

Positive diagnostic values and histological detection ratios from the Rotterdam cervical cancer screening programme

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- Background** In organized screening programmes for cervical cancer, pre-cancerous lesions are detected by cervical smears. However, during follow-up after a positive smear these pre-cancerous lesions are not always found. The purpose of the study is to analyse positive diagnostic values of smears of at least mild dysplasia, made under the organized screening programmes in the Rotterdam area (1979-1991), and detection ratios of histologically confirmed CIN ≥ 3 , among women participating in these screening programmes.
- Methods** Positive diagnostic values and histological detection ratios, by age and history of previous smears, recorded during the national screening programme (1989-1991), were compared with those of the experimental cervical cancer screening project (1976-1984).
- Results** The positive diagnostic value of a smear with at least severe dysplasia (histologically confirmed CIN ≥ 3) remains approximately 78%. For smears with mild and moderate dysplasia only lower limits of the diagnostic value could be determined. This was 9% for a smear with mild dysplasia obtained during the national screening programme and 25% and 35% for smears with moderate dysplasia taken during the experimental and national screening programmes respectively. Histological detection ratios for CIN ≥ 3 in the three rounds of the experimental screening project were 4.7, 2.9 and 1.9. In the first round of the national screening programme the ratio was 4.7, and about three times higher in younger compared to older women.
- Conclusion** Immediate referral for colposcopy after a smear showing moderate dysplasia seems questionable. Whether the increased detection ratio among young women indicates a rise in the risk of cervical cancer is unclear.
- Keywords** Cervical cancer screening, positive diagnostic value, histological detection ratio
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In the Netherlands each year, under a national screening programme, about 650 000 women are invited to have a cervical smear. Approximately 1.5% of these women receive recommendations for further cytological or histological examination

because of an abnormal smear. Unfortunately, a number are followed up unnecessarily due to a false positive result. By considering the histological findings as the gold standard, the ratio of true cytological positives to all (true and false) cytological positives can be determined (diagnostic value). Also, the number of women with a histologically confirmed precursor of cervical cancer detected per 1000 participants (histological detection ratio) can be observed. Thus, insight can be obtained into the extent of both beneficial and unnecessary diagnostic activities as a result of the screening.

In 1976, as an experiment, cervical cancer screening was started in three areas in the Netherlands, one of which was Rotterdam. This experiment ended in 1984. By then in this area, three screening rounds had been organized. In total 479 014 invitations were sent, and 313 514 smears were taken (65%). In

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1988, after a lapse of 4 years, a national cervical screening programme was announced. The organization of this programme was somewhat different compared to the experimental project. Instead of being carried out by specially trained women in health centres, smears were taken by the family doctors. The age limit (33–55 years) and the screening interval (3 years) were unchanged. In Rotterdam, the national screening programme was started in 1989. During the first round (1989–1991) 95 125 women received an invitation and 44 330 participated (47%).

In both the experimental and national screening programmes women with a smear showing severe dysplasia or suspected carcinoma were referred for histological examination. Follow-up after a smear with mild or moderate dysplasia, however, changed over the years. During the first round of the experimental project a smear with mild or moderate dysplasia was followed by brief advice from the family doctor to have a repeat smear after one year. During the second and third rounds follow-up intensified. Only in 1987 was consensus reached: after a smear showing mild or moderate dysplasia up to three repeat smears have to be made after two successive intervals of 3 months and one interval of a year. If any of the repeat smears has a result of mild dysplasia or higher, referral for colposcopy is recommended, after which histology can be carried out.^{1,2}

The purpose of the study is to analyse positive diagnostic values of smears with at least mild dysplasia made under the organized screening programmes in Rotterdam area (1979–1991), and to study detection ratios of histologically confirmed CIN ≥ 3 , among women participating in these screening programmes.

Methods

Detection ratios and positive diagnostic values for the experimental project in the Rotterdam area (1976–1984), were obtained from the reports of this period.^{1,3}

Detection ratios and positive diagnostic values for the national screening programme (1989–1991), were obtained from three data sources.

Follow-up

For women who had a smear with at least mild dysplasia in the national screening programme 1989–1991 in the Rotterdam area, cytological and histological follow-up were obtained from the Pathological Anatomical National Computerized Archives. Included were the number of previous smears reported by the women, and age. The follow-up covers data up to June 1994, gathered from laboratories all over the country.

Participating women

The number of women who participated in the screening programme between 1989 and 1991 was defined on the basis of data, supplied yearly to the Municipal Health Service of Rotterdam, by four laboratories in the surrounding district (covering over 99% of all smears made under the organized screening programme). Age is reported, but the number of previous smears is not.

Participating women with known history of previous smears

The test result, the number of (self-reported) previous smears and age were registered for all the women whose smear, made

in the organized programme, had been analysed between 1989 and 1990 at the regional laboratory (approximately 80% of all smears made under the organized screening programme).

