# Improvements in the

# Dutch Cervical Cancer Screening Programme

# since 1995

Cover: Wilma Feller

ISBN-10: 90-9020716-3
ISBN-13: 978-90-9020716-2

# Improvements in the Dutch Cervical Cancer Screening Programme since 1995

Verbeteringen in het Nederlandse bevolkingsonderzoek naar baarmoederhalskanker na 1995

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de rector magnificus

Prof.dr. S.W.J. Lamberts

en volgens besluit van het College voor Promoties

De openbare verdediging zal plaatsvinden op
donderdag 1 juni 2006 om 13.30 uur

door

Anita Beatrijs Bos

geboren te Den Haag

**Promotiecommissie**

| | |
|---|---|
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Voor Wilma

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# 1

# INTRODUCTION

## *Screening for cervical cancer*

### Cervical cancer incidence and mortality

Worldwide, cervical cancer is the second most common cancer in women, and therefore an important public health problem (1). In developing countries, the age standardised incidence rate varies between 16 - 40 per 100,000 women in 1988-1992 (2). In the same period, in developed countries the incidence is much lower, ranging from 3.6 cases per 100,000 women in Finland to 15 cases in Denmark. The incidence in the Netherlands is one of the lowest in the world, with an age standardised incidence rate of 7.1 cases per 100,000 women per year (2). Until recently, some 730 revised cases of cervical cancer were diagnosed annually in the Netherlands and each year approximately 250 women died from this disease (3)The lifetime risk for cervical cancer in 1998 was 0.75%. Cervical cancer screening, which has been common practice in the Netherlands in some form or another since the late seventies, has contributed to achieve thess low incidence and mortality rates.

### Mass screening for cervical cancer

The natural history of cervical cancer is characterised by a long preclinical screen-detectable stage. This stage is divided in a long pre-invasive stage and a shorter (about 4 years) preclinical invasive stage. The mean duration of the total preclinical detectable stage was estimated at between 10-25 years (4-7, and chapter 6 of this thesis).

The pre-invasive stage, preceding cervical cancer is characterized with dysplastic changes in the transformation zone of the cervix epithelium. The cellular dysplastic morphological changes can be seen in the Pap smear, in which scraped cells from the cervix uteri are evaluated under the microscope.

A complicating factor in screening for cervical cancer is the fact that not all pre-invasive lesions will progress into cervical cancer (5, and chapter 6 of this thesis). As

yet, there is no way to distinguish non-progressive lesions from progressive lesions. Therefore, all women with such lesions are treated, leading to overtreatment.
The effect of mass screening for cervical cancer on incidence and mortality has never been established in a randomised controlled trial. The reason is that the (positive) effect of the screening seemed obvious, in a period when randomized controlled trials were not usual, was that a precursor of cancer could be detected and treated with an almost 100% cure rate. Non-experimental studies analysing the effects of the introduction of mass screening (8-10) have demonstrated that screening is effective in reducing incidence and mortality, although the extent of the effect remains uncertain.
Estimations for the sensitivity of Pap-smears for Cervical Intraepithelial Neoplasia (CIN) vary between 29%-80% (5, 11-14). These estimates differ depending on the estimation methods, the screening procedures, but also on the cut-off between a "positive" and a "negative" result. A high sensitivity, in which nearly all preinvasive lesions are detected, leads to a low specificity, with a high percentage of false-positive smears. Furthermore, women who participate in screening for cervical cancer are, as a group, found to be at a lower risk than non-participants (5, 15, 16).

**Screening for cervical cancer in the Netherlands**

In the mid-seventies, mass screening for cervical cancer was introduced in the Netherlands in three pilot regions, Nijmegen, Rotterdam and Utrecht. By the late seventies, programmes had been implemented in most parts of the Netherlands. Women between 35 and 53 years of age were invited for screening every three years, which means that each woman received a total of seven invitations in her life. Furthermore, it was common practice for (additional) spontaneous smears to be performed at the initiative of either the women herself or her physician.
In 1993, it was decided to reorganize the Dutch approach to cervical cancer screening. The main goal of this revision was to increase the effectiveness and to decrease the number of smears, as by the late eighties the Dutch cervical cancer screening programme was characterized by an excessive number of smears taken in too young age and at too short intervals. As usual in screening practice, there was a tendency towards intensive screening and follow-up in order to prevent interval cancer cases.
In 1996, the revised screening programme was introduced. The organisation was improved in order to increase the attendance, and to reduce smear taking outside the screening programme. Under the revised system, instead of inviting women for screening between the ages of 35 and 53 every 3 years, women aged 30 to 60 years

were invited every 5 years, leaving the 7 invitations per lifetime unchanged. To reduce the number of women in follow-up, the recommendations for follow-up after a smear classified as Pap 2 were changed. In particular, smears with morphological changes associated with infection were no longer to be classified as Pap 2. Furthermore, for quality control, the evaluation of the screening programme was improved.
Reducing the number of smears performed outside the programme was partly achieved by the method of financing: only smears obtained within the screening programme, or smears taken for medical reasons were to be reimbursed, while spontaneous smears were not.

### Screening policies

The balance of positive and negative effects of the screening programme serves as an important input for policy making, an aspect of screening that is further underlined by the Dutch Population Screening Act (WBO). In order to predict these effects of alternative screening strategies (e.g. different screening intervals and age-ranges), a microsimulation programme for cancer screening MISCAN was used. In MISCAN, the main factors that influence the effects of the screening are quantified and validated (4-6). The model includes incidence, sensitivity and specificity, non-progressive lesions, duration of the preclinical phase, attendance rates and the relative risk of participating women. Using MISCAN, alternative screening strategies can be simulated and their effects and costs calculated, resulting in a cost-effectiveness ratio for each strategy. The guidelines of the present Dutch screening programme were based on estimates by MISCAN (17).

## *Evaluation of cervical cancer screening in the Netherlands*

The work described in this thesis forms part of a continuous evaluation of the Dutch screening programme, before and after an important reorganisation of 1996. For the evaluation, the national pathological data collected by the PALGA (Dutch Network and National Database for Pathology) were retrieved and transformed into a comprehensive database for cervical screening, follow-up results and clinical diagnoses (PALEBA, described below). We used these data to describe the practice of cervical cancer screening in the Netherlands in 1994, which is representative for the situation before the reorganisation. This served as a baseline to evaluate the practice in the years after the reorganization.

### Pathology data: PALGA and PALEBA

In the PALGA, all cytological and histological examinations performed in the Netherlands are registered. The registration started in 1975, and " the coverage" of PALGA , i.e. the proportion of examinations registered in the database, constantly increased until 1990, when nearly all cytological and histological examinations, including all Papanicolaou smears, were registered. A PALGA registration consists of the identification of the patient, the date, type, topography and method of examination, the results and conclusion. For cervical smears there is an extra method for registration of important factors for the evaluation, the so called Cervical Registration and Information System (CRIS) In the CRIS, among others things, the reason for obtaining the smear and the so-called KOPAC-B result (see Table 1.1) are registered.
The identification used in the PALGA consists of the first four characters of the surname (or maiden name, in the case of a married woman), gender, and date of birth. This can lead to misclassifications when combining the data, as commonly occurring names can yield identical identity codes, which means that data belonging to different individuals may be erroneously assigned to a single person. On the other hand, (typing) errors will result in false identifications.

From the PALGA, all examinations concerning the cervix were retrieved into a large database called 'PALEBA'. In this database, women were followed over time on basis of the PALGA identification. For each woman, we defined different episodes. An episode always started with a primary examination (cytological or histological). If the primary examination was negative, the episode ends where it started. If the primary examination was positive, the next examination was considered a follow-up (secondary) examination. An episode ended after two or three (depending on the most severe previous result) consecutive negative follow-up smears or after no further examinations were registered during a four-year period.

The cytological result of a screening Pap smear was categorized according to the corresponding recommendations: (1) follow the screening schedule (normal smears), (2) have an additional smear (smears with ASCUS, light dysplasia and unqualified smears and, until the 1$^{st}$ of January 2002, for smears without endocervical cells), (3) a recommendation for referral to a gynaecologist for colposcopic evaluation of the cervix (smears with moderate dysplasia or worse) (Table 1.1). The histological results were categorized into three pre-invasive stages CIN 1, CIN 2, CIN 3 and

invasive cervical cancer (distinguishing between squamous carcinomas and adenocarcinomas).

**Table 1.1**
Overview of the different cytological diagnoses, the KOPAC-B results, the diagnosis according to the Bethesda system and the Pap-classification, and the recommendation after the 1996 revision of the screening programme

| **Cytological result**<br>- KOPAC-B classification<br>- Bethesda-classification<br>- pap-classification | **Recommendation** |
|---|---|
| **Severe abnormalities**<br>- p>4 or c>5 or a>3<br>- Moderate or high grade SIL<br>- Pap 3a2 or worse | referral to the gynaecologist |
| **Light abnormalities**<br>- p>0 or c>2 or a>2[1]<br>- ASCUS or low grade SIL<br>- Pap 2 and pap 3a1 | additional smear (after 6-12 months) |
| **Unqualified smears**<br>- p<2 and (a< 3 or a=9) and c<3 and (k=0 or p=0 or a=0 or c=0)[1]<br>- Pap 0 | additional smear (immediately) |
| **Without endocervical cells**<br>- p<2 and (a< 3 or a=9) and c<3 and c=2[1]<br>- Pap 0 or pap 1 | additional smear (after 6 months) |
| **Negative**<br>- p=1 and c<3 and a<3[1]<br>- Pap 1 | remain in screening programme |

1. The definitions of the KOPAC-B are presented hierarchically, so in each category previous categories are excluded.

In the PALEBA, about 13,000,000 examinations of the cervix had been registered by the year 2003. This national database, where smears and their follow-up can be analysed on a national level, is unique for the evaluation of cervical cancer screening.

### Attendance and coverage

The proportion of women who participate in cervical screening is important for the effectiveness of the programme, also because non-participants as a group appears to have a higher risk for cervical cancer than participants (5).

In the early nineties, the programme attendance rate, defined as the number of invited women who actually underwent screening was estimated at 50% for the Netherlands (18). Based on the PALGA data, we estimated that the coverage in 1994, defined as the proportion of women between 35 and 54 years of age who had had a smear (of any type) in the preceding 5-years, was 72% (the population in the denominator was smaller due to the assessed numbers of women who had undergone a hysterectomy)(19, 20). Hence the proportion of women protected by mass screening was higher than suggested by the programme attendance rate. This is attributable to screening and diagnostic activity outside the programme.
Despite the low programme participation rate, the total number of smears taken in 1994 was high: 940,000 (Table 1.2). Of these, 680,000 were taken as a primary smear, while 260,000 (28%) were performed after a non-negative smear and thus classified as follow-up smears (Table 1.2). During this period, there were 1.8 million women between the ages of 35 and 57, which implies that 600,000 smears (screening interval of 3 years) would have been needed to achieve a 100% attendance rate, and 430,000 smears to achieve 72% coverage. In 1994, therefore, 680,000 primary smears were taken, while only 430,000 were necessary to yield the actual 72% coverage achieved. Hence some 240,000 excess smears were taken outside the programme schedule. This number includes smears taken for medical reasons other than prevention.

**Table 1.2**

Number of smears by reasons for smear taking, 1994, PALGA

| Reason for smear | Number in 1994 | Percentage in 1994 |
|---|---|---|
| Mass screening | 209169 | 22% |
| Spontaneous screening | 55593 | 6% |
| Medical indication | 61648 | 7% |
| Primary, unknown reason | 349873 | 38% |
| Secondary | 256696 | 28% |
| Total | 932979 | 100.0% |

### Spontaneous screening

Spontaneous or opportunistic screening refers to screens performed outside the screening programme, at the initiative of either the women involved or her physician. Such screens are thought to be less efficient compared with programme screening,

because they are obtained from women at low risk for cervical cancer because of their young age. Moreover, the intervals between the smears tend to be too short. The reason for half of the primary (not obtained for follow-up reasons) smears taken in 1994 was not registered (classified as "unknown"). When assuming that these smears were taken for the same reasons as smears with a known reason, 64% of the primary smears (433,373 smears) were taken within the mass screening programme, 17% were spontaneous smears (115,182 smears) and 19% (127,727 smears) were taken for medical reasons. In that case, over 20% of all preventive smears were taken outside the screening programme.

One of the indicators for the efficiency of screening is the detection rate (the number of cases detected per 1,000 smears) for severe neoplasia. The detection rates were 4.7, 5.7 and 8.5 for mass screening, spontaneous screening and medical indication, respectively (19).

**Table 1.3**

Results of the mass screening smears, obtained in women 35-54 year of age in 1994, PALGA

| Cytological result | Percentage (n= 196,000[1]) |
|---|---|
| Severe abnormalities | 0.47% |
| Light abnormalities | 10.0% |
| Unqualified smears | 1.3% |
| Without endocervical cells | 7.2% |
| Negative | 81.1% |
| Total | 100.0% |

1. The number of mass screening smears (n=196,000) is lower compared with the number of Table 1.1, because of the age-range used.

The highest proportion of severe abnormalities was detected in smears taken for medical reasons, although the difference in comparison with the other type of smears was not remarkable. Obviously the 'medical indication' was not very specific for cervical neoplasia. This is in line with the fact that cervical neoplasia is asymptomatic.

In 1994, over 100,000 smears were taken for preventive reasons outside the screening programme (spontaneous screening). The proportion of severe abnormalities detected in spontaneous smears was higher than that detected in mass screening smears. This suggests that spontaneous screening may not be as

inefficient as expected, although the results must be confirmed by histological diagnoses.

**Follow-up of minor abnormalities**

Before the reorganization of the screening programme, a relatively high percentage of the women received follow-up after each preventive smear, while the risk for invasive cervical cancer is low in the Netherlands. As a result, in 1994, 260,000 smears were taken for follow-up reasons; this was 28% of all smears taken in that year. This high number of follow up smears is an important negative effect of the cervical cancer screening programme.

Some 81% of the smears taken in 1994 in women between the ages of 35 and 54 within the screening programme were negative (Table 1.3). A small percentage (0.5%) of these smears showed severe cytological abnormalities, associated with a direct recommendation for referral to the gynaecologist, in 10% of the smears minor abnormalities were found, 1.3% was unqualified and 7.2% contained no endocervical cells; in these latter cases, (10+1.3+7.2), a repeat smear was recommended (see Table 1.1 for the definition of the various diagnoses).
Hence 10% of all women who had had a preventive smear were recommended for an additional smear because of (minor) abnormalities. The recommendations prescribed at least two consecutive negative repeat smears before ending the follow-up, which meant that the number of repeat smears and the length of the follow-up period could be extended. However, the recommendations were not very well adhered to. After a period of 1.25-2.25 years, 46% of the women in this group had no follow-up at all.
Since 1996, the Pap 2 classification has been redefined, in an attempt to lower the number of smears so classified. Moreover, the number of follow-up smears was reduced to 2 at most, after which women are to be referred either back to the screening programme or to the gynaecologist for colposcopy. This latter recommendation has raised concerns, especially among gynaecologists, was that too many women would consequently be referred for colposcopy.

**Smears without endocervical cells**

Up to 2002, women who had negative smears without endocervical cells were recommended to have an additional smear. The presence of endocervical cells was seen as an indicator for a representative smear, covering the complete transformation zone. The absence of endocervical cells in a cervical smear was

expected to be associated with false-negative results, because studies described a higher percentage of abnormalities detected in smears with endocervical cells compared to smears without endocervical cells (21-26). The relevance of the presence of endocervical cells was never examined in a longitudinal study-design with invasive cancer as an endpoint.

In 1994, over 7% of all primary smears obtained in the Netherlands were negative but lacking endocervical cells (19). The women in question were recommended to have an additional smear within 1 year. Compliance with this recommendation was poor: in 55% of the cases, even after 1.25 years there was no record of a repeat smear having been carried out. However, a considerable proportion of these women did have a repeat smear, while the positive effects were uncertain. For the cost-effectiveness of cervical cancer screening, the necessity of the repeat-recommendation of negative smears without endocervical cells is an important issue.

**Table 1.4**
Number of women diagnosed with cervical cancer in the Netherlands by age group, CR 1989-2003

| Age | Year | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **1989** | **1990** | **1991** | **1992** | **1993** | **1994** | **1995** | **1996** | **1997** | **1998** | **1999** | **2000** | **2001** | **2002** | **2003** |
| **< 30** | 33 | 44 | 45 | 29 | 38 | 24 | 43 | 32 | 35 | 42 | 39 | 15 | 28 | 29 | 21 |
| **30-40** | 183 | 180 | 193 | 207 | 211 | 183 | 214 | 214 | 194 | 186 | 197 | 193 | 169 | 149 | 137 |
| **40-50** | 141 | 157 | 144 | 156 | 147 | 164 | 151 | 135 | 170 | 170 | 166 | 136 | 123 | 151 | 147 |
| **50-60** | 91 | 103 | 79 | 92 | 90 | 90 | 96 | 104 | 96 | 99 | 97 | 105 | 98 | 102 | 96 |
| **60-70** | 127 | 121 | 116 | 106 | 97 | 87 | 89 | 83 | 82 | 90 | 70 | 76 | 58 | 77 | 60 |
| **70-80** | 97 | 113 | 97 | 114 | 95 | 103 | 87 | 99 | 103 | 97 | 89 | 97 | 65 | 88 | 73 |
| **> 80** | 46 | 42 | 61 | 47 | 43 | 65 | 45 | 54 | 55 | 65 | 44 | 57 | 50 | 48 | 50 |
| **All** | 718 | 760 | 735 | 751 | 721 | 716 | 725 | 721 | 735 | 749 | 702 | 679 | 591 | 644 | 584 |

### Incidence of cervical cancer

National data on incidence and mortality are available from the year 1989, (3). The incidence remained stable for a decade, but decreased since 1999 (Table 1.4). The coming years will show whether the incidence has settled at a lower level or decrease further. The average number of women diagnosed with cervical cancer, during 1989-2003, is 702 per year (Table 1.4). The incidence in the different age groups has not changed much. The cervical cancer cases are diagnosed in spite of widespread screening for cervical cancer. It is unclear from the cancer registration

how many cases occurred in women who attended the screening programme (interval cancer), how many in women outside the age range of the programme, and how many in women not participating in the programme at all.
The number of interval cancer cases is a measure for the sensitivity of the programme, because these women are missed by the programme. For the evaluation of the screening programme, it is necessary to study the screening history of these cases in order to advise on possible changes to improve the effectiveness of the screening programme.

**Non-progression**

Not all pre-invasive cervical neoplasia will progress into invasive cervical cancer if left untreated. If these regressive, or at least non-progressive, lesions are detected by screening in women, they are treated, because the lesions are indistinguishable of progressive lesions. The women involved have only negative effects of the screening. This ineffective follow-up and treatment generates extra costs.
The proportion of regression has been described as depending on age, i.e. in younger women the proportion of regression is higher than in women over 30 years of age. This, in combination with the long pre-invasive stage, is an important argument for starting mass screening for cervical cancer at about 30 years of age.

## *Research questions*

The research questions studied in this thesis had occurred while evaluating the cervical cancer screening programme in the Netherlands at time of the 1996 revision. From the starting point -the screening programme in 1994- the following questions had arised:

1. Is, after three decades of cervical cancer screening, an invitational programme still necessary for a high coverage?
2. How does the risk for cervical cancer in women using spontaneous screening compare with that of women using programme screening?
3. What is the effect of the revised definition of Pap 2 results and its follow-up?
4. Should negative smears without endocervical cells be followed by a repeat smear?
5. Why are there still 700 new invasive cervical cancers every year in the Netherlands, in spite of long-term screening with fairly high coverage ?
6. What proportion of the incidence of pre-invasive neoplasia is non-progressive?

## *Reading guide*

In chapter 2, the coverage for women invited for mass screening is compared with that of women who were not invited, on basis of data of the Dutch National Health Interview Survey (question 1).
In chapter 3, we compare the risk for cervical cancer in women who used spontaneous screening with that in women who used mass screening. This comparison is important for the effectiveness of an invitational programme and of additional opportunistic screening (question 2).
In chapter 4, the revised recommendations concerning the follow-up of 'Pap 2' (minor abnormalities) are evaluated (question 3). The proportion of Pap 2 smears were studied and the number and results of repeat smears, in order to predict the percentage of women referred to the gynaecologist.
In chapter 5 we explore the relevance of the presence of endocervical cells in otherwise negative smears, by comparing the cancer rates during follow-up after negative smears with and without endocervical cells (question 4).
In chapter 6, the screening history of all women diagnosed with invasive cervical cancer in 1994-1997 in the Netherlands is evaluated, to explore the major shortcomings of the screening programme (question 5).
In chapter 7, we estimate the proportion of non-progressive lesions, with data from Maribo County, Denmark (question 6).
In chapter 8, the research questions of the thesis are answered, the revised recommendations are evaluated by comparing screening data of 1994 and 2001, recent developments are discussed and conclusions and recommendations are drawn.

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# 2

# ORGANISED CERVICAL CANCER SCREENING STILL LEADS TO HIGHER COVERAGE THAN SPONTANEOUS SCREENING IN THE NETHERLANDS


## *Abstract*

In The Netherlands, early detection of cervical cancer by programme and spontaneous screening has been common practice for more than two decades. Both types of screening are mainly performed by the general practitioners. Therefore, the question is raised whether programme screening still enhances screening uptake. To answer this question, we analysed the national health interview survey in the years 1992-1996. The coverage rate, defined as the percentage of women with at least one smear taken in the previous five years, was 91% for women invited for programme screening compared with 68% for women not invited. The performance of the organised programme in reducing excessive screening, i.e. smears taken in excess to the recommended age and interval range, was not clear and the effect seemed small. Furthermore, we found that half of non-attenders were "protected" by a recent smear or a hysterectomy, and of the unprotected women 72% showed a positive attitude towards the programme. We conclude that even after a long history of cervical cancer screening, an organised programme is still required to ensure a high coverage.

