an even higher proportion of cases of death than of incident cases. Also, the mortality reduction by preventing these cases will be extremely limited.

In conclusion, even after more than 20 years of screening, incomplete participation is the main cause of cervical cancer incidence. Complete participation would improve screening performance much more than intensifying the screening policy to shorter intervals and broader age ranges, and also more than by having a screening test with better sensitivity. Therefore, exploring ways to increase attendance is of primary importance.

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