Histological findings during follow-up were encoded as Cervical Intraepithelial Neoplasia (CIN) grades 0–3, corresponding to the histological diagnoses 'no neoplasia' (0), 'mild dysplasia' (1), 'moderate dysplasia' (2), 'severe dysplasia or carcinoma *in situ*' (3). Furthermore, micro-invasive carcinoma, invasive squamous cell carcinoma, and adenocarcinoma were determined. In cases of successive histological examinations, the most severe diagnosis is taken as the final histological diagnosis and considered as the gold standard.

The positive diagnostic value is defined as the fraction of women with a positive smear in the organized screening programme who participate in (cytological or histological) follow-up, and that are found to have histologically confirmed CIN ≥ 3 .

The histological detection ratio is defined as the number of women with histologically confirmed CIN ≥ 3 , detected during follow-up after a positive smear in a full round of the organized screening programme, per 1000 women participating in this particular screening round. Histological detection ratios were stratified according to history of previous smears (never/ever) and age (<37 and ≥ 37 years). For this purpose follow-up data were selected from women whose positive smear in the screening programme was analysed at the regional laboratory in 1989 and 1990. Of these, the number of women with CIN ≥ 3 was determined and divided by the number of participating women in 1989–1990, whose smear was analysed at the regional laboratory. The age groups <37 and ≥ 37 years were chosen, as for these groups detection ratios on previous smears during the experimental screening project (1976–1984) were available.

Results

Positive diagnostic values

During the experimental screening project 1.7% of the participating women were found to have an abnormal smear. In the first round of the national screening programme this was 1.4%. During the experimental screening project (1976–1984) no data were collected about follow-up after a smear showing mild dysplasia, and follow-up after a smear with moderate dysplasia was only monitored from 1980. In Table 1 a summary of the follow-up is presented for the experimental screening project and the national screening programme.

Mild dysplasia

During the first round of the national screening programme (1989–1991), 271 women had a smear with mild dysplasia; for 33 (12%) of these no follow-up was found. Of 238 women who had follow-up, histology was performed in 116. In 22 women (9% of 238 women being followed up) CIN ≥ 3 was found.

Moderate dysplasia

Since 1980, 683 of the women who participated in the experimental screening project had a smear with moderate dysplasia. In 110 (16%) no follow-up was found. Of 573 women who were followed up, histology was carried out in 205. In 141 of these cases (25% of 573 women being followed up) CIN ≥ 3 was found.

During the national screening programme 181 women had a smear of moderate dysplasia. In 159 cytological or histological

Table 1 Follow-up after a positive smear during the experimental cervical cancer screening project (1976–1984) and the national screening programme (1989–1991) in the Rotterdam area

	Experimental project 1976–1984	National programme 1989–1991
No. of women invited	479 014	95 125
No. of women participating	313 514	44 300
Smear test result: mild dysplasia		271 (100%)
No follow-up found		33 (12%)
Only cytological follow-up		122 (45%)
Histological follow-up, <CIN 3		94 (35%)
Histological follow-up, \geq CIN 3		22 (8%)
Smear test result: moderate dysplasia^a	683 (100%)	181 (100%)
No follow-up found	110 (16%)	22 (12%)
Only cytological follow-up	368 (54%)	45 (25%)
Histological follow-up, <CIN 3	64 (9%)	58 (32%)
Histological follow-up, \geq CIN 3	141 (21%)	56 (31%)
Smear test result: \geq severe dysplasia	1119 (100%)	181 (100%)
No follow-up found	29 (3%)	15 (8%)
Only cytological follow-up	30 (3%)	2 (1%)
Histological follow-up, <CIN 3	225 (20%)	34 (19%)
Histological follow-up, \geq CIN 3	835 (75%)	130 (72%)

^a During the experimental screening project follow-up after a smear moderate dysplasia was only fully monitored from 1980 until 1984. In this period 181 646 women participated in the screening program.

follow-up was carried out, and 22 women (12%) had no follow-up. Of 114 women with histology, 56 showed CIN ≥ 3 (35% of 159 women being followed up).

Severe dysplasia or suspected carcinoma

Histology was performed in 95% of the 1119 women who had a smear with severe dysplasia or suspected carcinoma in all three rounds of the experimental screening project. In 29 women (3%) no follow-up was found, and 30 women (3%) only had repeat smears. The overall diagnostic value of a smear showing a minimum of severe dysplasia during the experimental project is 77% (835 out of the 1090 women who were followed up, had results CIN ≥ 3).

During the national screening programme 181 women had a smear with severe dysplasia or suspected carcinoma. In 15 women (8%) no histological or cytological follow-up was found and in two women (1%) only cytological follow-up was done. The diagnostic value of a smear showing a minimum of severe dysplasia during the national screening programme is 78% (130 out of the 166 women who were followed-up, had CIN ≥ 3).