## Introduction

Since the seventies, both programme screening and spontaneous screening have been used in the early detection of cervical cancer in The Netherlands. In programme screening, all women of the target population within a municipality are invited for a pap-smear. This is usually seen as the most effective method of providing screening (1, 2, 3). In spontaneous screening, preventive smears are taken on the initiative of the woman and/or her physician. The supposed superiority of programme screening concerns its achievement of a higher coverage and possibly also of a smaller number of smears taken in excess to the official age and interval guidelines. A counter argument could be that both physicians and women are well aware of the pap-smears, and that the flexibility of spontaneous screening will lead to higher coverage, although not with constant intervals between screens.

The long tradition of screening for cervical cancer in The Netherlands must have increased the awareness of guidelines for effective screening both in women and in physicians. Moreover, both systems of early detection are performed by the general practitioner. Therefore, the question is raised of whether an organised programme is still important. Our aim was to study coverage and excessive smear taking for programme screening and for spontaneous screening. Furthermore, we studied the attitude of non-attenders to screening as a proxy for the maximum achievable participation rate.

We used data from the health interview survey (HIS) of the years 1992-1996, in which questions about cervical smear uptake were included. These questions concerned attendance, reasons for non-attendance and attitude towards the programme. In this period, programme screening was running in approximately 80% of the municipalities.

## Material and methods

The national health interview survey (HIS) is held yearly by the Statistics Netherlands (CBS) and collects information on health, medical consumption and life style of a random sample of households. Part of the interview is personally obtained by an interviewer, the remainder, including the questions about mass screening, consists of a written questionnaire, filled in personally. The population interviewed in the HIS is

standardised for the Dutch population according to gender, age, marital status and a combination of geographical region and urbanisation rate. Accordingly, all *n* values and percentages presented in this article are standardised. In the period studied, the non respondent rate was 44%, and 9,857 women over the age of 16 participated in the HIS.

There is no complete information available on which municipalities organised mass screening in the period studied (1992-1996). We considered a municipality as having an organised programme if at least one women aged 35-54 reported that she received an invitation for cervical cancer screening in the year studied.

Up to 1996, screening was recommended every three years for women between the ages 35 and 54 years. After 1996, the Dutch guidelines changed, recommending screening for women between 30 and 60 years every five year. The coverage rate was defined as the proportion of women aged between 35 and 54 years with at least one smear in the previous five years. As a proxy for the amount of excessive screening, we considered the proportion of women with at least three smears in the previous five years for women within the target age range (35-54 years), and the proportion of women under the age of 30 that had been screened. We did not include women between the ages of 30 and 34 years in the analysis of excessive smears, because the starting age changed from 35 to 30 during the study period.

Non-attendance was analysed in women who reported receiving an invitation. Women who did not attend were divided into protected and unprotected non-attenders, according to the reported reasons for not attending. Women who answered 'I have been treated or underwent surgery', 'I am under surveillance' or 'I recently had a smear taken' were considered as protected, and those 'I do not think it is necessary' 'I think the examination is unpleasant', or 'I did not have time' as unprotected.

Unprotected non-attenders were compared with protected women (both attenders and protected non-attenders) for age, level of income, marital status and level of education. The characteristics were studied in a multivariate model, of which the odds ratios (OR) and their 95% confidence intervals (CI) were calculated.

## Results

### Coverage

Of the women between 35 and 54 years of age, 66% (3,827/5,773) reported receiving an invitation for cervical cancer screening (*Table 2.1*). Only 9% of the invited women had no smear taken in the five years prior to the study. Of the women who did not receive an invitation for mass screening, 32% had no smear taken in the previous five years. Hence, the coverage rate for women who were invited was 91% and for women not invited it was 68%.

A coverage comparison was also made on the municipality level. Of the women between 35 and 54 years living in municipalities with a screening programme (defined as municipalities with at least one woman who had received an invitation) 84% (4,500/5,336) had a smear taken in the preceding five years, compared with 68,5% (306/447) for women in municipalities without a screening programme.

**Table 2.1**
Smear frequency for women aged between 35 and 54 years with and without an invitation for mass screening (HIS 1992-1996)

| Number of smears taken in the previous five years | Women invited for mass screening *n* = 3,827 (%) | Women not invited for mass screening *n* = 1,946 (%) |
|---|---|---|
| 0 smears | 344 (9) | 630 (32) |
| 1-2 smears | 2,871 (75) | 1,092 (56) |
| ≥ 3 smears | 612 (16) | 224 (12) |

### Frequency of excessive smears

Of women between 35 and 54 years who received an invitation for cervical cancer screening, 16% had three or more smears in the previous 5 years compared with 12% for women who were not invited (*Table 2.1*). Of the women who had received at least one smear, 18% (612/3,483) had received at least three smears for programme screening and 17% (224/1,316) for spontaneous screening (*Table 2.1*). For the young (< 30 years) age group, 30% of the women in municipalities with programme screening had at least one smear taken in the five years prior to the study (*Table 2.2*). In municipalities without a screening programme, the proportion was higher at 39%.

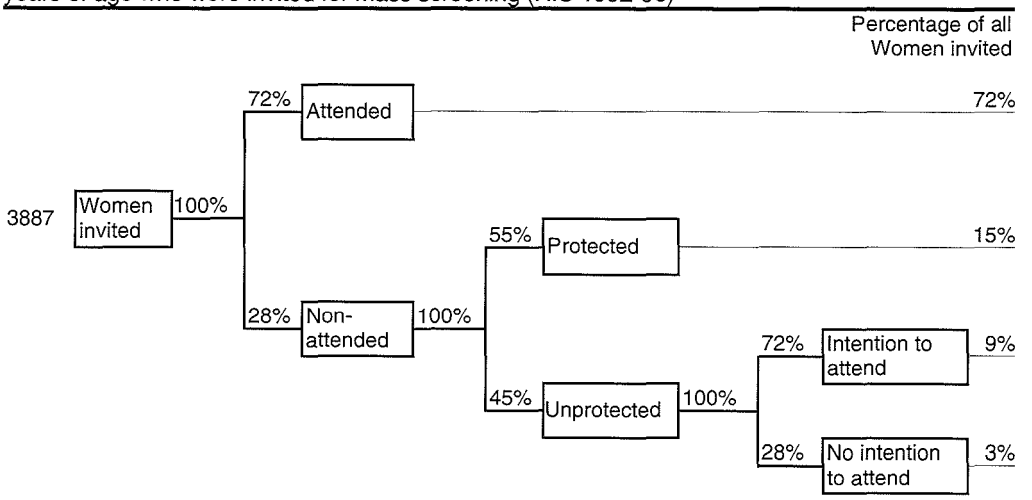
**Table 2.2**
Smear frequency for women aged between 16 and 30 years in municipalities with and without an invitation programme (HIS 1992-1996)

| Number of smears taken in the previous five years | Municipalities with programme screening | | Municipalities without programme screening | |
|---|---|---|---|---|
| | *n*=3,770 | (%) | *n*=314 | (%) |
| 0 smears | 2,635 | (70) | 192 | (61) |
| ≥ 1 smear | 1,135 | (30) | 122 | (39) |

## Non attendance

In the period 1992-1996, 72% of the invited women attended the programme screening (*Figure 2.1*). Fifty-five per cent of the non-attenders were protected by previous surgery or a recent smear. Thirteen percent (490/3,887) of the invited women did not attend while unprotected; of this group 72% reported that they planned to attend the next time, whilst the remaining 28% did not show this positive attitude to screening.

**Figure 2.1**
Attenders rates and reasons for non-attendance for responding women between 35 and 54 years of age who were invited for mass screening (HIS 1992-96)



### Characteristics of unprotected non attenders

Characteristics of unprotected non-attenders compared with protected women (both attenders and protected non-attenders) are shown in *Table 2.3*. Older women (50-54 years) were less likely to be protected compared with younger women (OR 0.71, 95%CI: 0.53-0.96). Women with a low income were over-represented in the unprotected group, but the difference was not significant (OR 1.39, 95%CI:0.96-2.01 for net income of < 25,000 dfl). Concerning marital status, we found that women who were never married were significantly more likely to be unprotected (OR 2.18, 95%CI:1.56-3.04). Women with only primary school education were more likely to be unprotected than the other categories.

**Table 2.3**
A comparison of unprotected and protected women: odds ratios and 95% confidence intervals (CI) (HIS 1992-1996)

| Variables | Number | Being unprotected | |
|---|---|---|---|
| Categories | | Odds ratio[1] | 95% CI |
| Age (years) | | | |
| 35-39 | 1165 | Reference | |
| 40-44 | 1107 | 0.74 | 0.57 - 0.95 |
| 45-49 | 904 | 0.93 | 0.72 - 1.22 |
| 50-54 | 763 | 0.71 | 0.53 - 0.96 |
| Education | | | |
| Primary school | 689 | Reference | |
| Junior education | 1304 | 0.56 | 0.42 - 0.74 |
| Senior education | 1264 | 0.67 | 0.51 - 0.89 |
| Vocational collage | 562 | 0.75 | 0.53 - 1.06 |
| University | 120 | 0.63 | 0.35 - 1.14 |
| Net income (dfl) | | | |
| < 25 000 | 414 | 1.39 | 0.96 - 2.01 |
| 25 000-40 000 | 892 | 1.00 | 0.73 - 1.36 |
| 40 000-55 000 | 934 | Reference | |
| > 55 000 | 1078 | 1.15 | 0.85 - 1.54 |
| Unknown | 721 | 0.94 | 0.68 - 1.31 |
| Marital status | | | |
| Married | 3222 | Reference | |
| Divorced | 376 | 1.26 | 0.90 - 1.75 |
| Widowed | 89 | 1.52 | 0.85 - 2.71 |
| Never maried | 252 | 2.18 | 1.56 - 3.04 |

1. Odds ratio estimated in a multivariate model

## Discussion

The non-response rate in the health interview survey (HIS) was 44%. Usually, this creates a bias by which screening attendance is overestimated in interviews (4). We therefore think that the absolute level of coverage will be also overestimated in our study. However, the comparison made between programme screening and spontaneous screening will be less influenced by the non-response rate.

We found a higher coverage in women aged between 35 and 54 years invited for screening (91% had a smear taken in the previous five years) compared with non-invited women (66%). This difference in coverage could be an overestimate, if attenders are more likely to remember receiving an invitation than non-attenders. Therefore, we also compared the coverage rate on the level of municipalities with and without organised screening, defined as a municipality in which at least one women reported receiving an invitation. This approach will, to some extent, result in an underestimate of the difference, due to municipalities which started the programme shortly before or during the period studied. The coverage for women in municipalities with a screening programme was 84%, compared with 69% for municipalities without a screening programme. In view of the importance for the (cost-) effectiveness of cervical cancer screening (2, 5, 6), the difference in coverage is still high.

The influence of the screening programme on excessive smear taking was studied by looking at the frequency of smear taking. For women within the target age group (35-54 years), we found a higher proportion of women with at least three smears in the previous five years in women who were invited for mass screening. However, of those women who received a cervical smear, the same proportion of woman had received at least three smears in the programme screening (18%) and spontaneous screening (17%). For the age group under the target age range (< 30 years), the percentages of screened women was lower (30%) in municipalities with an organised programme compared with municipalities without an organised programme (39%). A possible explanation is an effect of organised programmes that start screening at a specific age, resulting in less screening under the starting age. Overall, the influence of the screening programme on the reduction of excessive screening is not clear-cut. The favourable influence, if any, was probably small. According to the data in this study, the proportion of excessive screening in The Netherlands is still high:

approximately 16% of women between 35 and 54 years had three or more smears in the previous five years and 30% of women between 16 and 30 years of age had already had a smear taken.

We found that more than half of the non-attenders to the screening programme were women who were protected by a previous hysterectomy or a recent smear. Of the unprotected non-attenders, 28% showed a negative attitude towards the programme. The last group may be considered as 'hardline refusers': it is unlikely that many of these women will be persuaded by additional information on the benefits of screening for cervical cancer. To increase the coverage rate, the unprotected women with positive attitude are of special interest. According to our data, this corresponds to 72% of the unprotected women.

We tried to characterize the unprotected non-attenders. Similar to other studies, we found that women who were never married, with a low income and low education were over-represented in the unprotected group, and that older ages were usually less protected (7, 8). For a proportion of the never married group, this could be justified in view of low risk. The "unprotected women" are a specific proportion of the "non-attenders", which are usually studied (7, 8, 9). Women with a high level of education were less likely to be unprotected (OR 0.63; 95%CI: 0.35-1.14), but they were also more likely to attend (OR 1.37; 95% CI: 0.90-2.07, comparison of attenders with non-attenders; results not shown). An explanation is that these women use spontaneous screening. Although both differences are not significant, it shows that unprotected women can differ from non-attenders.

From our data, the presence of a screening programme was accompanied by high coverage, which is the main factor for high (cost-)effectiveness. Therefore, we conclude that despite a long tradition of cervical cancer screening in The Netherlands and despite the fact that both organised and spontaneous screening are performed by the general practitioner, an organised programme is still required to achieve high coverage.

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# 3

# WOMEN WHO PARTICIPATE IN SPONTANEOUS SCREENING ARE NOT AT HIGHER RISK FOR CERVICAL CANCER THAN WOMEN WHO ATTEND PROGRAMME SCREENING


## *Abstract*

Up to 1995, programme screening for cervical cancer in the Netherlands was targeted at women between 35 and 54 years of age at 3-yearly intervals. Spontaneous screening in addition to programme screening was common practice. Our aim was to compare the underlying risk for cervical neoplasia for women involved in both types of screening. From the national pathological database, we retrieved all primary smears (n= 693318) taken in 1994 in the Netherlands. Among the smears registered for screening purposes (39%), 79% was taken within the mass screening programme and 21% was taken for spontaneous screening. The underlying risk was studied from the detection rates of histological confirmed severe dysplasia or worse, using a multivariate loglinear model, including age and screening history. The detection rate of at least severe dysplasia, adjusted for age and screening history, was equal for women who had a spontaneous smear and for those who had a programme smear (odds ratio: 0.97; 95% Confidence Interval (CI): 0.84-1.14). In our data, women participating in spontaneous screening were not at higher risk for cervical cancer than women who used programme screening. Therefore, all asymptomatic women in the Netherlands should follow the general guidelines for age-range and screening-interval.

## Introduction

In the Netherlands, as in many European countries, the efficiency of screening for cervical cancer suffers from an incomplete coverage combined with an excessive use due to spontaneous smear taking (1-3). The lack of coverage decreases the effectiveness, also due to a higher risk for cervical cancer in non-participants (4). Excessive use of cervical smears will result in a proportional increase in costs and negative side-effects, while the extra effect on mortality and incidence will be relatively small (5). The effectiveness of this public health programme depends on the frequency of screening and the age-ranges. The corresponding guidelines were determined to give a positive balance between negative side effects (costs and iatrogenic harm) versus the positive effects (reduction of incidence and of mortality from cervical cancer).

Screening for cervical cancer in The Netherlands is organised by sending out personal invitations to all women at specific ages. In this way, the programme aims at a high attendance rate and a limited frequency of smear taking. Spontaneous screening, however, in addition to programme is common practice. Both types of screening are funded by the national health services. In spontaneous screening, preventive smears are taken on the initiative of the women and/or her physician. Usually, there is no specific information available about the motives for these spontaneous smears. In the past, we have estimated the efficiency of spontaneous screening to be low, due to the low starting age and short screening-interval used in spontaneous screening (6,7). This is in line with international opinion (8,9). Accordingly, since 1995, the Dutch government has discouraged spontaneous screening by reducing possibilities for funding. Gustafsson and colleagues al (10) questioned this point of view, based on a comparison of detection rates of carcinoma in situ in smears taken within the mass screening programme with smears taken outside the programme. A factor that could increase the effectiveness of spontaneous screening is that women who use this type of screening might be at higher risk for cervical cancer, in other words, that these women have been selected on individual characteristics for a more frequent screening by themselves or by their physician.

In the present study, our aim was to investigate if there was a difference in the underlying risk of cervical cancer for women who use spontaneous screening compared with women who participate in the screening programme. To this end, we distinguished between programme screening and spontaneous screening on whether

or not the smear was registered as a programme smear. From both types of screening, we compared the detection rates for at least high-grade dysplasia, adjusting for age and screening history.

## *Material and methods*

In the Netherlands, all cytological and histological examinations are registered in a centralised database: the Pathological National Automated Archive (PALGA). The PALGA started on a limited scale in 1975. From 1990 onwards, over 95% of the cervical examinations were registered and the coverage has increased to 100% in 1994. We retrieved all relevant information on cervical cytology and histology from this national database. In 1995, the new national screening policy was introduced, targeting women 30-60 years at 5-year intervals. The present study was restricted to smears taken in 1994, because this year was before the introduction of the new screening programme and the high coverage in the years before 1994 guarantees a high degree of completeness in information about the screening history.

In the PALGA, persons are identified by the first four characters of their maiden name, their date of birth and gender. Although this identification method can lead to misclassifications (a proportion of persons will have equal identifying characteristics, and (typing) errors will result in false registrations) it provides the possibility to follow persons over time.

The study material was restricted to all primary smears taken in 1994, being registered as either programme smears or spontaneous smears. Primary smears, as opposed to follow up smears, were defined as smears with no positive (showing at least atypia) cytology or histology in the previous five years; smears with previous borderline (requiring a repeat smear) and unqualified smears (not suitable for diagnosis) that had a sufficient and negative follow-up were also included. According to the PALGA registry 932,805 smears were taken in 1994 in The Netherlands, of which 26% had a previous positive or inadequate result in the preceding five years. For all primary smears, we assessed whether a previous primary smear was available and if so the 'screening-interval' was calculated, defined as the interval since the last primary smear.

In the PALGA, the indication for taking the smear was registered for 48% of the primary smears taken in 1994. The indication is registered by the general practitioner and imported by the diagnosing pathology laboratory. On basis of the available categories, we distinguished between "programme smears", which were taken because of an invitation for mass screening, spontaneous smears, which were taken because of preventive reasons but outside of the screening programme, and smears taken because of a medical indication. Primary smears for which no information on the indication was available were classified as 'unknown indication'. Smears with a medical indication and those classified as unknown indication were excluded from the analysis.

The detection rates were estimated from the maximum histological diagnosis until 1 April 1998, which was classified as no neoplasia, cervical intra-epithelial neoplasia (CIN) I (mild dysplasia), CIN II (moderate dysplasia), CIN III (severe dysplasia and carcinoma in situ) or invasive cervical cancer. We compared the underlying risk for cervical cancer for spontaneous smears with that for programme smears, using the detection rate of histologically-confirmed CIN III or worse, adjusted for age and screening history. Screening history is a combination of rank of the smear and interval since the last smear. The independent effects of type of screening, age and screening-history were estimated by logistic regression, and the interactions between the variables age and screening-history, age and type of screening and screening-history and type of screening were included in the model if they significantly improved the fit. The regressions coefficients of the best fitting model and their standard errors were used to calculate odds ratios (OR) and their 95% confidence intervals (95% CI).

## *Results*

In 1994, there were 693318 primary smears taken in The Netherlands. Among the smears with a registered indication (48% of all primary smears) 64% was taken after an invitation for mass screening, 17% of the smears was taken for spontaneous screening and 19% of the smears was taken for medical indication. Within the mass screening programme, 924 lesions (histologically-confirmed CIN III or worse) were detected, giving a detection rate of 4.3 CIN III or worse per 1000 programme smears. Another 308 lesions were detected by spontaneous screening, leading to a detection rate of 5.3 CIN III or worse per 1000 spontaneous smears. Table 3.1 shows the

detection rates and the number of smears for spontaneous smears and for mass screening are presented by age and by screening history. The distribution of the number of smears by age and screening history differs for the two types of screening. Spontaneous smears were predominantly taken at younger ages and 30% of the spontaneous smears are first smears (rank 1). Although, the crude detection rate is higher for spontaneous smears than for programme smears, the detection rate of the first smears and for repeat screening within 3 years is lower for spontaneous screening compared with programme screening.

**Table 3.1**
Detection rates of mass screening and of spontaneous screening by age and by screening history, PALGA 1994

| Variable | Mass screening | | | Spontaneous screening | | |
|---|---|---|---|---|---|---|
| | Detection rate CIN III+ per | Smears | | Detection rate CIN III+ per | Smears | |
| Category | 1000 smears | Number | % | 1000 smears | Number | % |
| **Age** | | | | | | |
| < 25 | 1.7 | 2316 | 1% | 2.3 | 4430 | 8% |
| 25-29 | 6.1 | 7695 | 4% | 7.2 | 9763 | 17% |
| 30-34 | 9.3 | 6694 | 3% | 9.4 | 12296 | 21% |
| 35-39 | 6.6 | 67280 | 31% | 5.5 | 7813 | 14% |
| 40-44 | 3.7 | 55159 | 26% | 3.8 | 6633 | 11% |
| 45-49 | 2.7 | 36135 | 17% | 2.6 | 6054 | 10% |
| 50-54 | 1.4 | 35953 | 17% | 2.0 | 3981 | 7% |
| 55-59 | 3.1 | 1610 | 1% | 1.7 | 2982 | 5% |
| 60-64 | 3.2 | 632 | 0% | 3.0 | 1672 | 3% |
| 65 + | 12.5 | 720 | 0% | 5.3 | 2075 | 4% |
| Total | 4.3 | 214194 | 100% | 5.3 | 57699 | 100% |
| **Screening history** | | | | | | |
| first smear | 8.4 | 36333 | 17% | 7.8 | 17497 | 30% |
| Rank > 1, interval < 1 year | 4.5 | 17352 | 8% | 3.6 | 4673 | 8% |
| Rank > 1, interval 1-2 years | 2.5 | 16889 | 8% | 1.7 | 7548 | 13% |
| Rank > 1, interval 2-3 years | 2.4 | 48237 | 23% | 2.0 | 8006 | 14% |
| Rank > 1, interval 3-4 years | 2.6 | 52568 | 25% | 4.1 | 6749 | 12% |
| Rank > 1, interval 4-5 years | 4.3 | 12628 | 6% | 5.6 | 4990 | 9% |
| Rank > 1, interval 5 + years | 6.3 | 30187 | 14% | 8.5 | 8236 | 14% |
| **Total** | 4.3 | 214194 | 100% | 5.3 | 57699 | 100% |

In the multivariate model, the odds ratios for the detection of histologically-confirmed CIN III or worse for the variables age and screening-history confirm current knowledge: the detection rate is highest in age-group 30-34, is higher for first smears

than for repeat smears, and increases with longer screening-intervals (*Table 3.2*). An exception is that smears taken within a year of the preceding smear have a relatively high detection rate of CIN III or worse. This was seen for both programme and spontaneous smears (*Table 3.1*). Possibly these smears were taken in high-risk women, without specifying this as the indication for smear taking.

**Table 3.2**
Odds ratios (OR) for detection of CIN III or worse, estimated in a multivariate model for age, screening history and type of screening, PALGA 1994

| Variable<br>Category | Odds ratio | 95% confidence interval |
|---|---|---|
| **Age (years)** | | |
| < 25 | 0.17 | 0.10 - 0.29 |
| 25-29 | 0.62 | 0.49 - 0.79 |
| 30-34 | 1.00 | Reference |
| 35-39 | 0.75 | 0.62 - 0.91 |
| 40-44 | 0.50 | 0.40 - 0.62 |
| 45-49 | 0.35 | 0.27 - 0.45 |
| 50-54 | 0.20 | 0.15 - 0.27 |
| 55-59 | 0.26 | 0.14 - 0.50 |
| 60-64 | 0.31 | 0.15 - 0.66 |
| 65 + | 0.65 | 0.41 - 1.03 |
| **Screening history** | | |
| first smear | 1.00 | Reference |
| rank > 1, interval < 1 year | 0.55 | 0.44 - 0.70 |
| rank > 1, interval 1-2 years | 0.29 | 0.22 - 0.38 |
| rank > 1, interval 2-3 years | 0.33 | 0.27 - 0.40 |
| rank > 1, interval 3-4 years | 0.40 | 0.33 - 0.48 |
| rank > 1, interval 4-5 years | 0.58 | 0.46 - 0.74 |
| rank > 1, interval 5 + years | 0.87 | 0.74 - 1.02 |
| **Type of screening** | | |
| Mass screening | 1.00 | Reference |
| Spontaneous screening | 0.97 | 0.84 - 1.14 |

The detection rate of histologically-confirmed CIN III or worse in spontaneous screening, adjusted for age and screening history, was equal to that of programme screening (Odds ratio: 0.97; 95% CI: 0.84-1.14). The model which best described the data included interaction between age and screening-history. The inclusion of the

interaction hardly altered the estimation for the odds ratio (OR: 0.97; 95% CI 0.83-1.13).

## Discussion

We compared the detection rates of histologically-confirmed CIN III or worse in spontaneous screening to that of programme screening, as a proxy for the underlying risk for cervical cancer in the women involved. The crude detection rate of histologically-confirmed CIN III or worse was higher for spontaneous smears (5.3 per 1000 smears) compared with programme smears (4.3 per 1000 smears). In a multivariate model, which corrects for age and screening history, the adjusted detection rate was equal for spontaneous screening compared with programme screening. The results indicate that the underlying risk for women who had a spontaneous smear is not higher than for women who had a programme smear.

Detection rates in this analysis are used as a proxy for underlying risk. However, detection rates also could have been influenced by differences in management of the smears: the classification criteria of the smears, the quality of the smear (collection of material, fixation and cytological evaluation), the recommendations for an additional smear or referral and in the follow-up. We expect a similar management for spontaneous smears and programme smears in The Netherlands, because the two types of smears are taken by the same general practitioners, classified by the same cytological laboratories, and histological follow-up takes place at the same gynaecology departments. If there are differences in management of the smears, they must reflect differences in the *a priori* expected risk by the physician involved. Since programme smears are in principle taken in asymptomatic women, the expected risk will be low. Possibly, smears taken "outside the programme" are managed more carefully. This, however, would lead to higher detection rates of spontaneous smears, leading to an overestimation of the underlying risk for women who used spontaneous smears.

More than half of the smears was registered as 'unknown indication'. We explored whether these smears are a selected group, e.g. with relatively many smears taken for medical indication, by comparing the detection rates of histologically-confirmed CIN III or worse, adjusted for age and screening history, for smears taken for unknown indication with smears taken for known indication. We found no significant

difference (OR: 1.03; 95% CI 0.98-1.09). This suggests that the underlying risk for cervical cancer for smears taken for unknown indication is not significantly higher.

Is spontaneous screening less efficient than programme screening? In general, spontaneous screening does not follow the recommendations for age range and interval between successive screenings, because younger women are being screened and many screens are made at too short intervals, which is considered inefficient. In the Dutch data reported here, we also see these differences between spontaneous and programme screening: 57% of all spontaneous smears were taken in women outside the target age group of 35-54 years of age, and another 20% was taken in the target age group, but within three years after the preceding smear. However, 23% of all spontaneous smears were taken in women of 35-54 years of age, after a screening-interval of more than 3 years, which is in agreement with the guidelines of the programme.

However, it has been argued that spontaneous screening catches women at high risk who are identified by physicians on basis of the knowledge of individual characteristics of women. Gustafsson has questioned the inefficiency of spontaneous screening by pointing out that in Sweden the detection rates for high grade cervical neoplasm were on average higher in spontaneous screening compared with programme screening in the period 1969-1988, but with a sharp trend from higher CIN III rates for spontaneous screening in the early years to lower rates in the years 1984-1988 (10).

In the Dutch data as well, the crude detection rates for histologically confirmed CIN III or worse in spontaneous smears are higher than in programme smears. Use of detection rates of (high grade) CIN as a surrogate measure for prevention of cancer and related mortality would favour more screening in younger age, since detection rates of CIN III are relatively high in young age. But the progression rate of (high grade) CIN is rather slow, and a considerable proportion will never progress to invasive cancer, especially in young ages (11). This means that especially at younger age many CIN is detected and treated without health benefits, and detection is associated with considerable adverse health effects and costs. The (official) Dutch policy is based on the potential impact on incidence of invasive cancer and on cervical cancer mortality rather than on CIN detection rates and, therefore starts later. Spontaneous screening, before the starting age of the screening programme, reduces the efficiency of smears taken at the target ages.

To analyse whether spontaneous screening, with its smears taken at a younger age and at shorter intervals, is inefficient, the crude detection rates are not relevant, the question is whether there is an extra risk involved when the spontaneous smears were performed. Such an extra risk can be identified if spontaneous and programme smears are compared on the basis of detection rates that are adjusted for age and interval since the previous smear. Such an extra independent risk would imply that there was a good reason for more intensive screening than currently recommended. We compared detection rates while adjusting for differences in age and screening history (number of previous smears, interval since previous smear), and found no difference in the adjusted detection rates between spontaneous and programme smears. We conclude that women who used spontaneous screening have a similar underlying risk for cervical cancer as women who used programme screening. Therefore, there was no reason to depart from the recommended age-range and screening-interval when spontaneous smears were taken.

Having come to this conclusion, we can consider those smears that were performed extra to the recommended schedule as inefficient. For example, an extra spontaneous smear, after a programme smear at age 47, taken for example at age 48 produces a shorter than intended interval for both the spontaneous smear itself and the subsequent programme smear at age 50. Nineteen percent of all preventive smears (mass screening and spontaneous screening) were taken in women outside the age-range of 35-54 years. Furthermore, 33% of the smears were taken in women of the target age group, but the screening interval was less than three years; the mean interval was 1.9 year. From the point of view of a three years schedule, (1 - 1.9/3 =) 37% of these smears can be seen as unnecessary. An estimate for the number of extra smears (on top of the recommended age and interval schedule) is 19% + 33% x 37% = 31%. These extra inefficient spontaneous smears occur in many countries with an organised screening programme.

Smears taken within a year of the preceding smear showed relatively high detection rates in the multivariate model (Table 3.2). Similar high detection rates for smears taken within a short interval are usually seen in other registrations, such as in Sweden (10) and in British Colombia (4). These results can be explained by the hypothesis that a considerable proportion of these smears are taken within a short interval because of signs or symptoms, despite the fact that they are registered as preventive smears. If we calculate the smears taken within one year not as

excessive, the proportion of excessive programme smears becomes 25% of all preventive smears (mass screening and spontaneous screening).

In 1995, new guidelines for the screening programme were introduced, targeting women between 30 and 60 years of age with a screening-interval of 5 years. These new guidelines do not influence our conclusion, that women with spontaneous smears are not at higher risk for cervical cancer. However, the estimate of the number of inefficient smears is influenced by these new guidelines, because the proportion of smears taken after a short interval, is lower with the new guidelines. Therefore, our estimate of the number of extra smears will be an underestimate of the actual number of extra smears in the new setting.

We conclude that in The Netherlands, spontaneous screening is not selectively used by women at a higher risk for cervical cancer. Therefore, women participating in spontaneous screening do not represent a higher risk group and therefore should not be screened more intensively than according to the programme guidelines on age-range and screening interval, unless symptoms are involved. If all preventive smears are taken following the recommended age-range and screening-interval prescribed by the programme, in The Netherlands the number of primary smears will be reduced by approximately one fourth.

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# 4

# LESS PAP-2 RESULTS ('MINOR ABNORMALITIES') IN THE POPULATION SCREENING FOR CERVICAL CANCER SINCE THE INTRODUCTION OF NEW GUIDELINES IN 1996


## *Abstract*

To determine whether the 1996 implementation of new guidelines for the classification and management of cervical smears in the Dutch population screening programme for cervical cancer (i.e. inflammatory symptoms are no longer classified as moderate dysplasia and women with two smears with moderate dysplasia are referred directly to the gynaecologist) was followed by a reduction in both the number of women with repeat smears and the length of follow up.

The results of all smears of women aged 35-54 years from 1990 onwards, were retrieved from the Dutch Network and National Database for Pathology (PALGA). The percentage of smears with moderate dysplasia was analysed with respect to time. The percentage of women with a histological examination during the follow up phase of the population screening programme (1990 and 1991) was compared with that for the new screening programme (1996).

Following the implementation of the new guidelines, the percentage of smears with moderate dysplasia was reduced from 10% to 2%. The percentage of women with a histological examination during the follow up of two smears with moderate dysplasia remained the same. The new recommendations for additional smears were not followed: for 28% no repeat smear was available after 2-2,25 years versus 10% in 1992. There were indications that the referral of women with two cases of moderate dysplasia to a gynaecologist was not strictly adhered to either. Since the introduction of the new guidelines, the estimated percentage of women that should be referred to the gynaecologist following smears with moderate dysplasia has not changed.

The new recommendations have lead to fewer smears being classified as moderate dysplasia. The long term effects, such as a reduction in the length of the follow up period, can only be analysed in a few years time.

## Introduction

Mass screening for cervical cancer aims to prevent mortality from cervical cancer in an efficient manner. To this end, a balanced policy is needed for women whose cervical smears are in the grey area between "no" and "clear" abnormalities. An active and aggressive policy will lead to more over-diagnostics and –treatment, while a more passive policy will lead to a higher rate of invasive cancers. In the early nineties, the prevailing Dutch guidelines for mass screening for cervical cancer underwent thorough revision. Radical changes were made in the organisational set-up, funding and the ages at which women received invitations for screening examinations (up to 1995, women aged between 35 and 54 years were invited every three years, while under the current guidelines, women between the ages of 30 and 60 are invited every five years), while modifications also occurred in the guidelines for follow-up. The changes were decided on in 1993, and implemented in 1996 (1).
Two major problems were established in connection with the follow-up examinations performed. In the first place, due to the very considerable group of women (almost 10%) with a Pap 2 smear, slightly more than 10% of all screened women per screening round were being recommended to undergo a follow-up examination (a minimum of one repeat smear). Compared to the 1.5% lifetime risk of developing cervical cancer, this was an extremely high percentage. The second problem concerned the fact that women could remain in follow up for years. After all, a cervical smear classified as "Pap 2" was to be repeated until either 2 consecutive smears were classified as 'negative' (no follow up necessary, woman returns to the screening programme), or a more serious abnormality is diagnosed (2 smears classified as Pap 3a, or a smear classified as Pap 3b, leading to a referral to the gynaecologist)(2).
The new guidelines aimed to improve both problems. The first problem (the high proportion of "Pap 2' results) was dealt with by reclassifying smears with inflammation as Pap 1, instead of Pap 2. The second problem was tackled by introducing the rule that women could be recalled twice, at the most, for a repeat smear, after which they after either returned to the screening programme (if both additional smears were negative), or they were to be referred to the gynaecologist (after one abnormal (at least 'Pap 2') additional smear). Furthermore, the interval for the additional smears was shortened from one year to six months. Obviously, however, the follow-up interval could not be shortened without reducing, at the same time, the number of Pap 2 smears, as otherwise the number of referrals to the gynaecologist would soar.

This study examined the consequences of the changed guidelines. To this end, the percentage of smears that had been assigned to the diagnostic category 'Pap 2' was looked at for the years 1990-1998 in the different regions of the Netherlands. Furthermore, we analysed the follow up practice of the old (on the basis of screening smears obtained in 1990 and 1991, and their follow up) and new guidelines (screening smears obtained in 1996, and their follow up). The required data were retrieved from the Dutch Network and National Database for Pathology (PALGA).

## *Material and methods*

### PALGA

The Pathological National Automated Archive stores all information about pathological (cytological and histological) examinations performed in the Netherlands; since 1990, more than 90% of all such examinations have been registered, a percentage that by 1994 was estimated to have reached 100% (3). A standardised extract from the original pathology report containing the date, the topography, the nature and the diagnosis of the examination is stored. Extra space is reserved for recording specific data on the cytology of the cervix (in the so called 'Cervical Registration and Information System'). Among other things, this system provides information about Quality, Inflammation, Squamous cells, Other abnormalities and cylinder epithelium cells (the KOPAC-diagnosis). The reason the smear was taken can also be indicated.

### Selection

For this study, all cytological and histological examinations of cervical tissue registered through March 31 1998 were retrieved from the PALGA database. Based on previous cervical cytological and histological evaluation of e.g. tissue biopsies obtained from a woman, smears were labelled either as 'primary' (stand alone) or as 'secondary' (made within four years of a previous abnormal smear or smear of inadequate quality with insufficient follow up). The women studied were identified by their date of birth and the first four letters of their maiden name. For the purpose of this study, we selected primary smears taken in 1990 and 1991, as well as smears dating from the year 1996 (the year the new recommendations for cervical cancer screening took effect), all of which were known to have been taken within the scope of the screening programme. In this way we were able to exclude smears that had been made outside the scope of the screening programme and smears taken either

for medical reasons or at the request of the women herself. In roughly half of all cases, the reason for taking the smear was unknown. These smears were also excluded from our selection.

The data recorded on the screening smears in the database included the date, the diagnosis, the nature (cytological or histological) and the results of any follow-up smear up to 2.25 years after the original primary smear. The used file provided information about examinations performed up to April 1st 1999, which meant that the follow-up period for smears made in 1996 was at least 2.25 years. An analysis of the smears taken in 1990 and 1991 was also made over a longer follow-up period as well, namely 7.25-9.25 years (until April 1 1999).

### Cytological diagnosis

The cytological findings were divided into the following diagnostic categories, corresponding with the recommendations for follow-up, which had been introduced in 1996(1):

Inadequate smears (Pap 0); these smears should be repeated immediately;

negative smears without endocervical cells (KOPAC-C=2); these should be repeated in 6 months;

negative smears (Pap 1); women in this category remain in the mass screening programme;

slightly abnormal smears: smears with KOPAC-P=2,3, or 4, KOPAC-C=3, 4 or 5, or KOPAC-A ≥ 4; these are Pap 2 and Pap3a (moderate dysplasia); women with these smears in this category should have a repeat smear in 6 months;

Severely abnormal smears; women with smears with severe dysplasia are referred to the gynaecologist: KOPAC-P ≥ 5, KOPAC-A ≥ 4, KOPAC-C ≥ 6; these are Pap 3a2 (moderate dysplasia or worse).

Our study comprised women participating in both the old and new mass screening programme, aged 35-54 years, to make the comparison as clear as possible. The age used was the age at December 31 of the year in question; for example, all women aged 30 in 1996 are women who turned 30 in that year.

## *Results*

### The proportion of PAP 2

In 1993, it was decided to modify the definition of Pap 2 by reclassifying inflammation as Pap 1, instead of as Pap 2, in an attempt to reduce the percentage of Pap 2

smears. The new guidelines were introduced in 1996. Table 4.1 shows that the percentage of Pap 2 smears subsequently plummeted, from 9.1 in 1994 to 2.2 in 1998.

**Table 4.1**
The percentage screening smears diagnosed as Pap 2, by region and calendar year, in women between 35 and 54 years of age

| Region[1] | 1990 | 1991 | 1992 | 1993 | 1994 | 1995 | 1996 | 1997 | 1998 |
|---|---|---|---|---|---|---|---|---|---|
| Unknown | 10.9 | 10.9 | 10.4 | 9.1 | 7.2 | 7.4 | 5.4 | 3.1 | 1.8 |
| Region I | 12.0 | 9.8 | 11.6 | 13.7 | 11.9 | 7.9 | 6.6 | 4.6 | 1.8 |
| Region II | 3.2 | 3.8 | 4.8 | 5.9 | 5.1 | 5.6 | 4.6 | 3.8 | 2.8 |
| Region III | 14.0 | 10.4 | 10.1 | 11.7 | 12.0 | 10.5 | 6.1 | 1.9 | 1.6 |
| Region IV | 10.4 | 10.8 | 10.4 | 12.1 | 10.9 | 11.3 | 5.0 | 2.3 | 2.3 |
| Region V | 15.1 | 19.8 | 15.4 | 11.7 | 10.9 | 11.9 | 8.2 | 2.6 | 2.2 |
| Region VI | 8.5 | 9.2 | 9.7 | 6.3 | 4.9 | 4.5 | 5.1 | 2.3 | 1.9 |
| Region VII | 8.1 | 5.9 | 6.1 | 9.3 | 6.7 | 6.7 | 5.8 | 2.9 | 2.2 |
| Region VIII | 8.5 | 6.2 | 7.1 | 4.0 | 4.6 | 5.1 | 4.5 | 2.3 | 2.1 |
| Region IX | 7.4 | 8.0 | 11.1 | 14.5 | 13.5 | 13.6 | 10.3 | 13.0 | 4.2 |
| The Netherlands | 10.5 | 9.2 | 9.8 | 10.5 | 9.1 | 8.8 | 5.9 | 3.6 | 2.2 |
| SD[2] | 3.5 | 4.3 | 3.0 | 3.5 | 3.4 | 3.2 | 1.8 | 3.3 | 0.7 |

1. The different regions are unrecognisable numbered.
2. Standard deviation was calculated in relation to the weighted mean.

As Table 4.1 also clearly illustrates, when broken down according to region, the differences between regions are very considerable. The percentage decreased sharply in all regions. As can be read in the bottom row of this table, the deviation of the individual regions from the mean declined over the years, while the standard deviation from the mean remained constant at approximately 1/3.
The following question that arose was whether all the cervical smears that were now no longer being classified as Pap 2, were instead being classified as having 'no evidence of abnormalities'. In order to find an answer to this, the results of all the smears taken within the scope of the screening programme from the year 1990 on are shown in Table 4.2. The table shows that the proportion of smears with 'severely abnormal' test results and with the classification Pap 3a1 did not increase; on the contrary, a clear downward trend is seen in Pap 3a 1 after 1995. The proportion of smears classified as Pap 1 or Pap 2, on the other hand, remain constant over time.

We therefore concluded that the majority of smears that would previously have been classified as Pap 2 were now instead being classified as normal.

**Table 4.2**
Diagnoses (in percentages) of smears obtained in the screening programme for cervical cancer, by calendar year, for women aged between 35 and 54 years.

| Diagnoses | 1990 | 1991 | 1992 | 1993 | 1994 | 1995 | 1996 | 1997 | 1998 |
|---|---|---|---|---|---|---|---|---|---|
| Severe dysplasia (≥ Pap 3a2) | 0.54 | 0.51 | 0.53 | 0.45 | 0.45 | 0.44 | 0.46 | 0.49 | 0.52 |
| Light dysplasia (Pap 3a1) | 0.8 | 0.7 | 0.8 | 0.9 | 0.9 | 0.8 | 0.6 | 0.5 | 0.4 |
| Light dysplasia (Pap 2) | 10.5 | 9.2 | 9.8 | 10.5 | 9.1 | 8.8 | 5.9 | 3.6 | 2.2 |
| Unqualified | 1.6 | 1.2 | 1.2 | 1.1 | 1.2 | 1.5 | 0.9 | 0.8 | 0.9 |
| Without endocervical cells | 9.8 | 8.9 | 8.4 | 7.9 | 7.2 | 6.8 | 8.0 | 7.7 | 7.5 |
| Negative | 76.8 | 79.5 | 79.4 | 79.2 | 81.1 | 81.8 | 84.0 | 86.8 | 88.5 |

### Follow-up after a Pap 2 smear

Another question that remained to be answered was whether or not the new policy had led to more or to fewer referrals to the gynaecologist. This was in part dependent on the results of the repeat smears and on the type of follow-up received by the women. Table 4.3 shows the follow-up results from examinations carried out within 2.5 years after a slightly abnormal smear was taken in 1996, i.e. a smear which, according to the new guidelines, would be accompanied by a standard recommendation for cytological follow-up. It can be seen that a small proportion of the women with an initial slightly abnormal smear had repeat smears showing severe abnormalities (1.5%). Follow-up histological information was available from an examination carried out within 2.25 years following the initial smear for 87% of these women; of the women in whom the repeat smear again came back with minor abnormalities, the percentage with histological follow-up was only 40.9%. According to the new guidelines applied by the mass screening programme, women are to be referred to the gynaecologist after a single smear with minor abnormalities. These women may well have been referred in accordance with the guidelines, but may still be waiting to see the gynaecologist. The other possibility is that no biopsy was taken during colposcopy for pathological evaluation, which means that no histological findings were registered in the PALGA.