Detection ratios

In the first round of the experimental screening project (1976–1978) the detection ratio was 4.7, as 4.7% of the participating women were found to have CIN ≥ 3 during follow-up after a smear showing at least mild dysplasia. During the second and third rounds (1979–1984), this number was 2.9 and 1.9 respectively. The detection ratio during the first round of the national screening programme in the Rotterdam area was 4.7 (208 women with CIN ≥ 3 after a smear with a minimum of mild dysplasia).

N (\geq CIN 3) per 1000 participants

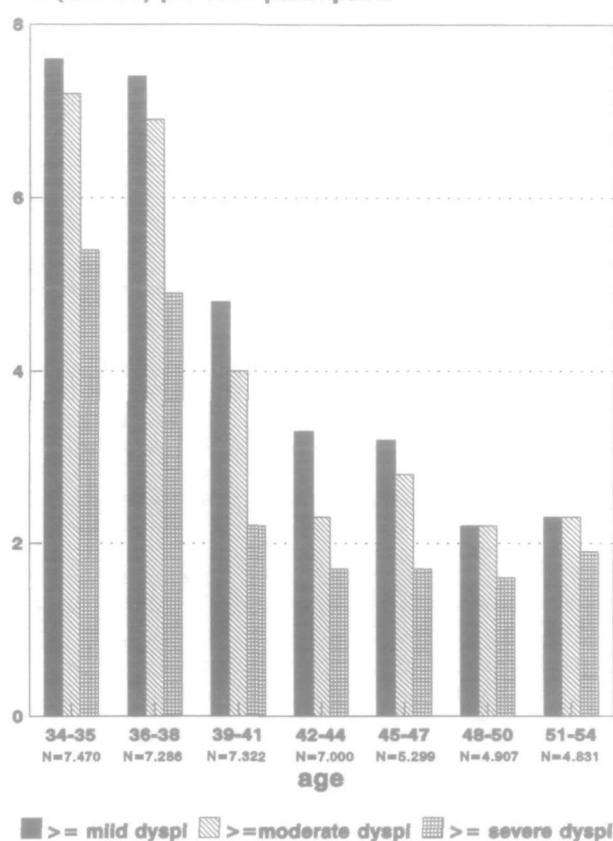


Figure 1 Distribution in age groups of the number of women with CIN ≥ 3 per 1000 participants (detection ratio), detected during follow-up after smears of at least mild, moderate or severe dysplasia, in the first round of the national screening programme in the Rotterdam area (1989–1991)

As follow-up after a smear with mild and moderate dysplasia has intensified over the years, this may have caused an increase in the detection ratios mentioned. Detection ratios following smears with severe dysplasia or higher, however, may be compared more directly as follow-up guidelines and diagnostic values for these test results were unchanged over the years. During the successive rounds of the experimental project 4.4%, 2.4% and 1.1% of the participating women were found to have CIN ≥ 3 during follow-up after a smear with severe dysplasia or higher. Therefore, the corresponding detection ratios were 4.4, 2.4 and 1.1. The detection ratio after a smear with at least severe dysplasia during the national screening programme is 3.0.

Detection ratios by age and previous smears

The detection ratios during the national screening programme (1989–1991) appear to be about three times higher in the lowest age group, than in the highest (Figure 1). This age-related difference is greatest in women without previous smears. Among these women the histological detection ratio of those <37 years is about twice as high when compared to older women (Table 2, 11.3 versus 7.1). In Table 2, data for the experimental screening project are also presented. Among women without previous smears, in the successive rounds, the detection

Table 2 Number of women with CIN ≥ 3 detected per 1000 participants (detection ratio) and number of participants during the successive rounds of the experimental screening project (1976–1984), and during the national screening programme in the Rotterdam area (only smears analysed at the regional laboratory in 1989 and 1990). Relationship between age (<37, ≥ 37 years) and previous smears (self reported)

	Age	No previous smear		Previous smear(s)		Total	
		N (part)	Detection ratio	N (part)	Detection ratio	N (part)	Detection ratio
Experimental project							
First round, 1976–1978	<37	8469	3.9	9298	5.1	17 767	4.5
	≥ 37	50 238	6.1	41 563	2.2	91 801	4.3
Second round, 1979–1981	<37	7782	4.8	12 135	2.5	19 917	3.4
	≥ 37	5154	6.2	77 713	1.9	82 867	2.2
Third round, 1982–1984	<37	6855	3.2	13 182	1.8	20 037	2.3
	≥ 37	3435	2.9	74 469	0.7	77 094	0.8
National programme							
First round (only 1989–1990)	<37	970	11.3	2905	5.2	3875	6.7
	≥ 37	1548	7.1	17 940	4.1	19 488	4.3

ratio in young women has passed the detection ratio in older women. For women who have had previous smears the detection ratio is higher among young women in all three screening rounds. The detection ratios for women without previous smears in the third round of the experimental project are lower than would be expected, and may be considered as outliers.