**Table 4.3**
The number of women who had undergone follow up examinations in 2.25 year after the screening smear diagnosed as 'Pap 2' obtained in 1996, by diagnose of the first follow up smear

| First follow up smear diagnosis | Number (%) | Number (%) with a histological examination in 2.25 years | |
|---|---|---|---|
| Severe dysplasia (≥ Pap 3a2) | 227 (1.5) | 197 | (86.8) |
| Light dysplasia (Pap 3a1 and Pap 2) | 1737 (11.7) | 710 | (40.9) |
| No abnormalities | 8135 (54.9) | 271 | (3.3) |
| Unqualified | 108 (0.7) | 18 | (16.7) |
| Without endocervical cells | 424 (2.9) | 17 | (4.0) |
| No follow up smear | 4183 (28.2) | 308 | (7.4) |
| Total | 14814 (100) | 1521 | (10.3) |

There was no record of any cytological examination within 2.25 years of follow up for 28.2% of the women with a slightly abnormal smear at screening. The database records showed that histological evaluation had taken place immediately following the initial, slightly abnormal smear for a small percentage of women (7.4%). Such evaluation could, however, also be due to (histological) interventions such as dilatation and curettage or hysterectomies that were performed for reasons other than abnormal cervical cytology.

### Comparison with the previous guidelines

Table 4.4 shows the number of women undergoing follow-up examinations within 2.25 years after an initial, slightly abnormal smear was taken in 1990 and 1991 within the scope of the population screening programme. This table clearly illustrates the effects of the former guidelines compared to those currently in force: the percentage of women whose initial smear showed minor abnormalities and whose repeat smear also came back with minor abnormalities was considerably higher than after the implementation of the revised guidelines (27.6% in the former situation according to Table 4.4, versus 11.7% in the new situation (see Table 4.3). On the one hand, the effect of a non-negative result under the new, more stringent definitions is more extreme (referral to the gynaecologist). On the other hand, the smears currently being labelled as 'slightly abnormal' were now a selection of, on average, abnormalities that were more severe than the abnormalities previously classified in this category under the former guidelines for the population screening programme, implying that more abnormalities might be expected to be detected at the histological

follow-up. The percentage of slightly abnormal repeat smears was found to be lower, from which could be inferred that the effect of the first explanation was larger than that of the second. The percentage of severe abnormalities seen at follow-up remained largely unchanged.

**Table 4.4**
The number of women who had underwent follow up examinations in 2.25 year and in 8.25 year after the screening smear diagnosed as 'Pap 2' obtained in 1990 and 1991, by diagnose of the first follow up smear

| First follow up smear diagnosis | Number (%) | Number (%) with a histological examination | |
|---|---|---|---|
| | | in 2.25 years | in 8.25 year |
| Severe dysplasia (≥ Pap 3a2) | 578 (1.6) | 360 (62.3) | 498 (86.2) |
| Light dysplasia (Pap 3a1 and Pap 2) | 10163 (27.6) | 884 (8.7) | 1815 (17.9) |
| No abnormalities | 20479 (55.5) | 425 (2.1) | 1714 (8.4) |
| Unqualified | 293 (0.8) | 24 (8.2) | 48 (16.4) |
| Without endocervical cells | 1840 (5.0) | 40 (2.2) | 149 (8.1) |
| No follow up smear | 3526 (9.6) | 991 (28.1) | 1 092 (31.0) |
| Total | 36879 (100) | 2724 (7.4) | 5316 (14.4) |

The percentage of women for whom no record of a repeat smear having been performed within 2.25 years was found was 9.6 in the former situation (see table 4.4) versus 28.2 in the new (see table 4.3). The total percentage of women with a histological follow-up after an initial smear with minor abnormalities was 7.4 under the former, and 10.3 under the newly revised guidelines. However, the percentage of women with a smear with moderate dysplasia dropped in the new situation, to 5.9% in 1996 from 9.9% in 1990 and 1991 together (see table 4.1). Hence the estimated percentage for women referred and who had a histological evaluation after an initial smear with minor abnormalities was 9.9x7.4=0.73 in the former screening programme and 5.9x10.3 = 0.61 in the new screening programme.
In the new screening programme, a larger percentage of women failed to undergo a repeat test, i.e. 26%(=(4183-308 (= women immediately undergoing an examination for histological follow-up))/14,814 (see table 4.3)) compared to 6.9% in the old ((3526-991)/36,879 see table 4.4)). Had all the women undergone a follow-up examination with histological assessment as prescribed by the guidelines, the percentage of women that would have been referred to the gynaecologist after a smear with moderate dysplasia would have approximately been the same in the old

(0.73x100/(100-6.9)=0.78%) and in the new population screening programme (0.61x100/(100-26)=0.82%).
The percentage of histological examinations following smears taken in 1990 and 1991 can also be studied over a longer period of follow up, i.e. until April 1999 (average follow-up period of 8.25 years (extremes: 7.25-9.25) see table 4.4, final column). To some extent, these histological examinations are comprised of histological interventions performed for reasons other than cervical abnormalities. Of the women with a normal screening smear, it can be seen that 7.3% went on to have a follow-up examination with a histological evaluation. The total percentage of women with smears showing minor abnormalities at screening who subsequently had a follow-up examination with histological assessment during this period was 14.4%. In an estimated 7.3% of these cases, this could not be explained by any abnormal cervical cytology. The remaining 7.1% underwent follow-up examinations with histological evaluation in the subsequent 8.25 years following the initial smear taken within the scope of the screening programme.

## *Discussion*

Under the new guidelines, the national percentage of smears with 'Pap 2' was down by 75%. Whereas this was formerly approximately 10%, in 1998 this percentage had fallen to a mere 2.2%. In the light of the differences that continue to persist between the regions (see table 4.1), the percentage of Pap 2 smears may be expected to drop even further. It is still too soon after implementation of the new guidelines for follow up to determine the extent to which the 'repeat follow-up' (leading to the decision 'back to the screening programme' or 'referral to the gynaecologist) has indeed been shortened for women with a Pap 2 smear. A period of at least four years must have elapsed after a smear before it is possible to determine whether women with 2 negative repeat smears have had no further repeat smears taken.
As it now stands, the percentage of women initially recommended to have a repeat smear and who also had histological follow-up examinations within 2.25 years was slightly lower in the new population screening programme (0.61%) than in the original screening programme (0.73%). However, in the new situation, records of histological follow-up information were available for only 41% of the women who had two Pap 2 smears. We do not know whether the remaining 59% had a colposcopy without a histological examination, or whether they simply had not seen a gynaecologist. The former would imply that the number of referred women has doubled compared to the

previous situation, the latter that in less than half of the women with two Pap 2 results, follow-up failed to be carried out in accordance with the prevailing guidelines. Whichever the case, neither situation augurs well for the new screening programme.
Following the adjustment of the estimated percentage of women referred to the gynaecologist for women who had not yet had a repeat smear, the percentage of women referred to the gynaecologist who had had a histological follow-up examination was found to be almost the same in the new situation as in the old. This calculation was based on the assumption that the women who had not been followed had the same chance of a repeat smear with abnormal cytological findings as the women who had been followed. The percentage of Pap 2 smears declined even further after 1996. If the percentage of abnormalities detected by a repeat smear does not rise, it follows that the percentage of women referred to the gynaecologist for a histological follow-up examination may well decline.
The method of identification used by the PALGA (the first four letters of a woman's maiden name, date of birth and sex) can lead to misclassifications (both as a result of overlapping identification data and typing errors). Overlapping identification data will have a greater impact than misclassifications on the current analyses. As a consequence, the estimated percentage of histological follow-up examinations is very likely to have been too high, both in the former and in the prevailing situation. The effect on the observed difference between the two situations cannot be predicted with any certainty, but is not expected to be large.
The cost efficacy of various new screening methods, such as HPV testing or semi-automatic screening is currently being investigated. Pending the outcome of this investigation, any revision of the current guidelines should be postponed. The data presented in this study clearly show that it is imperative to base this on the most recent data available, and that the attainable benefits, in terms of less follow-up (lower costs and less of a burden on the woman) are likely to be lower in the current situation than in the previous situation.
To some extent, our study was able to establish that the new guidelines were having the purported effect, especially as regards the decrease in the number of women with Pap 2 smears, although the number of women with a histological examination remained virtually the same. Striking was the fact that, regarding the initial screening smears in 1996, the guidelines for repeat smears failed to be properly observed and what is more, were being adhered to far less stringently than was the case in the past. We also found indications that the guideline calling for referral to the gynaecologist after two Pap 2 smears was not being followed correctly. The follow-up period related to the years 1996 and 1997, i.e. shortly after the implementation of the

new guidelines. The long-term effect of the new policy will only be able to be analysed in a few years time.

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# 5

# ENDOCERVICAL STATUS IS NOT PREDICTIVE OF THE INCIDENCE OF CERVICAL CANCER IN THE YEARS AFTER NEGATIVE SMEARS


## *Abstract*

The clinical relevance of the lack of endocervical cells was never well established in a longitudinal study with histologically proven cervical cancer as an end point. From the Dutch Network and National Database for Pathology (PALGA), results for all negative smears obtained in 1990 and 1991 in the Netherlands were retrieved, as were data for all cytological and histological examinations performed after the negative smears before April 1998. There were no significant differences between the proportion of preinvasive lesions (Cervical Intraepithelial Neoplasia I, II and III) detected after negative smears without endocervical cells compared with negative smears with endocervical cells. The proportion of women in whom invasive cancer developed was the same in both groups. These data suggest there is no reason to advise women with negative smears without endocervical cells to undergo an additional smear.

## Introduction

In the literature, there is no agreement about the clinical relevance of negative Papanicolaou smears without endocervical cells. The presence of endocervical cells is usually considered an indicator of an adequate sample. This view is supported by cross-sectional studies, in which a lower proportion of abnormalities has been reported in smears without endocervical cells compared with smears with endocervical cells (1, 2, 3), and by retrospective studies, in which rescreened negative smears before the diagnosis of cervical intraepithelial neoplasia (CIN) III or invasive cancer showed a high proportion of negative smears without endocervical cells (4, 5, 6). These results suggest that smears without endocervical cells are associated with a higher false-negative rate. However, longitudinal studies showed no increase of detected abnormalities after a smear without endocervical cells compared with negative smears with endocervical cells (7, 8), although these studies are based on small numbers of smears, short follow up time and cytologically detected CIN as the end point.

Until 1996 in the Netherlands (9), all women with negative smears without endocervical cells were recommended to have an additional smear after one year; thereafter, they returned to the regular program of smears with a three year interval. In 1996, the guidelines were changed to recommend an additional smear after 6 months and a screening interval of five years. In the United States, the guidelines for management of abnormal cervical cytology advised against repeating smears based only on the absence of endocervical cells, but clinicians may decide to perform an additional smear after one year, before return to the regular program of three year intervals (10). In Europe, an additional smear is not generally advised, but most countries advise an additional smear under specific conditions, such as first smears or follow up smears. The presence of cells from the transformation zone again has been reported to be an important issue for an adequate sample (11, 12).

Our aim was to compare the incidence of invasive cervical cancer and the incidence of preinvasive lesions after negative smears with and without endocervical cells. We focused specifically on the endocervical cells, but the absence of metaplastic cells, which in itself in the study period was not a reason for an additional smear in the Netherlands, also was explored. From the Dutch Network and National Database for Pathology (PALGA), we retrieved results for all cervical smears obtained for screening purpose in 1990 and 1991 and for all cytological and histological

examinations performed before April 1998. This follow up period of 6.25 to 8.25 years is at least two times longer than the recommended screening interval in the Netherlands during the study period of three years. Therefore, a large proportion of the women with a negative smear with endocervical cells will have undergone at least one subsequent smear within the period studied. The large number of smears and long follow up period allow analysing not only histologically diagnosed CIN I, CIN II and CIN III but also invasive cancer as an end point.

## *Material and methods*

In the Netherlands cytologic and histological examinations are registered in a national database, PALGA, that started in 1975. From 1990 onwards, more than 94% of the Papanicolaou smears and an even higher proportion of the results of histological examinations were registered. By using the identification method used by the PALGA (four characters of the surname, the date of birth and the sex) the cervical screening history (rank and interval since previous smear) and follow up data for all smears were retrieved individually.

For the present study, we retrieved data for all cervical smears (n = 1,272,558) from the PALGA obtained in 1990 and 1991. This includes a period before the reorganisation of the Dutch screening program. We selected the smears registered as obtained for preventive reasons (n = 515,146 [40.5%]); smears obtained for medical indication (5.1% of the smears) and unknown reasons (54.4% of the smears [owing to incomplete registration of the reason for the smear) were excluded. Furthermore, preventive smears are from women, who have had no positive smears during the preceding 4 years; exceptions were made for previous borderline or unsatisfactory smears, for which the negative follow up was completed. Thus, smears that followed a positive smear within 4 years were not considered preventive but were considered follow up smears.

For the study, we included all preventive smears that had no cervical abnormality. Smears were classified based on the registration of the item "no endocervical cells present". The incidence of abnormalities was estimated on the basis of the highest histologically confirmed abnormality diagnosed before April 1998. Thus, women were followed up for 6.25-8.25 years. We considered CIN I, CIN II and CIN III (the latter includes severe dysplasia and carcinoma in situ) and invasive cervical cancer. The

preinvasive stage, CIN I, is equal to a low-grade squamous intraepithelial lesion (LSIL), whereas the stages CIN II and CIN III are high-grade SIL (HSIL).

The incidence of (pre-) invasive lesions after negative smears without endocervical cells was compared with that after negative smears with endocervical cells; a similar comparison was made for the difference between negative smears with and without metaplastic cells. We also estimated the difference with a multivariate logistic regression model, in which we adjusted for age (in 6 categories: < 25 years, 25-34 years, 35-44 years, 45-54 years, 55-64 years, 65 years or older) and screening history, which is a combination of first smear (first category) and the screening interval in case of a preceding smear (in the categories: < 1 year, 1-2 years, 2-3 years, 3-4 years, 4-5 years, 5 years or longer). Both variables increased the fit of the model significantly ($p < 0.05$). We calculated odds ratios and their 95% confidence interval (95% CI) using the regression coefficients and the standard errors estimated in the model.

## Results

In 1990 and 1991, 515,146 smears were registered as performed for screening purposes. Of these smears 87% were negative, of which most (88.3%) contained endocervical cells (*Table 5.1*). The proportion of negative smears without endocervical cells is relatively high at young age (< 25 years) and at older age (65 years or older), and lowest (10%) in women between 35 and 45 years of age.

In *Table 5.2* and *Table 5.3,* the intensity of follow up was compared for negative smears with and without endocervical cells. The proportion of smears without endocervical cells with no follow up registered in the study period (15%) was slightly higher compared with that for negative smears with endocervical cells (13%) (*Table 5.2*). In both groups, most women had at least two follow up examinations, which gives enough opportunity to detect any abnormality.

**Table 5.1**
Proportion of smears with (ecc+) and without (ecc-) endocervical cells of all preventive negative smears taken in 1990 and 1991 in the Netherlands by age of women (PALGA)

| Age (years) | Ecc+ | Ecc- | All negative smears[1)] |
|---|---|---|---|
| | Number (Percentage) | Number (Percentage) | Number |
| < 25 | 15389 (81.6) | 3465 (18.4) | 18854 |
| 25-34 | 90488 (87.3) | 13175 (12.7) | 103663 |
| 35-44 | 169684 (89.7) | 19554 (10.3) | 189238 |
| 45-54 | 107511 (87.9) | 14858 (12.1) | 122369 |
| 55-64 | 9022 (87.5) | 1293 (12.5) | 10315 |
| 65 or older | 3747 (82.5) | 797 (17.5) | 4544 |
| Total | 395841 (88.2) | 53142 (11.8) | 448983 |

1) Of all screening smears, 87.2% (448,983/515,146) were diagnosed as negative, for the age groups in the table, the percentages were 83.9, 87.5, 87.6, 87.0, 85.9 and 80.3, respectively

**Table 5.2**
Number of follow up examinations for negative smears with (ecc+) and without (ecc-) endocervical cells, after 6.25-8.25 years of follow up, PALGA

| Primary smear | No. of follow up examinations | | | | Total |
|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 or more | |
| Ecc+ | 51,423(13%) | 100,373(25%) | 126,109(32%) | 117,936(30%) | 395,841(100%) |
| Ecc- | 7,820(15%) | 115,18(22%) | 14,117(27%) | 19,687(37%) | 53,142(100%) |

The time from a negative smear until the subsequent examination is presented in *Table 5.3*. As expected, the subsequent examination after negative smears without endocervical cells was performed within a shorter interval after the initially smear: 19% of these smears had a follow up examination registered within one year, compared with 10% of the negative smears with endocervical cells. Within three years, 40% of all negative smears without endocervical cells had a follow up examination registered, compared with 21% for negative smears with endocervical cells. Thus, the number of examinations registered after the negative smears was about equal in both groups, but the time until follow up was shorter for negative smears without endocervical cells.

**Table 5.3**
Interval to subsequent examination for negative smears with (ecc+) and without (ecc-) endocervical cells, after 6.25-8.25 years of follow up, PALGA

| Primary smear | No follow up | < 1 year | 1-3 years | > 3 years | Total |
|---|---|---|---|---|---|
| Ecc+ | 51,423(13%) | 39,683(10%) | 44,965(11%) | 259,770(66%) | 395,841(100%) |
| Ecc- | 7,820(15%) | 10,106(19%) | 11,134(21%) | 24,082(45%) | 53,142(100%) |

The maximal histological diagnosis before April 1998 is shown in *Table 5.4*. The incidence of cervical neoplasia detected after negative smears without endocervical cells was about equal to that for the smears with endocervical cells. After negative smears with endocervical cells, there were 0.54 invasive cervical cancers (n=215) detected per 1,000 smears; after negative smears without endocervical cells, there were 0.53 invasive cervical cancers (n=28) detected per 1,000 smears.

**Table 5.4**
The number and proportion of maximal histological diagnoses detected during 6.25-8.25 years of follow up, after negative smears with (ecc+) and without (ecc-) endocervical cells, PALGA

| Follow up | | Ecc+ | | Ecc- | |
|---|---|---|---|---|---|
| | | Proportion ($10^{-3}$) | Number | Proportion ($10^{-3}$) | Number |
| Cin I | LSIL | 4.6 | 1818 | 4.3 | 227 |
| Cin II | HSIL | 2.2 | 870 | 2.2 | 116 |
| Cin III | HSIL | 3.9 | 1538 | 4.0 | 213 |
| Invasive | | 0.54 | 215 | 0.53 | 28 |

There was no significant difference in the incidence of any of the histological categories (*Table 5.5*). When we compared incidence of CIN I or worse, CIN II or worse, and CIN III or worse, again, no significant differences were found. We also adjusted the incidences for age and screening interval. The estimated odds ratios are only slightly different from those estimated in the univariate analysis. None of the analyses showed any prognostic difference between negative smears without endocervical cells and negative smears with endocervical cells; in fact, all odds ratios were very close to 1.00 (*Table 5.5*).

We also estimated the difference of cervical neoplasia between smears with and without metaplastic cells. During the study period, the absence of metaplastic cells was not an indicator for an additional smears. In our data, the proportion of smears

registered as without metaplastic cells is 52%. All estimated odds ratios were less than one, and the differences between smears with and without metaplastic cells were significant (CIN I or worse: odds ratio, 0.82; 95% CI, 0.77-0.87; and CIN III or worse: odds ratio, 0.81; 95% CI, 0.75-0.89), except for invasive cancers. Thus, in our data, the absence of metaplastic cells was not associated with an higher risk for cervical neoplasia.

**Table 5.5**

Odds ratios (OR) expressing the differences in maximal histological diagnosis, after 6.25-8.25 years of follow up, estimated for negative smears without endocervical cells compared with negative smears with endocervical cells, PALGA

| Follow up | | Univariate | | Multivariate[1)] | |
|---|---|---|---|---|---|
| | | OR | 95% CI | OR | 95% CI |
| Cin I | (LSIL) | 0.93 | 0.81 - 1.07 | 0.95 | 0.83 - 1.09 |
| Cin II | (HSIL) | 0.99 | 0.82 - 1.21 | 0.97 | 0.80 - 1.18 |
| Cin III | (HSIL) | 1.06 | 0.92 - 1.22 | 1.04 | 0.90 - 1.20 |
| Invasive | | 0.97 | 0.65 - 1.44 | 1.01 | 0.68 - 1.49 |
| Cin I or worse | (LSIL +) | 0.99 | 0.91 - 1.08 | 0.99 | 0.91 - 1.08 |
| Cin II or worse | (HSIL +) | 1.03 | 0.92 - 1.15 | 1.01 | 0.91 - 1.13 |
| Cin III or worse | (HSIL +) | 1.05 | 0.92 - 1.20 | 1.03 | 0.91 - 1.18 |

1) The multivariate model included age and screening history

## *Discussion*

In our data, the histological follow up after a negative smear without endocervical cells was not significantly different from that of a negative smear with endocervical cells. We estimated that the risk of an invasive cervical carcinoma within eight years after negative smears without endocervical cells was equal to the risk after negative smears with endocervical cells (odds ratio, 1.01; 95% CI, 0.68-1.49); the same conclusion applies when CIN I, II, III, or worse were used as the endpoint.

The intensity of follow up could have influenced our results, as it was recommended that women with negative smears without endocervical cells undergo an additional smear after one year instead of the routine screening interval of 3 years in the study period. The proportion of women who had no follow up was equal in both groups, but the average interval to the subsequent smear was slightly shorter for negative

smears without endocervical cells. A more intensive follow up could have led to an increase in sensitivity of the follow up and, thus, to a reduced incidence of invasive cancers, owing to successful treatment of preinvasive lesions. At the same time, this should lead to a higher proportion of preinvasive lesions. In fact, the difference in intensity in follow up was small, and the incidence of preinvasive lesions after smears without endocervical cells was not higher in our data.

In our analysis, smears were regarded as without endocervical cells when this specific category (no endocervical cells present) was selected explicitly in the cytology report on the item "endocervical cells". Some laboratories used the item "quality of the smear" to indicate the cell types that were present. This would imply an incomplete analysis with possibly biased results. However, it seems that 95% of the smears, which had a quality report in which the presence of endocervical cells was not explicitly reported (4 categories), also had the registration of no endocervical cells present. Thus, the influence on the results can not be important. Another possible factor in the Dutch data is that some laboratories included smears without squamous metaplastic cells within the category of 'without endocervical cells', which is more in line with the findings in the United States. After the reorganisation of the screening program in the Netherlands, much attention has been given to standardization of the screening procedures. It would be interesting to repeat the analysis, when these more recent smears have a sufficient follow up period.

In the literature, the clinical relevance of endocervical cells has been explored in different types of analyses that seemed to lead to opposite conclusions. Cross-sectional analyses described that the proportion abnormalities detected in smears without endocervical cells is lower compared with smears containing endocervical cells (1, 2, 3). To explore whether differences are due to differences in data or to differences in methods, we also subjected our data set to the cross-sectional study design, in which we found that the proportion of abnormal smears (cytologically atypical cells or worse) was 11.5% in smears with endocervical cells, compared with only 5.7% in smears without endocervical cells, estimated for all preventive smears taken in 1990 and1991 in the Netherlands (n=515,146). Hence, in this respect, our results are in line with the studies previously described (1, 2, 3). This shows that the apparent contradictory results from the cross-sectional study compared with the longitudinal design also are found within a data set. Theoretically, lower detection rates found in smears without endocervical cells can reflect a true lower incidence of abnormalities. This also may be caused by less complete registration of absence of

endocervical cells once abnormalities are found in a smear. It is important to realise that a cross-sectional design that does not include follow-up data is not appropriate to study the prognostic relevance of endocervical status in negative smears.

Retrospective analyses, previously described, reported high proportions of (false-) negative smears without endocervical cells before the diagnosis of invasive cervical cancer (4, 5). These differences in results between the retrospective and the prospective analyses can be explained only by differences in data or in definitions. If retrospective and prospective analyses are studying the same data from different perspectives and under similar assumptions, conclusions should be consistent. The proportion of (false-) negative smears without endocervical cells before invasive cancer has been reported to be 64% (n = 47) (5) and 78% (n = 55) (4). A serious problem with these two studies is that the endocervical status was assessed retrospectively during the study, without a similar assessment in controls. However, it is unclear whether this may explain the high percentages of negative smears without endocervical cells before development of invasive cancers.

Kristensen et al. (4) found that the absence of metaplastic cells was an important indicator of false-negative smears obtained before diagnosis of invasive cancer. We found that the number of abnormalities within 6-8 years of follow up after negative smears without metaplastic cells was lower compared to that of negative smears with metaplastic cells (CIN III or worse: odds ratio, 0.81; 95% CI, 0.75-0.89), suggesting that the absence of metaplastic cells is associated with lower risk for cervical neoplasia. However, in view of the low percentage of smears registered as containing metaplastic cells and the fact that there were no recommendations for follow up, the usefulness of the registration in this respect is questionable.

In the present analysis, we used all invasive cancers of the uterine cervix, including squamous carcinoma and adenocarcinoma. We also estimated the incidence of these carcinomas separately to explore the differences. After a negative smear with endocervical cells 144 squamous carcinomas (0.36 per 1,000 initially negative smears) and 65 adenocarcinomas (0.16 per 1,000 initially negative smears) were detected. For six cases, the morphologic features were not clearly described. After a negative smear without endocervical cells 20 squamous carcinomas (0.38 per 1,000 initially negative smears) and 8 adenocarcinomas (0.15 per 1,000 initially negative smears) were detected. Thus, no relation between endocervical status and the proportion of squamous carcinomas or adenocarcinomas could be established.

Based on these data, we conclude that the risk of severe cervical neoplasia in the next 6-8 years for women that had a negative smear does not depend on endocervical status. Hence, an additional smear for women with negative smears without endocervical cells is not justified.

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# 6

# NON ATTENDANCE IS STILL THE MAIN LIMITATION FOR THE EFFECTIVENESS OF SCREENING FOR CERVICAL CANCER IN THE NETHERLANDS


## *Abstract*

Objective Although mass screening for cervical cancer is operational for more than two decades in the Netherlands, still 700 women are diagnosed with this cancer each year (9 per 100,000). We investigated why these cases still occurred, in order to evaluate opportunities to further increase the effectiveness of the programme.

Method We analysed the screening history of women diagnosed with cervical cancer between 1994-1997 from the Dutch national pathology file, including cervical cytological and histological results.

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. For the future, we estimate that two third of all Dutch women with invasive cervical cancer will be unscreened or under-screened, with the current screening participation of more than 70%.

Conclusion Increasing screening participation has much more potential for further reducing cervical cancer incidence in the Netherlands than reducing the screening interval, increasing the age range or having a screening test with higher sensitivity.

## Introduction

In the Netherlands, screening for cervical cancer is widespread since the early eighties. In the nineties more than 1,000,000 smears are taken yearly with roughly 3.5 million women in the target age group of the population (1). 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 programmes are capable to strongly reduce the incidence of cervical cancer. For the present programme we have estimated that by responding to all 7 invitations the risk of dying from cervical cancer is reduced by 75% (2). The percentage of women with any smear in the preceding 5 years in the Netherlands is estimated at over 80%(1). The effect of screening on a population level, however, will be lower than expected on basis of these figures, since non participating women have a higher than average risk (3).

Since 1993, at least seven studies described the screening histories of women with invasive cervical cancer (4-11). The number of cases in these studies was between 46 (9) and 481 (4). All studies concluded that the lack of a cervical smear history is the major explanatory factor for the still occurring disease. The percentage of women with invasive cervical cancer that had no screening history varied between 28% in Connecticut, USA [8] and 54% for Maori women in New Zealand (9). 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 causes about 250 deaths yearly (12). Were most of the women diagnosed with invasive cancer never invited, because of their age, for screening, were they missed by screening, or did they not or not regularly participate?

To answer this question, we analysed the screening history of 3175 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 possibilities to improve the current Dutch programme.

## *Material and methods*

In the Dutch Network and National Database for Pathology (PALGA) all cytological and histological examinations carried out in the Netherlands are registered (13). 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 (13).

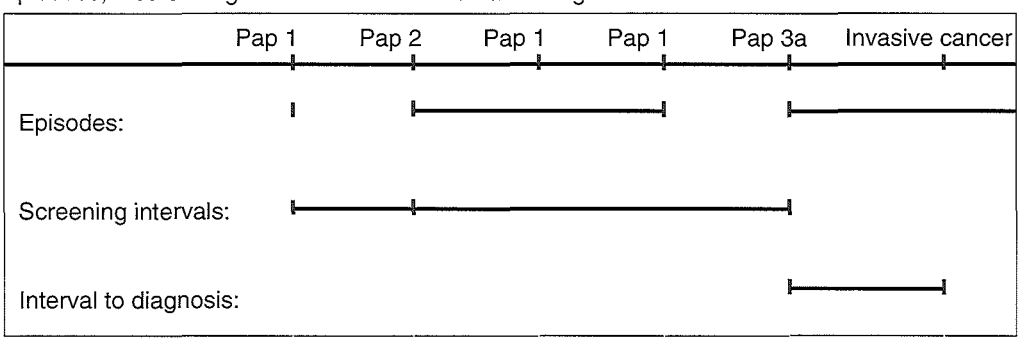
We found 3175 women diagnosed with histologically confirmed invasive cervical cancer in the years 1994-1997, with 787, 805, 790 and 793 women in the respective years. The numbers in the national cancer registry (which is not linked to the screening history) are about 10% lower: 715, 723, 718 and 721 cases, respectively (12).
The identification code used in the PALGA consisted of the first four characters of the maiden name, gender, and date of birth. Women who's 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 four characters of the maiden names (14). This resulted in a reduction of number of cancer cases by 34,7% to 2074.

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 (18). Women received an invitation for the programme; remainders were not send. Next to the programme, spontaneous smears were taken on the initiative of the women 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, since when the geographic coverage of the programme was 100%, and remainders have been send 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 for 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 two consecutive negative follow up smears are registered or when there is no examination during four consecutive years (Figure 6.1).

**Figure 6.1**
Overview of the definitions of our study using one exemplary screening history with 3 episodes, 2 screening intervals and the interval to diagnosis.




We categorised the cases by their age on 31 December of the year of diagnosis. A case was considered as being 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 had 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 (Figure 6.1).

## 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 6.1). Seventeen percent of the women were not invited, because they were over 53 years of age when the programme was introduced.

**Table 6.1**
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%) |
| Total | 2074 | (100%) |

The group of women with cervical cancer that was invited for mass screening was broken down according to the individual screening history (Table 6.2). Fourteen percent was 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 was 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 de period studied). Finally, 19% of the women had a smear taken in the last 6 years preceding the cancer diagnosis.

**Table 6.2**
Screening history of women with cervical cancer 1994-1997 and ever invited for mass screening, PALGA

| Screening history | Women with cervical cancer | |
|---|---|---|
| | Numbers | (Percentages) |
| Diagnosed at first screening invitation (age 30 or 35)[1] | 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%) |
| Total | 1458 | (100%) |

1. Screening at age 30 or 35, depending on year of diagnosis (see material and methods)

Of this latter group, consisting of the missed cases with as only explanation that they were not picked up by screening, we retrieved the highest cytological or histological diagnosis ever in the past, which is before the episode in which the cervical cancer was found (Table 6.3). We found that 31% of these women had a diagnosis of light dysplasia and 5% of at least moderate dysplasia.

**Table 6.3**
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.

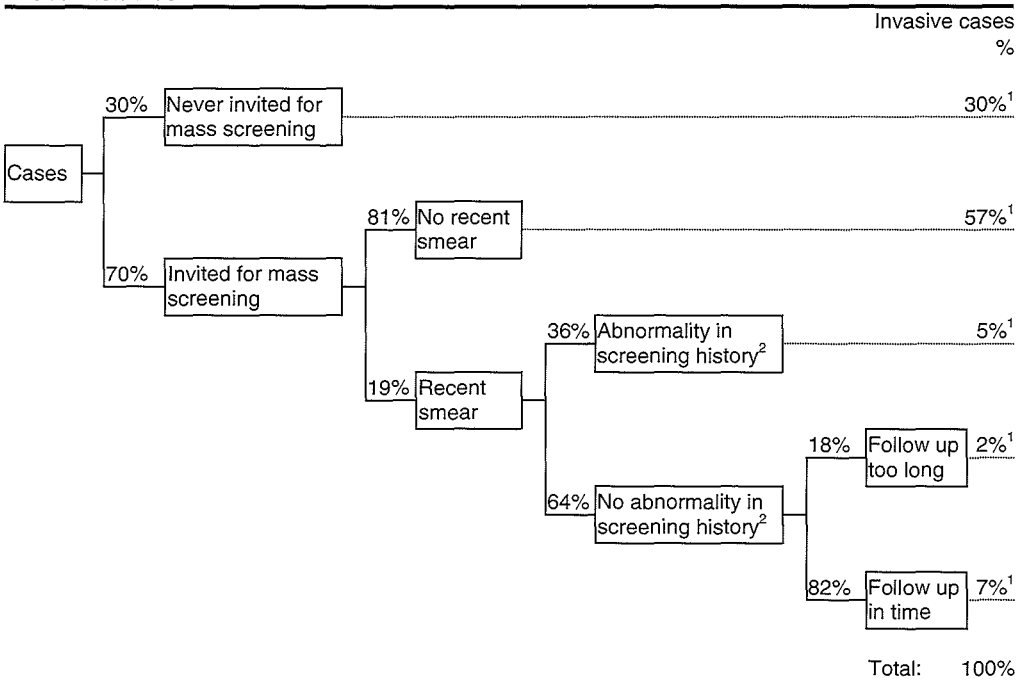
| Highest diagnosis in the screening history | Women with cervical cancer | |
|---|---|---|
| | Numbers | (Percentages) |
| Negative | 183 | (64%) |
| ASCUS and light dysplasia | 87 | (31%) |
| Moderate or severe dysplasia | 14 | (5%) |
| Total | 284 | (100%) |

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 Table 6.1-6.3, we found (see figure 6.2) that among all women diagnosed with cervical cancer between 1994 and 1997, 30% was 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 in any of these categories: they had a negative smear within 6 years previously, a "clean" history and no delay in diagnosis.

**Figure 6.2**
Overview of screening history categories under which invasive cervical cancer cases occurred in The Netherlands




1 The percentages for the categories are combinations of the percentages in table 6.1-6.3.

*Never invited for screening:* 30% (= 17%+ 12% of Table 6.1); remaining 70% invited.

*No recent smear: 81% (= 70% x (14% + 55% + 7% + 4% of Table 6.2)); remaining 19% with a recent smear.*

*Abnormality in screening history: 36% (=70% x 19% x (31% + 5% of Table 6.3)); remaining 64% without abnormality.*

*Follow up too long: 2% (=70% x 19% x 64% x 18% who had a delay, as described in the results).*

*Follow up in time: 7% (=70% x 19% x 64% x (100-18)% who had a delay, as described in the results).*

2. Abnormality (cytological of histological) detected prior to the episode in which the cancer is diagnosed (see material and methods).

## Discussion

In our study, 30% of the women were never invited for cervical cancer screening. In the 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 decreases to approximately 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 Table 6.2 and 6.3 will increase. Therefore, we expect that 10-15% of all women with invasive cervical cancer will be detected at first screening, 15-20% will be detected in women who did follow 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, due to fact that we have no data for women over 75 years of age who had the opportunity to participate in the screening programme at earlier age. We also expect a decrease in the total incidence due to the enlargement of the screening target age-range as well as the completion of all cohorts to having been exposed to the programme. So an increase in a percentage of one of the categories described above may well correspond with a decrease in number of cases.

Our results evaluated the reasons for the missed cases, based on the guidelines of the programme. However, in the Netherlands, spontaneous screening next to the programme was common, leading to smears taken outside the programme. 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 accounted for; 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 opportunist screening has been reduced recently in The Netherlands, particular under the starting age of the programme, its influence will show 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 with 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 (15, 16).

As far as decreasing non-participation is concerned, the question is to what extent the behaviour of nowadays non-participants can be influenced. In a Dutch study, 72% of all non-participants declared they would participate the "next" time, suggesting that they do not have a negative attitude towards screening (17). 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% (6) up to 77% (10). Our study, with 57%, is on the lower end of this range. However, this percentage depends strongly on the participation rate to screening. A higher participation rate will lower the fraction of un(der)screened cancer cases. And the participation rate depends amongst others 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, searching the ways to increase attendance is of primary importance.

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# 7

# NON-PROGRESSION OF CERVICAL INTRAEPITHELIAL NEOPLASIA ESTIMATED FROM POPULATION-SCREENING DATA


## *Abstract*

Non-progression and duration of preclinical neoplastic lesions of the cervix uteri were studied using screening data from a previously unscreened population, Maribo County, Denmark (1966-82). To estimate regression rates, the incidence of clinical cancer before the screening programme was related to the prevalence and incidence of preclinical lesions estimated from the detection rates of first smear and third and subsequent smears respectively. Duration was estimated from the time lag between the cumulative incidence of preclinical lesions and the combined cumulative incidence of clinical cancer and the estimated 'incidence of regression'. Of all preclinical lesions in women aged 25-50, 24% progressed, 39% regressed and 38% remained. Even if we assume no onset of preclinical lesions above age 50, we estimated that 48% of the preclinical lesions would not progress tot clinical cancer in the women's lifetime. The estimated mean duration of preclinical lesions was 16 years. In Maribo County during the 1970s, the positive rate (1.6%) was low compared with current rates in several countries. We conclude that the detection of non-progressive lesions was outweighed by the prevention of clinical cancer.

## Introduction

A thorough understanding of the natural history of a disease is among the basic requirements for the initiation and evaluation of screening programmes (1). However, the natural history of cervical cancer can only be learned directly from the experience of women with positive smears followed without treatment until development of invasive cervical cancer. As observation without treatment has been considered unethical for many years, such data on the natural history of cervical cancer are available only for small groups of women (2). Nevertheless, data from the first and subsequent rounds of mass screening in a previously unscreened population can give insight into crucial aspects of screening for cervical cancer, such as regression and duration of the preclinical stage (3).

Maribo County in Denmark is an area in which cervical smears were not used before an organized screening programme was started in 1967 for all women aged 30-49 years (4). From the beginning, the local pathologists ensured registration of all smears and cervical biopsies taken in the area (5,6). This combination of screening started from scratch and complete registration makes Maribo County an ideal setting for the study of the natural history of cervical cancer.

We analysed the data of Maribo County focusing on the estimation of non-progression rates and duration of the preclinical stage. Estimates were obtained by relating detection rates among first smears ('prevalence of preclinical lesions') and detection rates of repeated smears ('incidence of preclinical lesions') to the incidence of clinical cancer in the unscreened population. Non-progression contributes to the negative side-effects of screening. Duration of the preclinical lesion is an important parameter in relation to the time interval in screening programmes.

## Material and methods

### Screening data of Maribo County

In the Maribo County screening programme, women aged 30-49 were invited for an examination every fourth year. In the analysis, we included data from August 1966, when the pathology department began operation, until December 1982, when the fourth round of the screening programme ended. For the women in the cohort, data on cervical smears and biopsies (Maribo County pathology department), data on surgery involving the cervix uteri (Maribo County hospitals) and data on invasive

cervical cancer, migration and death (national data) had previously been merged into one register (5,6). Data for the present study were retrieved from this merged register.

In the database smears were registered either as 'primary smears' or as 'follow-up smears'. Primary smears were taken within Maribo County by general practitioners, either following an invitation from the organized screening programme or outside the organized programme. A total of 109 278 primary smears were registered in Maribo County during the study period. Smears were classified as: unqualified, negative, atypical cells, cells slightly suspicious for malignancy, cells moderately suspicious for malignancy or cells highly suspicious for malignancy. An unqualified smear was followed by a new smear and, in the present analysis, the smear taken directly after an unqualified smear is used as the primary smear. Patients with at least atypical cells were followed up mostly with a biopsy, which was classified as normal, light dysplasia (cervical intraepithelial neoplasia (CIN) I), moderate dysplasia (CIN II), severe dysplasia or carcinoma in situ (CIN III) or invasive cervical cancer.

We considered all 99 022 primary smears (consisting of 28 403 first smears, 22 869 second smears and 47 750 third and subsequent smears) without any history of cervical abnormality. Smears in women with a previous positive smear, biopsy or a surgical intervention (hysterectomy, collum amputation, conisation, electrocauterization or cryotherapy) have been excluded. To avoid cases in which symptoms had led to the primary smear, we excluded smears with a biopsy registered within 4 days after the smear. These biopsies were most probably taken on the same day as the smears or at least they were not taken as a result of the smear.

The follow-up after a smear with at least atypical cells (in the following referred to as positive smear (1595 cases)) was summarized into one diagnosis, the highest diagnosis. If the histological follow-up was negative, or if there was no histology and all follow-up smears were negative, the case was considered to have a negative diagnosis. Smears with at least CIN I as the maximum histological follow-up were considered to be positive cases. As symptomatic women were excluded, all positive cases were considered to be preclinical invasive lesions.

**Estimation of non-progression rates**

If no regression occurs all preclinical lesions stay or progress to clinical invasive cancer. The sum of the prevalence ($P_1$) of preclinical lesions in unscreened women at age $a_1$, plus the incidence ($I_d$) of preclinical lesions during the age interval $a_1$ to $a_2$ is equal to the prevalence ($P_2$) of preclinical lesions in unscreened women at age $a_2$

plus the incidence of clinical cancer ($I_c$) of invasive cancer in the situation without screening, during the age interval $a_1$ to $a_2$: $P_1+I_d = P_2+ I_c$ (Figure 7.1A). If regression occurs, part of the preclinical lesions present at $a_1$ or developed during the interval ($I_d$) are no longer present at $a_2$ as preclinical stage ($P_2$) or as invasive cancer ($I_c$). The part of preclinical lesions 'missing' at $a_2$ (X) is equal to : $(P_1+I_d) - (P_2+ I_c)$ (Figure 7.1B).

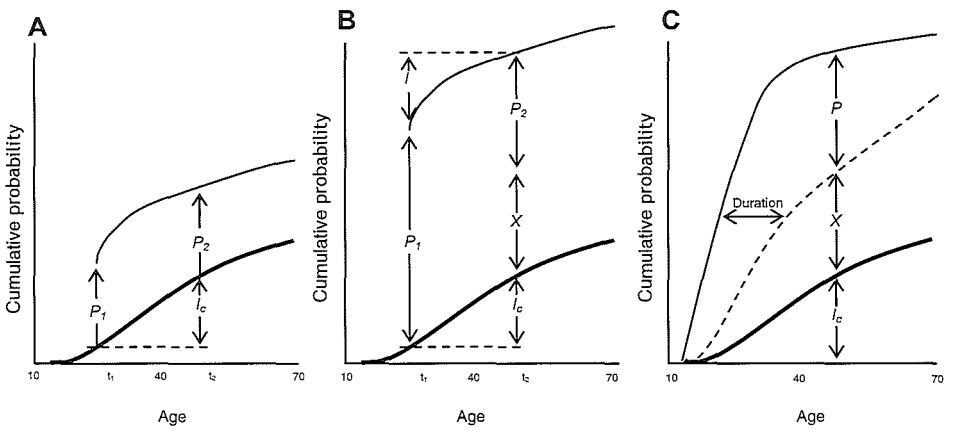


**Figure 7.1**
Relation between prevalence of preclinical lesions ($P_1$ and $P_2$), cumulative incidence of preclinical lesions ($I_d$) and cumulative incidence of clinical cancer ($I_c$) in (**A**) a situation without regression ($P_1+I_d = P_2+ I_c$), (**B**)a situation with regression and (C) for the duration of the preclinical lesion, *X* represents all 'missing' cases; —, Preclinical incidence; —, clinical incidence; ----, no longer preinvasive

The proportion of lesions that regressed during the interval ('interval regression') was estimated by the number of 'missing lesions' divided by all preclinical lesions known between $a_1$ up to $a_2$: $[(P_1+I_d) - (P_2+ I_c)]/ (P_1+I_d)$. The 'interval progression' was estimated by the number of progressed lesions divided by all preclinical lesions in the interval: $I_c/ (P_1+I_d)$. The proportion of lesions that are still prevalent at a2 was calculated by the rate of prevalent lesions at $a_2$ divided by all preclinical lesions: $P_2/ (P_1+I_d)$.