Discussion

During the national screening programme histology was carried out in less than half of the cases with a smear showing mild dysplasia and in over half of those having a smear with moderate dysplasia who received at least cytological follow-up. Considering the guidelines for follow-up, all women with a positive repeat smear will have received histology. Analyses of follow-up after a smear showing mild or moderate dysplasia under the Rotterdam national screening programme (1989–1991) however, showed that in 18% of cases, follow-up ended prematurely: second or third repeat smears, or histological examinations recommended were not carried out.⁴ Therefore the percentage of CIN ≥ 3 found in women with at least cytological follow-up after a smear with mild or moderate dysplasia in the organized screening programme, can be considered as a lower limit of the positive diagnostic value. This lower limit diagnostic value for a smear with mild dysplasia is 9% in the national screening programme and for a smear with moderate dysplasia it is 25% and 35% in the experimental and national screening programmes respectively. In other parts of the Netherlands, 14% of women with cytological or histological follow-up after a smear with mild or moderate dysplasia made under the national screening programme in 1991, were found to have histologically confirmed CIN ≥ 3 . In these areas, the positive diagnostic value of a smear with at least severe dysplasia for CIN ≥ 3 amounted to 80%.⁵

According to new guidelines for follow-up which were recently introduced, women with a smear with moderate dysplasia in the organized screening programme will immediately be referred for colposcopy, instead of repeating the smear.⁶ Our results indicate that a minimum of 35% of women with a smear of moderate dysplasia will have CIN ≥ 3 . The detection ratios have shown that a significant number of these women are

young. Considering the possibility of high regression among young women,⁷ the necessity of this immediate referral can be questioned.

The histological detection ratio for CIN ≥ 3 in the first round of the national screening programme in the Rotterdam area (1989–1991) has doubled since the third round of the experimental screening project. This is in line with the increased rate of smears showing a minimum of severe dysplasia, found during the national screening programme in this area (1.5%: 1982–1984 and 4.0%: 1989–1991).^{1,8} As spontaneous screening in the years 1984–1989, after the end of the experimental project, was mainly directed towards young women aged 20–35 years,⁹ it could only partly replace the organized programme. The rising detection ratio, therefore, may be due to an accumulation of pre-cancerous lesions in this period. Furthermore, follow-up after smears with mild and moderate dysplasia has been intensified, and detection has been improved by the introduction of colposcopy in the early 1980s. This technique recognizes pre-invasive and early pre-clinical invasive carcinomas with higher sensitivity. The rise in histological detection ratio, however, appears to result particularly from an increase in the number of young women with CIN ≥ 3 detected, which is also true after controlling for previous smears. Between 1974 and 1986 an increase in cervical carcinoma *in situ*, in the group of young women (<35 years), was observed in the Netherlands.¹⁰ In other European countries high detection ratios among young women have also been found. In Sweden the ratio of CIN 3 detected through organized or opportunistic screening peaks around ages 25 to 35 and then declines rapidly in order to become four to five times lower at the age of 50.¹¹ In Florence, Italy, detection rates of CIN 3 within 5-year age groups among women with no previous smear for at least 10 years showed a significant increase over 20 years for women aged 30–54. The increase was most obvious for the age group 30–34.¹² Researchers have pointed out a possible relationship between the rise in CIN 3 detected and changes in the sexual activity of young women. The large-scale provision of oral contraceptives may have caused increased exposure to human papillomavirus.

Whether the risk of cervical cancer has actually increased among young women is difficult to assess. If regression of pre-invasive lesions is high in this group,⁷ a rise in pre-invasive

lesions would only lead to a small rise in the risk of cervical cancer. In several European countries, after a sharp decrease since the 1950s, the mortality rate for cervical cancer among women between 25 and 39 years has increased.¹³ The rise is most pronounced in England, Wales, Scotland, Ireland, and Eastern European countries, but it is also present to a much lesser extent in Belgium. In the Netherlands the mortality rate of young women is still decreasing, but the rate of decrease has levelled off from about 1970. The Cancer Registry in the south-east of the Netherlands found a small increase in the incidence of invasive cervical cancer in women below the age of 40 in the years 1975–1988.¹⁴ This may indicate a rise in the risk of cervical cancer. Van Ballegooijen *et al.* who studied national data on first admissions to hospital for invasive cervical cancer from 1975 to 1990, found that the incidence of cervical cancer in women aged 35–39 was fairly constant during this period. They concluded that a significant rise in the risk of cervical cancer in young women in the Netherlands does not exist. A small rise may exist, when the effects of screening and treatment on the incidence are taken into account.¹⁵

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