The interval regression, interval progression and lesions which stay prevalent were estimated for the age interval 25-50. The prevalences $P_1$ and $P_2$ at age 25 and age 50, respectively, and the incidence $I_d$ were estimated from the screening results. The cumulative incidence $I_c$ was estimated from the cumulative incidence over the age interval 25-50 of clinical cancer.

The age interval 25-50 years was used because of the small number of screen-detected cases in younger and older women. An estimate for the progression of lesions still prevalent at age 50 was obtained by dividing the cumulative incidence $I_c$ from age 50 to age 80 by the prevalence $P_2$ at age 50. The derived estimate of non-progression in women over 50 years of age, which is given by $(1-I_c/P_2)$ was obtained with the above estimated interval regression, in women between 25 and 50 years of age, to calculate the non-progression for women over 25 years of age.
Confidence intervals for interval regression, interval progression, proportion prevalent lesions and minimal non-progression were estimated using approximate interval estimation techniques for rate ratios adapted for this particular situation (7).

*Prevalence of preclinical lesions: $P_1$ and $P_2$*

Detection rates of the first smear were calculated for ages 20, 25, 30, 25, 40, 45, 50, 55 and 60 as the proportion of positive smears in the interval [age –2,5 to age +2,5]. The prevalence of preclinical lesions in unscreened women was estimated by correcting the detection rates for false-negative test results, assuming a sensitivity of 80% (8). Fro comparison we also used sensitivities of 70% and 90%.

*Incidence of preclinical lesions during the age interval $a_1$ to $a_2$: $I_d$*

The incidence of preclinical lesions was estimated from the detection rates at the third and subsequent smears. We excluded the second smear due to the bias caused by detection of false negatives from the first smear. We estimated the age at onset of preclinical lesions as the age halfway between the last negative smear and the first positive smear (age at midpoint). We calculated the corresponding incidence rate per woman-year at risk for the third and subsequent smears. For example, a woman with a negative smear at age 23 and a positive smear at age 31 (age at midpoint = 27) will contribute 2 women-years to the age group 20-24 in de denominator. For the age group 25-29 it will result in one positive diagnosis in the numerator and 2 women-years in the denominator. In case both smears were negative this woman would contribute 2 woman-years to the age group 20-24, 5 woman-years to the age range 25-29 and 1 woman-year to the age group 30-34 in the denominators. Cumulated incidence rates ($I_d$) were calculated by adding the incidence rates from each of the 5-year age groups and multiplying by 5.

*Incidence of clinical cancer during the age interval $a_1$ to $a_2$ given no screening: $I_c$*

Incidence rates for Maribo County are available from 1958 to 1962, the period just before screening started. The age-specific incidence rates form all of Denmark from 1958 to 1962 (9) did not differ significantly from those of Maribo County. The Maribo County rates show an irregular age trend because of the relative small numbers; in the analysis we therefore used the national incidence rates. This incidence of clinical cancer is corrected for women not at risk (without a cervix), using age-specific hysterectomy data from Maribo County.

**Estimation of preclinical duration**

Preclinical lesions will stay prevalent for some time after which they will regress to normal or progress to clinical invasive cancer. The time they will remain screen-detectable is known as the preclinical duration. As can be seen from Figure 7.1C the cumulative incidence of $I_c$ up to a certain age of lesions that are no longer prevalent because of progression ($I_c$) or regression (X), can be estimated by subtracting the prevalence at that age from the cumulative incidence of preclinical lesions up to this age, $I_c + I_d - P$. A rough estimate of the preclinical duration is then the number of ears between the age where $I_d$ reaches a certain level and the age where $I_c$ reaches the same level.

It is assumed that the duration of the preclinical stage is described by a Weibull probability distribution F(x;m,b) with two parameters: mean duration m and shape (or concentration parameter) b (8). For a given Weibull distribution the expected cumulative rate of lesions that have regressed or progressed can then be calculated for each 5-year age group i:

$$I_{ci}^* = \Sigma j \leq i \; I_{dj} \, F(\bar{a}_i - \bar{a}_j)$$

Where $\bar{a}_k$ is the age at midpoint of a given 5-year age group k, $I_{dj}$ the incidence of preclinical lesions in the age group j, and F(x) the Weibull distribution of the duration of the preclinical stage. The best-fitting parameters m and b are obtained by minimizing the difference between the observed ($I_c$) and the expected ($I_c^*$)cumulative incidence of lesions that have regressed or progressed.

## Results

### Insufficient follow-up and predictive values

During the study period 1595 women had a positive primary smear in Maribo County: 61% of these had a histologically confirmed preclinical lesion, 31% no preclinical lesions and 9% were insufficiently followed up. For cases with sufficient follow-up, the positive predictive value of a positive smear (atypia+) for at least CIN was 67%. This value varied with the cytology of the primary smear, from 25% for 'atypical cells' to 88% for 'cells highly suspected for malignancy' (Table 7.1).

**Table 7.1**
Histological follow-up by cytological result of all positive primary smears, Maribo County 1966-82

| Cytology of primary smear | All smears | Smears without sufficient follow-up | Smears with sufficient follow-up | | | |
|---|---|---|---|---|---|---|
| | | | No preclinical lesion | | Preclinical lesion | |
| | | | Cases | Percentage | Cases | Percentage |
| Atypical | 326 | 97 | 171 | 75 | 58 | 25 |
| Light suspect | 628 | 28 | 222 | 37 | 378 | 63 |
| Moderate suspect | 498 | 7 | 82 | 17 | 409 | 83 |
| Severe suspect | 143 | 5 | 16 | 12 | 122 | 88 |
| All | 1595 | 137 | 491 | 33 | 977 | 67 |

### Incidence and prevalence

The detection rates of preclinical lesions at the first smear are shown in Table 7.2. The prevalence of preclinical lesions in unscreened women, derived from these detection rates by correcting for an assumed 80% sensitivity, was 2.9% in women over 20 years of age. The highest prevalence (4%) was found at age 40.

The incidence of preclinical lesions is estimated by the detection rates per 100 women-years of the third and subsequent smears (Table 7.3), and shows a peak in age group 25-30 years. The incidence rate for women over 20 years of age was two cases per 1000 women-years.

**Table 7.2**
Detection rates of the first smear and estimation of prevalence of preclinical cervical lesions in Maribo County, 1966-1982

| Age[1] | Number of positive cases[2] | Number of smears | Detection rate (x $10^{-3}$ smears) | Estimated prevalence[3] (x $10^{-3}$ women) |
|---|---|---|---|---|
| 20 | 3.0 | 1382 | 2.2 | 2.7 |
| 25 | 33.3 | 4059 | 8.2 | 10.3 |
| 30 | 174.3 | 7523 | 23.2 | 29.0 |
| 35 | 141.5 | 4470 | 31.7 | 39.6 |
| 40 | 129.7 | 4006 | 32.4 | 40.5 |
| 45 | 106.7 | 3570 | 29.9 | 37.4 |
| 50 | 60.9 | 2986 | 20.4 | 25.5 |
| 55 | 3.0 | 307 | 9.8 | 12.2 |
| 60 | 1.0 | 85 | 11.8 | 14.7 |
| 60+ | 0.0 | 15 | 0.0 | 0.0 |
| 20+ | 653.4 | 28403 | 23.0 | 28.8 |

1. The prevalence is estimated for the age $a_1$, by mean of [$a$ -2.5, $a$ +2.5].
2. First smears without sufficient follow-up have been redistributed based on their cytology of the primary smear (see Table 7.1).
3. Assuming an 80% sensitivity.

**Table 7.3**
Estimation of incidence and cumulative incidence of preclinical cervical lesions by age, based on detection rates of the third and subsequent smears, in Maribo County, 1966-1982

| Age | Number of positive cases[1] | Number of women-years | Incidence of preclinical lesions (x $10^{-3}$ years) | Cumulative incidence of preclinical lesions (x $10^{-3}$ years) |
|---|---|---|---|---|
| < 20 | 0 | 43 | 0.00 | 0.0 |
| 20-25 | 2.6 | 1890 | 1.37 | 6.9 |
| 25-30 | 56.5 | 10698 | 5.28 | 33.3 |
| 30-35 | 51.8 | 20377 | 2.54 | 46.0 |
| 35-40 | 34.5 | 23550 | 1.47 | 53.3 |
| 40-45 | 24.7 | 19615 | 1.26 | 59.6 |
| 45-50 | 17.5 | 17752 | 0.99 | 64.5 |
| 50-55 | 13.2 | 8950 | 1.47 | 71.9 |
| 55-60 | 0.7 | 3396 | 0.21 | 72.9 |
| 60+ | 0 | 388 | 0.00 | 72.9 |
| All ages | 201.5 | 106228 | 1.90 | - |

1. Third and subsequent smears without sufficient follow-up have been redistributed based on their cytology of the primary smear (see Table 7.1).

The incidence of clinical cancer before the start of the screening in Denmark and Maribo County increases steeply at a young age and decreases after age 50 (Table 7.4). The incidence of clinical cancer for women between 30 and 60 years of age was between 0.4 and 0.9 per 1000 women-years, and the highest incidence was found for women in their forties. Incidence of clinical cancer is estimated for women at risk (with a cervix uteri) in Maribo County.

**Table 7.4**

Incidence of clinical cervical cancer in Denmark and in Maribo County, 1958-62, and estimated incidence of clinical cervical cancer ($I_c$) for women at risk in Maribo County

| Age | Maribo County 1958-62 | | Denmark 1958-62 | | $I_c$ |
|---|---|---|---|---|---|
| | Rates ($10^{-5}$ years) | Cases | Rates ($10^{-5}$ years)[1] | Cases | Rates ($10^{-5}$ years at risk)[2] |
| < 20 | 0.0 | ( 0) | 0.1 | ( 1) | 0.1 |
| 20-25 | 0.0 | ( 0) | 2.0 | ( 15) | 2.0 |
| 25-30 | 17.3 | ( 3) | 15.9 | (112) | 16.0 |
| 30-35 | 41.1 | ( 8) | 42.1 | (306) | 42.8 |
| 35-40 | 87.3 | (19) | 75.3 | (589) | 77.8 |
| 40-45 | 65.5 | (14) | 85.1 | (651) | 90.4 |
| 45-50 | 111.9 | (24) | 85.8 | (661) | 94.5 |
| 50-55 | 98.6 | (21) | 76.7 | (568) | 86.7 |
| 55-60 | 83.3 | (16) | 69.4 | (462) | 79.5 |
| 60-65 | 55.3 | (10) | 58.6 | (345) | 67.7 |
| 65-70 | 19.4 | ( 3) | 52.6 | (252) | 61.1 |
| 70-75 | 57.5 | ( 7) | 39.0 | (145) | 45.5 |
| 75-80 | 35.7 | ( 3) | 36.8 | ( 93) | 43.1 |
| 80+ | 69.4 | ( 5) | 41.6 | ( 84) | 49.0 |

1. Incidence of clinical cancer rates in Denmark (Doll et al, 1995).

2. Calculated from incidence of clinical cancer in Denmark and hysterectomy rates from Maribo County.

## Regression and non-progression of preclinical lesions

The estimated interval regression for women 25-50 years of age is shown in Table 7.5. The prevalence at age 25 was 10.3 per 1000 women (from Table 7.2), the cumulative incidence of preclinical lesion over the age 25 to 50 was 57.7 per 1000 woman-years (from Table 7.3). The prevalence at age 50 was 25.5 per 1000 women (from Table 7.2) and the cumulative incidence of clinical cancer of women between

25 and 50 years of age was 16.1 per 1000 woman-years (from Table 7.4). The estimated proportion of lesions that regressed during the interval (interval regression) was therefore [(10.3 + 57.7) – (25.5 + 16.1)]/(10.3 + 57.7) = 0.39 or 39%. The interval progression was 16.1/(10.3 + 57.7) = 0.24 or 24%, and at age 50, 38% [25.5/(10.3 + 57.7)] of all lesions was still prevalent.

The cumulative incidence in women aged 50-80 is 19.2 per 1000 woman-years (From Table 7.4). If we assume that there is no progressive onset of preclinical lesions after age 50, the proportion of prevalent preclinical lesions at age 50 that will progress to clinical cancer can be estimated to be 19.2/25.5 = 0.75 or 75%. The minimal non-progression is than 0.39 = 0.38 x 0.25 = 0.48 or 48% (see table 7.5). This is a minimum, as we assume no onset of preclinical lesions after age 50 and survival to age 80.

**Table 7.5**
Estimation of proportion regressed, progressed and prevalent lesions for women 25-50 years of age (and confidence intervals of the estimations)

| Sensitivity (%) | $P_1$ | $I_d$ | $P_2$ | $I_c$ | Missing (X) | Interval regression | Interval Progression | Prevalent at age 50 | Non-progression after age 25 |
|---|---|---|---|---|---|---|---|---|---|
| 80 | 10.3 | 57.7 | 25.5 | 16.1 | 26.3 | 0.39 (0.25-0.50) | 0.24 (0.20-0.27) | 0.38 (0.28-0.50) | 0.48 (0.39-0.56) |
| 70 | 11.7 | 57.7 | 29.1 | 16.1 | 24.2 | 0.35 (0.19-0.47) | 0.23 (0.20-0.27) | 0.42 (0.32-0.56) | 0.49 (0.40-0.57) |
| 90 | 9.1 | 57.7 | 22.7 | 16.1 | 28.0 | 0.42 (0.29-0.53) | 0.24 (0.21-0.28) | 0.34 (0.25-0.45) | 0.47 (0.38-0.55) |

$P_1$, prevalence at age 25 (per 1000 women); $I_d$, incidence preclinical lesions (per 1000 women-years) between ages 25 and 50; $P_2$, prevalence at age 50 (per 1000 women); $I_c$, incidence clinical cancer (per 1000 women) between age 25 and 50. Missing (X), $(P_1 + I_d) - (P_2 + I_c)$; interval regression, $[(P_1+I_d) - (P_2+I_c)]/(P_1+I_d)$; interval progression, $I_c/(P_1+I_d)$; prevalent lesions at age 50, $P_2/(P_1+I_d)$. Non-progression after age 25 = interval regression + prevalent at age 50 x non-progression after age 50 (= $I_c$, women 50-80,/$P_2$).

For the estimations above we used a sensitivity of 80%. Table 7.5 also shows calculations for a sensitivity of 70%, 80% and 90%. The impact of the different assumptions about sensitivity on the estimates is small. For a sensitivity of 70%, 80% and 90%, respectively, the estimated interval regression before age 50 years is 0.35, 0.39 and 0.42 and the non-progression rate for lesions in women aged 25-50 is, respectively, 0.47, 0.48 and 0.49.

Figure 7.2, for women at risk and if no screening had taken place, shows the relation between the probabilities of having developed a preclinical lesion (= incidence of preclinical lesions), of having developed a clinical cervical cancer (= incidence of clinical cancer) and of having a preclinical lesion (=prevalence). At a young age the proportion of regression and progression was small, due to the average long duration of preclinical lesions. The fact that the regression widens more than linearly with age suggests that interval regression increased with age. Between age 45 and 55 the probability of regression increases considerably.

In the estimation of non-progression we assumed that all women survive up to age 80. However, a proportion of women with progressive lesions will die from other causes before the cancer is diagnosed clinically. After correction for mortality [using 1993 mortality rates (10)], the cumulative incidence of clinical cancer for women aged 50-80 years will be 17.0. The proportion of lesions which progress after age 50 will be 17.0/25.5 = 0.66 or 66%. Under these assumptions, the minimal non-progression is 0.39 + 0.38 x 0.34 = 0.51 or 51%.

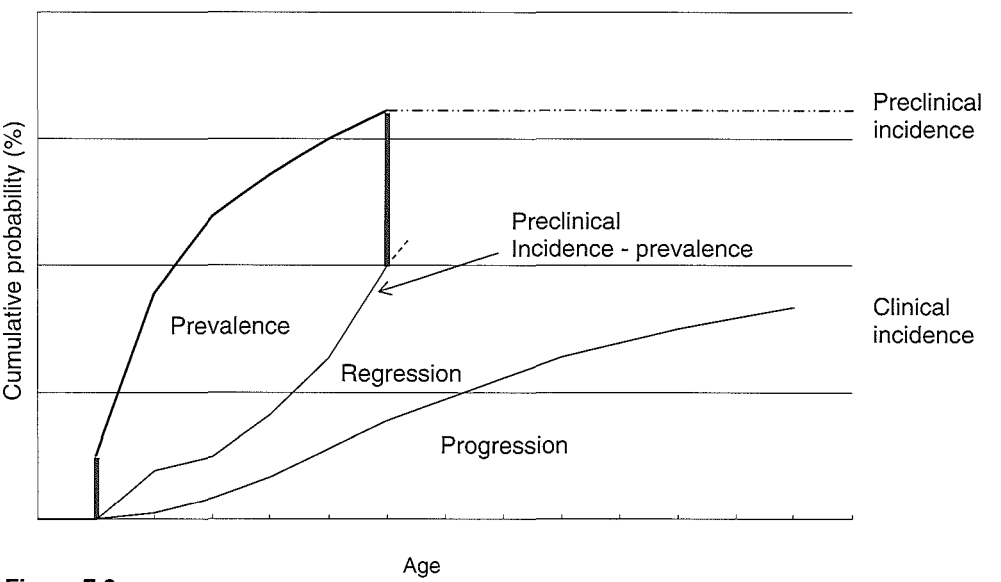


**Figure 7.2**
The probability of developing a preclinical cervical lesions, and probabilities of prevalence, progression and regression, under the assumption that there is no onset of preclinical lesions in women over 50 years of age. The preclinical incidence is the prevalence (from Table 7.2) at age 25+ the cumulative incidence of preclinical cervical lesions (from Table 7.3) in women after age 25. The cumulative incidence of preclinical cervical lesions ($I_d$ from Table 3) is converted into probabilities using the formula: $P = 1 - \exp(-\sum I_d)$. The clinical incidence in this figure is the cumulative incidence of clinical cervical cancer ($I_c$ from Table 7.4).

### Duration of the preclinical lesion

For a sensitivity of 70%, 80% and 90%, respectively, we estimated the mean duration of the preclinical lesion to be 17.6, 15.7 and 14.2 years, respectively (Table 7.6). The estimated duration is only marginally influenced by the sensitivity.

**Table 7.6**
Estimated mean duration *m* and shape *b* of the Weibull distribution function of the preclinical duration (and confidence interval)

| Sensitivity (%) | Mean duration *m* (years) | Shape *b* |
|---|---|---|
| 80 | 17.6 | 5.8 |
| | (14.8-23.8) | (2.0-∞) |
| 70 | 15.7 | 3.2 |
| | (13.4-24.6) | (1.2-∞) |
| 90 | 14.2 | 2.0 |
| | (10.0-181.9) | (0.3-∞) |

## *Discussion*

The natural history of the detectable preclinical phase of cervical cancer can only be studied indirectly on the basis of screening data. We estimated non-progression and duration from the Maribo County data using a two-step procedure. Firstly, the prevalence and incidence rates of preclinical disease were estimated from the observed detection rates. Secondly, the non-progression and duration were assessed, also using the pre-screening incidence of clinical cancer as a proxy for the expected incidence if no screening had taken place. The main findings were that at least 48% of the lesions in women between 25 and 50 years of age do not progress into clinical cancer. If one accounts for death from causes other than cervical cancer, this minimum percentage increases to around 51%. The mean duration of all preclinical lesions was estimated at 16 years.

Our estimate for non-progression is based on detected lesions. Short regressive lesions would have stayed undetected if they developed and regressed within a screening interval. This causes an underestimation of the proportion of non-progression. The side-effects associated with the detection of non-progressive lesions however, are not underestimated.

This estimation procedure for regression and non-progression was performed under the assumption that there is no cohort effect in the observed period. In an age-period-cohort analysis of incidence of clinical cancer in Denmark before 1967, we found that women born in the years 1918-29 were presumably at higher risk than women born later. If such a cohort effect occurred, the prevalence at age 50 and the incidence of clinical cancer were overestimated, leading to an underestimation of the non-progressive rate, Such a cohort effect would also lead to a decrease in detection rates with ascending calendar years. However we found that the detection rates for 1975-82 were in fact higher than the rates of the period 1966-74. This cannot be explained by an increase in incidence of cervical cancer at a young age, because such an increase was only modest in Denmark and seen only after 1983. Furthermore, the increase in detection rates was seen in all age groups. An explanation for this observation could be a drift over time towards a lower 'follow-up threshold' and in consequence, a higher sensitivity at the expense of specificity.

We used the incidence of invasive cervical cancer before the screening programme started, to estimate the incidence of clinical cancer in the screened women if no screening had taken place. For participants however, the incidence of cervical cancer has been found to be relatively low (4,8, 11). Not accounting for this lower incidence leads to an underestimation of the non-progression. Assuming an incidence level in participants of 74% of the total population (8), the minimal non-progression fraction would increase from 48% to 54%, or from 51% to 58% if one accounts for death from other causes.

Using prevalence and incidence of preclinical lesions and incidence of clinical cancer from British Columbia, Canada in 1949-69 (3), we estimated hat 48% of the lesions in women between 25 and 50 years of age regressed before the age of 50, which is somewhat higher than the 39% found in Maribo County. Gustafsson et al (12) analysed in Swedish screening data and estimated the progression rate for carcinoma *in situ* at 12%, which is considerably lower than the maximum proportion of progression for all preclinical lesions of 51% found for Maribo County. At least part of the difference is explained by the fact that the Swedish study included onset of preclinical lesions also after the age of 50. Hence, a smaller proportion of the clinical cancer after age 50 is explained by the preclinical cancer developed before this age.

The estimated mean duration of the preclinical lesions in Maribo County was 16 years, compared with 15.8 years in British Columbia (8) and 17.3 years in Sweden (12). These estimates are remarkably similar, despite differences in calculation methods and between the screening programmes. These estimates of duration represent an average for the regressive, stable and progressive lesions. They may well have different mean durations, but it is not possible to separate these using this rather straightforward analysis. For the purpose of screening it is the duration of progressive lesions that is important. Van Oortmarssen et al (13) showed that an average duration of 15.8 years for preclinical progressive disease is compatible with the interval cancer data collected by the IARC in the eighties, which also involved data derived from the Maribo County data set studied in this paper (6,14).

Our study confirmed that non-progression is a common phenomenon that should be taken into account in the evaluation of cervical cancer screening. Of the screened women in Maribo County, 1.5% had a positive smear with at least atypia, and the majority of these women were followed up: one-third with a negative diagnosis and two-third with a histologically confirmed preclinical lesion. Our analysis shows that at least half of these confirmed preclinical lesions would not have progressed into clinical cancer in the women's lifetime. Thus, among the women screened in Maribo County, 5 per 1000 were diagnosed with a false-positive smear, 5 per 1000 were diagnosed and treated for a non-progressive preclinical lesion, and 5 per 1000 were diagnosed and treated for a preclinical lesion that would otherwise have developed into invasive cervical cancer. The screened women thus pay a price in overtreatment in order to minimize the incidence and mortality from cervical cancer. But given the severity of the disease and the relatively mild treatment with conization, cryotherapy and laser therapy, this price – as it is estimated for Maribo County in the period studied – seems reasonable.

Analysis of data from the cervical cancer screening programme in Bristol (15) in the years 1988-93, showed that 7% of the screened women had smear abnormalities, and 2.7% were referred to colposcopy. This latter proportion is close to double that for Maribo County, which is high, taking into account that incidence of invasive cancer was, and still is, appreciably higher in Denmark than in the UK (37 per 100,000 in Denmark in 1958-62 (9) and 17 per 100,000 in England and Wales in 1960-62 (16); 16 per 100,000 in Denmark and 12 per 100,000 in England and Wales in 1983-87 (17). The cervical cancer screening data from the Netherlands from 1987 to 1990 show more than 10% positive smears (18). Similarly, up to 10% of cervical

smears from the United States currently have ASCUS or more severe abnormalities (19) and 5% of all smears have low-grade squamous intraepithelial lesions (20).
It is clear that there is a considerable variation in the cost in terms of overtreatment paid by different populations to prevent progressive preclinical lesions. It is therefore worrying that over recent decades, there has been a tendency in several counties to advise more intensive follow-up after slightly abnormal Pap smears. Owing to the estimated long duration in combination with a relatively high sensitivity for the preclinical lesion, the extra incidence and mortality reduction from more intense follow-up of slightly abnormal Pap smears in regular attenders, to a 3-5 yearly screening, is expected to be very low.

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# 8

# DISCUSSION

In this chapter, we will first answer the research questions formulated in chapter 1, based on the results described in this thesis. Next, the results of the screening programme in 2001, the screening year in which the revised programme is settled, are compared with the results from 1994, the last year before the changes in the programme were implemented. Thirdly, recent developments and new opportunities are discussed. And finally, we will formulate a number of conclusions and recommendations.

## *Answering the research questions*

**Research question 1:**

| Is, after three decades of cervical cancer screening, an invitational programme still necessary for a high coverage? |
|---|
| Yes, an invitational programme still increases the coverage. |

Cervical cancer screening has been common practice since the late seventies and most women and physicians are aware of the possibility of screening. Therefore an organised screening programme may be outdated. However, we found that 91% of the women in regions with an invitational programme had a smear taken in the past 5 years, compared to 68% of the women in other regions (chapter 2).

The coverage of cervical cancer screening is an important issue, especially because it has been shown that non-participants constitute a high risk group. Not being (recently) screened is the most important explanation of currently occurring cervical cancer (chapter 6). From a survey it appears that 72% of the non-participating women showed a positive attitude towards the programme (chapter 2). This will be an overestimation due to an association between non-participants in the survey and

a negative attitude to screening. Nevertheless, it would seem worthwhile to investigate possibilities to improve the attendance rate. In the Netherlands, an increasing number of general practitioners are sending out the letters of invitation for cervical cancer screening instead of leaving this task to the regional screening organisation. This has been showed to lead to a higher participation rate (1). If high risk women can be stimulated to attend screening, with preservation of the free choice of women, this could markedly increase the effectiveness and cost-effectiveness of the programme.

**Research question 2:**

| How does the risk for cervical cancer in women using spontaneous screening compare with that of women using programme screening? |
|---|
| The risk for cervical cancer is the same in both groups of women. |

The Dutch government seeks to discourage spontaneous screening, as these smears are often taken below the recommended starting age and at too short intervals, which makes them inefficient. However, spontaneous smears are usually considered to catch higher risk women, also based on the higher detection rate of abnormalities as compared to programme screening. The main reason for this higher rate, however, is that the age of the women undergoing spontaneous screens is usually lower. Detection rates are usually higher at young age, because of the high incidence of regressive lesions in young age. After correcting for age and screening interval, we found no difference in the detection rates for cervical smears taken within the screening programme with those taken outside the screening programme, and concluded that the underlying risk was the same in both groups of women (chapter 3). Therefore, there is no reason for the symptomless women concerned to have smears performed at a younger age or at smaller screening intervals than recommended for the average population.

In the national screening programme, women who miss a programme screening smear, are offered other possibilities to have a smear. In this way, all women can have 7 preventive smears during their life, which ensures high protection against cervical cancer. More intensive screening is not efficient and should be discouraged.

**Research question 3:**

| What is the effect of the revised definition of Pap 2 results and its follow-up? |
|---|
| The number of screening smears diagnosed as "Pap 2" has decreased from 10% to 2%, which sharply reduced the number of women who require follow up smears. The proportion of women referred to a gynaecologist remained the same. |

Before 1996, about 10% of all primary programme smears were diagnosed as 'Pap 2'. The women concerned were recommended to have follow up smears until 2 consecutive smears were negative (after which the follow-up ended) or otherwise until more severe abnormalities were found (leading to a referral to the gynaecologist). These guidelines yielded an large number of follow-up smears, and women could stay in cytological follow-up for years. The revised recommendations defined stricter diagnosis criteria for 'Pap 2' (excluding cytological changes consistent with infection) and the follow-up was shortened to a maximum of two follow-up smears. The follow-up leads to a referral to a gynaecologist after a repeat smear yielded a diagnosis of 'Pap 2' or worse, or to return to the regular programme after two negative follow-up smears. This was expected to reduce the number of follow-up smears and to shorten the follow up period.

Between 1990 and 1998, the proportion of smears classified as 'Pap 2' has been reduced from 10% to 2% (chapter 4). We estimated that the number of women referred to the gynaecologist would stay the same. The revised recommendations were not strictly adhered to; 28% of the women with a 'Pap 2' result had no follow up after 2,25 years. Even though this is an improvement - the percentage was 46% in the old screening programme - this should be carefully followed. The current stricter criteria for a 'Pap 2' diagnosis means that smears so classified are expected to represent on average more serious abnormalities than before. In a way, therefore, it has become more important to adhere to the follow-up recommendations.

The sensitivity of the screening programme will decrease with this large increase in specificity. We expect only a very small loss of sensitivity, because the percentage of women who are referred to the gynaecologist remains the same, and can be considered as a proxy for the detection of high risk cases. The possible loss of sensitivity can be studied after several years. An update of the analysis of the screening history of women with cervical cancer (chapter 6) will be needed: a loss of sensitivity will be reflected in an increased number of interval cancer cases in relation with the number of women screened.

**Research question 4:**

| Should negative smears without endocervical cells be followed by a repeat smear? |
|---|
| The absence of endocervical cells in negative smears is not associated with a decreased negative predictive value for cervical cancer compared to negative smears with endocervical cells. Therefore, an additional smear with a shorter screening-interval is not indicated. |

The absence of endocervical cells in a smear is usually seen as an indicator for an inadequate sample, not representative of the complete transformation zone of the cervix. This is confirmed by studies in which the proportion of abnormalities in smears without endocervical cells is lower than that in smears with endocervical cells. The conclusion that smears without endocervical cells are likely to contain a higher percentage of false-negatives results would appear warranted.

In the Dutch data analysed in chapter 5, at least 6 years of histological follow-up was studied after negative smears with and without endocervical cells. The proportion of neoplasia (both pre-invasive and invasive) detected during follow-up was found to be equal for both types of smears.

Using the same data, we found that the proportion of abnormalities in smears without endocervical cells was indeed lower than that in smears with endocervical cells. This is consistent with the studies previously described. The apparent contradiction between the cross-sectional and longitudinal findings may be due to the fact that the absence of endocervical cells in primary smears revealing abnormalities went unregistered, because these abnormalities would anyhow lead to follow-up.

Based on these results, the Dutch guidelines no longer (since 2002) advise a special follow-up recommendation for women who had a negative smear without endocervical cells. This has contributed to a further decrease in the number of follow-up smears taken in the Netherlands after 2002.

The labelling of negative smears without endocervical cells is still considered an important issue for quality control, that should be monitored carefully. However, since the absence of endocervical cells does no longer affect follow-up recommendations, the accuracy of this registration may decrease.

**Research question 5:**

| Why are there still 700 new invasive cervical cancers every year in the Netherlands, in spite of long-term screening with fairly high coverage ? |
|---|
| More than half of the invasive cervical cancers develop in women who have never had a cervical smear. Only 14% of the cases concerned women who had a Pap test within 6 years of the diagnosis. |

The number of women diagnosed with invasive cervical cancer has been declining since the introduction of screening. The incidence has stabilized since the eighties at about 700 cases per year, although since 1999 the incidence showed a decrease. The potential effectiveness of the screening programme is most strongly reduced by the lack of participation. We found that 30% of the women with cervical cancer was never invited for screening, because of their age, 57% of the women with invasive cancer was unscreened or underscreened (chapter 6), while the Dutch coverage is about 75%. Only 14% of all women with cervical cancer had a smear taken within 6 years prior to the diagnosis. Women not covered by the programme are at high risk for cervical cancer. The effect of an improvement of the sensitivity of the screening programme is limited to at most 20% of the current cases of cervical cancer, which would be 150 cases per year in the Netherlands. Therefore, it will not be easy to improve the sensitivity in a cost-effective way.

**Research question 6:**

| What proportion of the incidence of pre-invasive neoplasia is non-progressive? |
|---|
| More than 50% of all pre-invasive lesions will not progress into invasive cancer. Furthermore, the average duration of the progressive pre-invasive lesions was estimated to be at least 15 years. |

An understanding of the natural history of cervical cancer is important for the evaluation and optimisation of cervical cancer screening. The natural history was studied in screening data from Maribo County, Denmark, by relating the detection rates for pre-invasive lesions to the pre-screening incidence of invasive cervical cancer. It was found that less than half of the detected pre-invasive lesions progress to cancer (chapter 7). As long as progressive lesions are indistinguishable from

regressive (or at least non-progressive) lesions, women detected with histologically confirmed neoplasia must be treated or, in case of low-grade disease, at least be intensively followed up. The number of women detected with neoplasia is much larger than the number of invasive cancer. In our data, we estimated the proportion of non-progression for a broad age range. The study was too small for age specific estimates. But in previous studies, the proportion of lesions that progressed was found to depend on age. It was found earlier that the proportion of progression is lower at young age (2). The detection of non-progressive lesions is an important negative side effect of the screening programme, because it leads to overtreatment. The fact that progression is lower at young age supports the conclusion that screening at young ages is less efficient than screening in women over 30 years of age.

The mean duration of the preinvasive stage of about 16 years resulting from this analysis is also an argument for the low extra effect of screening at young ages versus screening that starts at about 30 years of age.

## *The current screening programme*

Since the introduction of the revised screening programme in 1996, a number of changes have been implemented. The main goals were to maintain or improve the coverage, to reduce the number of smears that do not contribute to the coverage in the target population and to reduce the number of follow up smears.

**Table 8.1**
Number of smears by reasons for smear taking in the Netherlands in 1994 and in 2001, PALGA

| Types of smears | 1994 | | 2001 | |
|---|---|---|---|---|
| | Number | Percentage | Number | Percentage |
| Primary smears (total) | 676471 | 75% | 642546 | 89% |
| (↳ Of which spontaneous) | (325353) | (36%) | (21550) | ( 3%) |
| Follow up smears | 229795 | 25% | 78697 | 11% |
| All (primary + follow up) smears | 906266 | 100% | 721243 | 100% |

In the PALGA data, we retrieved the number of smears of the year 2001 (in which the revised screening programme has completed the first round) and those of 1994 (the year before the revised screening programme started). We compared the number of primary and of follow up smears for both years (Table 8.1).

### Coverage and attendance

The coverage rate, defined as the proportion of women between 35 and 54 years of age with at least one smear in the preceding 5 years, has increased from 72.3% in 1994 to 75.0% in 2001. Another outcome measure is the attendance rate, which is the percentage of women who had a smear taken after receiving an invitation for the programme. Since 1996, when the revised programme was introduced nation wide, both coverage and attendance rates have been monitored over time. In the early nineties, attendance was around 40% for women at risk (excluding women who had a hysterectomy)(3). The attendance rate in 1994 is not known, but the programme attendance rate for women at risk was in 1997 estimated at 63%, and in 2001 at 66%. Hence both coverage and attendance in the cervical cancer screening programme are on the rise. Future years will show if this trend has continued.

### The number of smears

Table 8.1 shows that the number of primary smears has decreased between 1994 and 2001, mainly because the number of spontaneous smears is reduced from over 300,000 smears in 1994 to about 20,000 smears in 2001. This spectacular decrease is important, because these smears increased screening beyond the recommended frequency, whereas the risk for cervical cancer for women using spontaneous screening was not higher than that for women using the mass screening (chapter 3).

### The number of follow up smears

The annual number of smears taken for follow up reasons decreased from 229,000 smears in 1994 to 79,000 smears in 2001 (Table 8.1). This is predominantly the effect of the decreased number of 'Pap 2' smears from 10% tot 2%, and the reduction of the length of the cytological follow up. The number of follow up smears is probably still decreasing, because the revised definitions of Pap 2 and the associated follow up recommendation were not completely implemented in all regions (chapter 4), and because the changed guidelines concerning the omission of follow up after a negative smear without endocervical cells was introduced in 2002.

In a stable screening situation, the percentage of women in follow-up for non negative screening smears, should decrease to about 3% per screening round or less, as only women diagnosed with a slightly abnormal smear (± 2%) or unqualified smears (± 1%) will receive follow up smears during one or two years.

### Conclusion

The main goals of the revised screening programme, a maintainance or improvement of the coverage, a reduction of the number of smears taken in excess of the programme and a reduction of the number of follow up smears, have all been reached. It is too early to assess the number of prevented cervical cancer incidence and mortality cases in the revised situation. However, the prospects are good because most important predictor for effectiveness, the coverage, has remained at its previous high level, but now for a wider age range.

## *Future developments*

The Dutch screening programme reduces the risk for cervical cancer for acceptable costs. Women who attend the complete Dutch screening programme reduce their lifetime risk for cervical cancer with 75%, or in absolute terms with about 1%. The revised screening programme has improved the cost-effectiveness by reducing the negative side-effects, while the positive effects are expected to increase. Moreover, there are several promising developments: testing for high risk Human Papilloma Virus (hrHPV) infections, including self lavage tests, for primary screening or for triage. In cytomorphological screening computer aided evaluation and thin layer techniques have been developed. Finally, there are recent developments in the field of (HPV) vaccination.

### Testing for high risk HPV

There is overwhelming evidence that infections with hrHPV types play a conditional role in the development of cervical cancer (4-5). Case-control studies demonstrated a very high risk ratio of hrHPV infections in women for having (pre-) invasive cervical cancer (6-9). The association between CIN and hrHPV is stronger in high-grade than in low-grade abnormalities (10-12). The presence of hrHPV can be demonstrated in 99% to 100% of the invasive cases (13). In a retrospective study, nearly 100% of archived negative smears of women with invasive cancer were found to contain

hrHPV types (14). Next to these cross-sectional and retrospective findings, the results of an increasing number of prospective cohort studies are becoming available. Follow-up studies have found that almost all women with persistent hrHPV combined with dysplasia showed progression to higher grades of dysplasia (15,16). Important for extending the screening interval in double testing is the predictive value of negative tests for the (lasting) absence of significant cervical neoplasia, which is still being studied.

A problem for screening is that the hrHPV prevalence in the Dutch female population is very high up to the age of 30 years (10% or more, depending on the test) and is still around 4% in women over 35 years of age (17). Because of the high rate of clearance of infections, the cumulative incidence of HPV-infections is very high (life time incidence it is estimated as 50% or higher). Since the lifetime cumulative risk for invasive cervical cancer in the absence of screening in the Netherlands is estimated at about 1.5%, only a small minority of HPV-infections will develop into cervical cancer. Again, like in cytology screening, distinguishing between harmless and dangerous conditions is vital. Testing for persistence of infection and/or viral load will be helpful; to what extent is still under investigation.

As we mentioned earlier, the attending women are very well protected by the current programme, so any additional gain will be limited. Adding HPV testing without considerably reducing the screening frequency will therefore not be cost-effective. A more promising possibility is to use HPV testing in stead of cytology for primary screening, and to perform cytology for triage in HPV positive women. For primary cytology screening, data are accumulating that show that HPV-triage during follow-up of BMD smears (with borderline or mild dyscaryosis) identifies low risk women who do not require further follow-up, and is more cost-effective than cytology triage.

**Human Papilloma Virus (HPV) vaccination**

Vaccines for HPV types 16 and 18 (18,19) are in the stage of being tested in trials for their effectiveness, and so far (2-3 years of follow up) show a 100% protection for persistent HPV-infection (20). Longer follow up is needed to measure the effectiveness of vaccination in preventing neoplastic changes, to assess the need of boosters and to estimate its value as replacement of or addition to screening.

**Computer aided evaluation and thin layer technique**

In cytomorphological screening new techniques have been developed. Automated pattern recognition has improved over the last decade, leading to the development of several systems for computer-aided cytomorphological screening such as AutoPap™ 300QC and AutoCyte ™ SCREEN. Also, liquid-based or monolayer systems have been developed, by which the cervical material is first prepared and filtered before it is stained on a glass slide. The process results in smears with barely overlapping cells, which should improve the evaluation possibility of the smear. Examples of this monolayer techniques are ThinPrep ™ and SurePath™. All the techniques described above, have been compared with the conventional Pap test as to their cost-effectiveness (21), given the characteristics for the Dutch situation (cancer incidence level, screening policy with 5 year-interval and 30-60 years of age range, attendance level and the percentages of non-negative smears). The conclusion was that the incremental cost-effectiveness ratio of these new techniques is less favourable than that of the conventional Pap smear for the Netherlands. Only if the costs would be considerably reduced, they could become cost-effective.

## *Conclusions*

- Women should keep receiving a personal invitation for the cervical cancer programme, in order to maintain the high coverage in the Netherlands.
- Women who had used spontaneous smears taken are at similar risk for cervical cancer as women who used programme screening.
- The new guidelines for the definition of Pap 2 and for follow up resulted in a large reduction of the number of women in follow up.
- Women with negative smears without endocervical cells do not need an additional smear.
- Most of the recent cases of invasive cervical cancer never had a smear, in spite of the long term screening with good coverage.
- An increase in the sensitivity of the screening test will result in only a small reduction in the number of women diagnosed with cervical cancer.
- More than half of histologically confirmed CIN's will not progress into invasive cervical cancer.

- The negative side effects and the associated financial costs of the Dutch screening programme have declined as a consequence of the smaller number of women recommended for follow-up.
- The national evaluation of the cervical cancer screening programme should be continued in order to maintain and improve the quality of the programme.

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# SUMMARY

The aim of screening for cervical cancer is to prevent death from the disease. For this, cervical cells are collected by smear taking and evaluated. In this way, eventual abnormal cells can be detected which are usually from a precursor of cervical cancer. By treatment these lesions will not progress into cervical cancer.

Mass screening for cervical cancer has been introduced in The Netherlands in the seventies. Women between 35 and 53 years of age were invited every three years to have a cervical smear. In addition, many spontaneous smears were taken on the initiative of the women or her physician. About 800,000 smears were taken yearly and given the low risk for cervical cancer (lifetime risk is about 1.5% for Dutch women in a situation without screening) and the even lower risk for dying from the disease, the mass screening programme was relatively expensive. Moreover, the programme covered only around 70% of all women and probably women with a high risk for cervical cancer were underrepresented. In 1996, a number of important changes in the organization of the mass screening programme were made. Also, the age range was enlarged to 30 to 60 years of age. Because the interval between two successive invitations became 5 years, the total number of smears per women remained 7. In addition, the definition for borderline and mildly abnormal smears was changed as well as the guidelines for the follow up after such cytologic evaluation. As a disincentive to making spontaneous smears, they were not reimbursed anymore by the National Health Service.

The aim of the work presented in this thesis was to monitor and improve the mass screening programme.

*Personal invitations*

In the screening programme, women are sent an invitation at specific ages to have a cervical smear taken. Because spontaneous smears were common in The Netherlands and given the long history of screening, it was questionable whether a personal invitation still increases the participation of screening. In chapter 2, we

compared the participation rate of women living in regions with a mass screening programme with women in regions without a mass screening programme. The results showed that in regions with an invitational programme more women had a cervical smear taken compared with regions without an invitational programme. We concluded that, even in a situation with a 20-year history of screening, invitations still contribute to a higher percentage of women who had a smear taken.

*Spontaneous smears*

After the revision in 1996, spontaneous smears were no longer reimbursed. However, these smears could be valuable, if they were taken in women with a high risk for cervical cancer, based on e.g. information concerning the specific women available to the general practitioner. In chapter 3, we examined if women who had spontaneous smears had a higher risk then those who had a smear on invitation from the screening programme. There was no such differences. Therefore, we concluded that there is no indication for the practiced smear taking outside of the screening programme.

*Endocervical cells*

The presence of endocervical cells in a cervical smear was seen as an indicator for the quality of the smear. In smears without these cells, women were advised to have an additional smear. This concerned about 8% of all mass screening smears. In order to investigate whether this special advise was necessary, we compared the incidence of cancer in women in the 7 years following negative smears with and without endocervical cells taken. There were no differences. Based on these results, the absence of endocervical cells is no longer an indication for an additional smear.

*Pap 2*

Before the revision of the screening programme, 10% of the women had a borderline smear result ('Pap 2'). They were advised to have follow up smears. Two consecutive negative smears lead to return to the screening programme. A more severe abnormality leads to a referral to the gynaecologist. With these guidelines women could have follow up smears for a long time, sometimes for many years. After the revision, the definition of Pap 2 was sharpened and the follow up advise was shortened to a maximum of 2 additional smears. The aim of these changes was to

reduce the number of women in follow up. In chapter 5 the consequences of the changes are evaluated. The percentage smears diagnosed as Pap 2 was reduced to 2%. The percentage women referred to the gynaecologist was unchanged. Due to the reduction of the number of abnormal smears, the number of follow up smears strongly decreased, which is favourable for the costs and for the burden for the women involved. If the sensitivity remains at its pre-revision level, can only be evaluated in the future.

*Invasive cancer*

In chapter 6, the screening history of women with cervical cancer is analysed. This is important, because these cancers have not been prevented in spite of the screening programme. The analysis demonstrated that more than half of the women with cervical cancer, never had a cervical smear taken. Only a small proportion (14%) of all women with cervical cancer had a smear taken within 5 years before the diagnosis. The effect of the mass screening programme can therefore only become much larger when the participation rate further increases.

*Non-progressive lesions*

In chapter 7, it was estimated what proportion of preinvasive lesions which do not progress into invasive cervical cancer. To this end, data from Denmark were used, which had a good registration from the beginning of mass screening onwards. This made it possible to compare incidence of cervical cancer before the programme started with the prevalence of preinvasive stages, detected at screening. The analyses showed that at least half of the preinvasive lesions would not progress into invasive cancer. Because it is unclear which lesions will progress, all women with screen detected lesions are treated, while only a part of these women would ever have developed clinical cervical cancer. This causes an important negative side effect of screening.

*Number of smears*

Finally, the number of smears taken in 1994, the last year before the revision, was compared with the numbers of 2001, the year in which the revised programme has completed a 5-year round. The data demonstrate that the number of smears has decreased considerably, mainly due to a reduction in number of follow up smears

from 230,000 to 80,000 per year. This reduction is the effect of the revised definition of Pap 2 and guidelines for the follow up. The number of follow up smears is expected to reduce even further, because since 2002 negative smears without endocervical cells no longer have been advised to have an additional smear (see above and Chapter 4).

*Summary*

The revised mass screening programme has an improved efficiency compared with the old situation. There are more women reached in a broader age-range and the number of smears is decreased.

*Conclusions and recommendations*

- Women should keep receiving a personal invitation for the cervical cancer programme, in order to maintain the high coverage in the Netherlands.
- Women who had spontaneous smears taken are at similar risk for cervical cancer as women who used programme screening.
- The new guidelines for the definition of Pap 2 and for follow up resulted in a large reduction of the number of women in follow up.
- Women with negative smears without endocervical cells do not need an additional smear.
- Most of the recent cases of invasive cervical cancer never had a smear, in spite of the long term screening with good coverage.
- An increase in the sensitivity of the screening test will result in only a small reduction in the number of women diagnosed with cervical cancer.
- More than half of histologically confirmed CIN's will not progress into invasive cervical cancer.
- The negative side effects and the associated financial costs of the Dutch screening programme have declined as a consequence of the smaller number of women recommended for follow-up.
- The national evaluation of the cervical cancer screening programme should be continued in order to maintain and improve the quality of the programme.

# SAMENVATTING

Het bevolkingsonderzoek naar baarmoederhalskanker heeft als doel om sterfte aan baarmoederhalskanker te voorkomen. Hiertoe wordt er bij vrouwen een uitstrijkje gemaakt, waarin afwijkende cellen kunnen worden aangetoond, die meestal een voorstadium van baarmoederhalskanker betreffen. Door behandeling van het voorstadium kan de afwijking niet uitgroeien tot baarmoederhalskanker.

Het bevolkingsonderzoek naar baarmoederhalskanker is in Nederland ingevoerd aan het eind van de zeventiger jaren. Toen kregen vrouwen tussen de 35 en 53 jaar iedere drie jaar een uitnodiging voor het laten maken van een uitstrijkje. Naast het bevolkingsonderzoek werden er veel spontane uitstrijkjes gemaakt, op initiatief van de vrouw of haar dokter. Omdat er jaarlijks veel uitstrijkjes (ca. 800,000) werden gemaakt en de kans op het krijgen van baarmoederhalskanker verhoudingsgewijs klein is (ongeveer 1,5% van alle vrouwen als er geen bevolkingsonderzoek zou zijn) en het sterven eraan nog kleiner, was het bevolkingsonderzoek relatief kostbaar. Bovendien werd slechts ca. 70% van de vrouwen bereikt en vermoedelijk voornamelijk vrouwen met een laag risico op de ziekte.
In 1996 is het bevolkingsonderzoek ingrijpend veranderd. Naast een aantal organisatorische veranderingen, zijn de leeftijdsgrenzen verbreed naar 30 tot 60 jaar. Doordat nu iedere vijf jaar tot een uitstrijkje wordt uitgenodigd, bleef het aantal uitstrijkjes per vrouw 7. Tevens zijn de definities voor licht afwijkende uitstrijkjes en de richtlijnen voor vervolgonderzoek na lichte afwijkingen veranderd. Spontane uitstrijkjes werden niet meer vergoed door het ziekenfonds.

Het doel van het proefschrift is om een aantal belangrijke vragen over de herstructurering van het bevolkingsonderzoek te beantwoorden.

*Persoonlijke uitnodiging*

Bij het bevolkingsonderzoek wordt aan vrouwen op specifieke leeftijden een uitnodiging verstuurd om deel te nemen aan het onderzoek. Omdat het maken van spontane uitstrijkjes gebruikelijk was in Nederland en er al een lange geschiedenis was van het bevolkingsonderzoek, werd onderzocht of het versturen van uitnodigingen de deelname aan het bevolkingsonderzoek nog wel verhoogt. Een

hoge deelname is belangrijk voor het gunstige effect van het bevolkingsonderzoek. In hoofdstuk 2 is de deelname van vrouwen die woonden in een regio waar bevolkingsonderzoek werd uitgevoerd vergeleken met vrouwen die woonden in een regio zonder bevolkingsonderzoek. Uit de analyse bleek dat in regio's met uitnodigingen meer vrouwen een uitstrijkje hadden laten maken dan vrouwen in regio's waarin geen uitnodigingen werden verstuurd. Dus ook in een bevolkingsonderzoek dat al 20 jaar loopt leidt het versturen van uitnodigingen tot een hogere deelname.

*Spontane uitstrijkjes*

Na de herstructurering van het bevolkingsonderzoek worden spontane uitstrijkjes doorgaans niet meer vergoed. Deze uitstrijkjes zouden echter een meerwaarde hebben, indien gemaakt bij vrouwen met een verhoogd risico op baarmoederhalskanker. In hoofdstuk 3 is daarom onderzocht of het risico op baarmoederhalskanker hoger is bij vrouwen die spontaan uitstrijkjes laten maken dan bij vrouwen die een uitstrijkje laten maken na een uitnodiging van het bevolkingsonderzoek. Dit bleek niet het geval te zijn. Hieruit werd geconcludeerd dat er geen goede reden is om uitstrijkjes buiten het bevolkingsonderzoek om te maken.

*Endocervicale cellen*

De aanwezigheid van endocervicale cellen in een uitstrijkje werd gezien als een kwaliteitskenmerk voor een goed uitstrijkje. Vrouwen met een uitstrijkje zonder endocervicale cellen kregen een herhalingsadvies. Het ging om ongeveer 8% van alle bevolkingsonderzoek uitstrijkjes. Om na te gaan of dit herhalingsadvies wel nodig is, werd voor uitstrijkjes zonder afwijkingen met en zonder endocervicale cellen uit 1990 en 1991 gekeken naar afwijkende bevindingen erna tot 31 maart 1997. Er werd geen verschil gevonden tussen uitstrijkjes met en zonder endocervicale cellen. Mede op basis van dit onderzoek is het ontbreken van endocervicale cellen niet langer een reden voor een herhalingsadvies.

*Pap 2*

Voor de herstructurering bedroeg het percentage vrouwen met de uitslag 'Pap 2' (lichte afwijkingen) 10%. Deze vrouwen kregen een herhalingsadvies totdat er ofwel 2 negatieve uitstrijkjes na elkaar waren gevonden, wat leidde tot terugkeer naar het

bevolkingsonderzoekschema, ofwel tot er een meer afwijkende uitslag werd gevonden, wat leidde tot een verwijzing naar de gynaecoloog. Deze regel maakte dat vrouwen lange tijd, soms zelfs tot jarenlang, vervolguitstrijkjes moesten laten maken. Bij de herstructurering van het bevolkingsonderzoek is de definitie van Pap 2 aangescherpt en is het bijbehorende herhalingsadvies verkort tot maximaal 2 herhalingsuitstrijkjes. Het doel van deze veranderingen was om het aantal vrouwen met vervolgonderzoek kleiner te maken. In hoofdstuk 5 zijn de veranderingen betreffende 'Pap 2' in kaart gebracht, waarbij een inschatting is gemaakt van het aantal vrouwen dat moet worden doorgewezen naar de gynaecoloog. Het percentage uitstrijkjes met de uitslag 'Pap 2' was gedaald van 10% naar 2%. Het percentage doorverwijzingen naar de gynaecoloog bleef gelijk. Door de daling van het aantal afwijkende uitstrijkjes is het aantal herhalingsuitstrijkjes enorm gedaald, hetgeen gunstig is zowel voor de kosten als voor de beleving van de vrouwen. Belangrijk blijft natuurlijk dat de sensitiviteit van het bevolkingsonderzoek op peil blijft. Dit zal in de nabije toekomst geëvalueerd dienen te worden.

*Invasieve kanker*

In hoofdstuk 6 is de voorgeschiedenis van vrouwen met baarmoederhalskanker geanalyseerd. Dit is zeer belangrijk omdat deze vrouwen in feite de missers vertegenwoordigen van het bevolkingsonderzoek; zij werpen licht op de belangrijkste knelpunten voor een grotere effectiviteit van het bevolkingsonderzoek. Uit de analyse bleek dat meer dan de helft van de vrouwen met baarmoederhalskanker nooit een uitstrijkje heeft gehad. Slechts een klein deel (14%) van de vrouwen met baarmoederhalskanker heeft een uitstrijkje gehad in de 5 jaar voorafgaand aan de diagnose. Het effect van het bevolkingsonderzoek kan dus het meest worden vergroot door de deelname te verbeteren. Evengoed moet deelname aan het bevolkingsonderzoek een vrije keus blijven van iedere vrouw.

*Niet progressieve voorstadia*

In hoofdstuk 7 is een schatting gemaakt van hoe vaak voorstadia van baarmoederhalskanker niet doorgroeien naar een invasief stadium. Hiervoor zijn gegevens uit Denemarken gebruikt, omdat daar een centrale invoering van het bevolkingsonderzoek heeft plaatsgevonden, met een goede registratie direct vanaf het begin. Hierdoor is het mogelijk de incidentie van baarmoederhalskanker voor het bevolkingsonderzoek en de prevalentie van voorstadia van baarmoederhalskanker,

gemeten bij het bevolkingsonderzoek, met elkaar te vergelijken in een korte tijdsperiode. Uit de analyse bleek dat tenminste de helft van de voorstadia niet doorgroeit tot een invasief carcinoom. Dit veroorzaakt een belangrijk negatief effect van het bevolkingsonderzoek. Aangezien niet duidelijk is welke zich wel en welke zich niet zullen ontwikkelen, worden alle voorstadia als zodanig aangemerkt en behandeld, terwijl slechts een deel van de voorstadia zal uitgroeien tot baarmoederhalskanker.

*Aantallen uitstrijkjes*

Tenslotte zijn de aantallen uitstrijkjes in 1994, het laatste jaar waarin uitsluitend het oude schema met 3-jaars intervallen nog werd gehanteerd, vergeleken met de aantallen uit 2001, het jaar waarin het nieuwe schema met 5-jaars intervallen een volledige ronde was toegepast. Hieruit bleek dat het aantal uitstrijkjes is afgenomen, voornamelijk omdat het aantal herhalingsuitstrijkjes terugliep van 230.000 naar 80.000 uitstrijkjes per jaar. Dit komt voornamelijk door de veranderde definities voor 'Pap 2' en de bijbehorende vervolgonderzoeken. Het aantal herhalingsuitstrijkjes zal inmiddels nog verder zijn gedaald door de afschaffing van het herhalingsadvies na een negatief uitstrijkje zonder endocervicale cellen in 2002.

*Samenvatting*

Het bevolkingsonderzoek heeft na de herstructurering een betere kosteneffectiviteit ten opzichte van de oude situatie. Er worden meer vrouwen in een bredere leeftijdsrange bereikt en het aantal herhalingsuitstrijkjes is fors afgenomen.

*Conclusies en aanbevelingen:*

- Om de hoge deelname te bewaren zullen vrouwen ook in de toekomst door een persoonlijke uitnodiging moeten worden gestimuleerd om deel te nemen aan het bevolkingsonderzoek.
- Spontane uitstrijkjes worden gemaakt bij vrouwen met een zelfde risico op baarmoederhalskanker als bij vrouwen, die een bevolkingsonderzoek uitstrijkje laten maken.
- De nieuwe definitie van Pap 2 en aanbevelingen voor het vervolgonderzoek resulteerden in een afname van het aantal vrouwen met het vervolgonderzoek.

- Vrouwen met negatieve uitstrijkjes zonder endocervicale cellen hebben geen vervolgonderzoek nodig.
- Een verhoging van de sensitiviteit van de test van het bevolkingsonderzoek zal slechts een kleine vermindering geven in het aantal vrouwen met baarmoederhalskanker.
- Meer dan de helft van alle Nederlandse vrouwen met baarmoederhalskanker heeft nooit een uitstrijkje gehad, ondanks dat screening al lang loopt met een hoog bereik.
- Meer dan de helft van alle voorstadia van baarmoederhalskanker zullen niet uitgroeien tot invasieve baarmoederhalskanker.
- De negatieve effecten van het Nederlandse bevolkingsonderzoek zijn kleiner geworden, doordat veel minder vrouwen vervolgonderzoek hebben.
- De landelijke evaluatie van het bevolkingsonderzoek moet een continu proces blijven om het programma hoog kwalitatief te houden en verder te verbeteren.

# PUBLICATIONS

This thesis is based on the following papers:

*Chapter 2*

Bos AB, Ballegooijen M van, Gessel-Dabekaussen AAMW van and Habbema JDF (1998) Organized cervical cancer screening still leads to higher coverage than spontaneous screening in The Netherlands *Eur J Cancer 34 (10), 1598-1601.*

*Chapter 3*

Bos AB, Ballegooijen M van, Oortmarssen GJ van, Habbema JDF (2002) Women who participate in spontaneous screening are not at higher riskfor cervical cancer than women who attend to programme screening *Eur J Cancer 38(6): 827-31.*

*Chapter 4*

Bos AB, Ballegooijen M van, Akker-van Marle ME van den, Habbema JDF (2002) Less pap-2 results (' minor abnormalities') in the population screening for cervical cancer since the introduction of new guidelines in 1996 *Ned Tijdschr Geneeskd. 24; 146(34): 1586-90.*

*Chapter 5*

Bos AB, Ballegooijen M van, Akker-van Marle ME van den, Hanselaar AG, Oortmarssen GJ van and Habbema JDF (2001) Endocervical status is not predictive for the incidence of cervical cancer in the years after negative smears *Am J Clin Pathol 115(6): 851-5.*

*Chapter 6*

Bos AB, Rebolj M, Habbema JDF, Ballegooijen M van. Non attendance is still the main limitation for the effectiveness of screening for cervical cancer in the Netherlands *Int J Cancer (in press).*

*Chapter 7*

Bos AB, Ballegooijen M van, Oortmarssen GJ van, Marle ME van, Habbema JDF and Lynge E (1997) Non-progression of cervical intraepithelial neoplasia estimated from population-screening data *Br J Cancer 75 (1), 124-130*

# DANKWOORD

Mijn eerste dank gaat uit naar mijn begeleiders Marjolein van Ballegooijen en Dik Habbema. Zij hebben door hun jarenlange enthousiaste volharding er -mede- voor gezorgd dat het boekje af is gekomen. Verder zijn er vele mensen in het instituut Maatschappelijke Gezondheidszorg, zowel binnen als buiten het screencluster, met wie ik altijd prettig heb samengewerkt. Hiervan ben ik Gerrit van Oortmarssen veel dank verschuldigd. Zijn vakkundige commentaar ("raar", "puzzel", "ik begrijp er vrijwel niets meer van") leidde mij steeds opnieuw naar een betere versie. Een speciale dank gaat uit naar mijn allereerste kamergenootjes Elske en Carin. We vormden een bijzondere driehoek en hebben ontzettend veel gelachen en geleerd over elkaars volstrekt andere levenswijze.

Buiten het eigen instituut heb ik veel geleerd van de bijeenkomsten van de organisatoren van het bevolkingsonderzoek op de toenmalige ziekenfondsraad. Hun praktische kijk vulden mijn wetenschappelijke kennis over het bevolkingsonderzoek goed aan. Stichting PALGA, en met name Renso Kamps, dank ik voor de prettige samenwerking in het PALEBA project, dat als basis diende voor een groot deel van mijn werk. I thank Elsebeth Lynge for her collaboration in the study on the data from Maribo County. Verder dank ik Ton Hanselaar, prof Theo Helmerhorst en Heleen Doornewaard voor hun klinische aanvullingen op mijn onderzoek naar endocervicale cellen.

Mijn huidige collega's van de SMASH en de HKH wil ik bedanken voor hun gezelligheid, hun belangstelling en de bereidheid om in te springen als ik aan m'n promotie moest werken. Dit geldt in het bijzonder voor Manou Bleeker, die altijd soepel mijn klusjes opvangt, en Adriaan van Ooijen, die me de ruimte heeft gegeven om het boekje af te ronden.

Mijn ouders wil ik bedanken voor hun enthousiaste belangstelling voor mijn werk en de altijd aanwezige bereidheid om de kindertjes op te vangen; ik hoop overigens dat die laatste ook zonder promotiewerkzaamheden blijft bestaan. Ook mijn schoonouders, Willem en Josephine, bedank ik voor hun flexibiliteit om in te springen. Evert bedank ik voor de eindeloze belangstelling; wie weet inspireert dit tot een andere afronding?

Jolanda en Petra bedank ik voor het gemak waarmee ze altijd bereid zijn m'n zorgtaken thuis over te nemen.

Cornelieke en Tessa bedank ik voor hun positieve betrokkenheid waarmee ze altijd voor me klaar staan. Vanwege haar wetenschappelijke kant zal Tessa me bijstaan bij de promotie, maar Cornelieke had net zo goed 'para-engel' kunnen zijn.

Zeer speciale dank gaat uit naar Jacobine en Wilma, die ondanks hun eigen afschuwelijke situatie altijd interesse toonden en me motiveerden om mijn werk af te ronden.

Tenslotte, het allerbelangrijkst: mijn thuisfront, lieve Gerke, Casper en Iris, maar ook hond Ab en poezen Pim en Lotje dank ik voor de rommelige, relativerende gezelligheid. Het wordt hoog tijd dat we lekker op vakantie gaan.

# CURRICULUM VITAE

Anita Bos werd geboren op 24 mei 1967 in Den Haag. Zij heeft haar VWO afgerond op het Segbroek College in Den Haag. Vervolgens heeft zij biomedische wetenschappen gestudeerd in Leiden. Na enkele klinische stages in het Sophia Kinderziekenhuis en in het Leyenburg Ziekenhuis, betrof de afstudeerstage een meer basale studie naar collagenen bij het Instituut voor Veroudering en Vaat Onderzoek van TNO. In 1994 is zij begonnen als wetenschappelijk medewerker van het instituut maatschappelijke gezondheidszorg van het Erasmus MC. Zij heeft zich hier bezig gehouden met de landelijke evaluatie van het bevolkingsonderzoek naar baarmoederhalskanker. Vanaf 2001 is zij werkzaam als beleidsmedewerker bij de Stichting Mobiele Artsen Service Haaglanden, aanvankelijk om de overgang te ondersteunen van de "oude" doktersnachtdienst naar de SMASH, met een groter werkgebied, meerdere posten en langere openingstijden. Inmiddels is er meer ruimte voor de kwaliteit van de huisartsenpost, voor analyse van gegevens en andere beleidszaken.
Zij is getrouwd met Gerke Henkes. Zij hebben 2 kinderen: Casper en Iris.