Prophylactic cytological investigation for cervical cancer in relation to stage at diagnosis: a study of 420 women in Denmark

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SUMMARY. Despite widespread cervical smear testing 500–600 cases of cancer of the cervix are still diagnosed each year in Denmark, with over 200 deaths. The distribution of the different stages of cancer among 420 women who were diagnosed during 1983 was correlated with the number of previous cervical smears, whether done purely for screening reasons or for minor gynaecological problems. Of the women with cancer 56% had never been screened, and among these 42% were diagnosed at stage 1; 19% had been screened once; 61% of them at stage 1. The remainder (25%) had been screened at least twice, and 81% of them were diagnosed at stage 1. Among the patients who had been screened at least twice, with the last screening not more than three or five years ago, about 90% were diagnosed at stage 1 and the rest at stage 2.

The introduction of cervical smear testing will thus mean a considerably better stage distribution among cases which develop invasive cancer of the cervix, and both case fatality and mortality rates will be reduced by organized programmes, which have better participation rates than disorganized use of cervical smears.

Introduction

CANCER of the cervix uteri is characterized by a long preinvasive phase, during which the diagnosis can be made at an early stage (International Federation of Gynaecology and Obstetrics stage 1).[1,2] However, despite widespread use of cervical smear testing, 500–600 new cases of cervical cancer are diagnosed per year in Denmark, with 200–300 deaths.[2]

The mortality rate of cervical cancer has declined in the Nordic countries in the last decades, particularly in countries with well established nationwide screening programmes (Iceland, Finland, Sweden). The rate has declined less in Denmark and Norway, where preventive investigation has not been nationwide.[3] The Danish national health authorities have recommended that all counties should have organized screening programmes with individual invitations issued to all women aged 23–60 years who have not had a cervical smear for some reason (screening or gynaecological) during the last three years. Only when a woman has had at least two previous smears is she considered sufficiently investigated.[2] But since local health planning is the responsibility of the counties, only half of the Danish counties have introduced organized screening programmes, while the investigation is used in an opportunistic way in the others. In some organized programmes an opportunistic investigation, whether for gynaecological or screening purposes, postpones the next invitation to organized screening, but in other programmes it does not. While in organized programmes the participation rate is 70–90%, in counties without organized preventive programmes only 40–60% of women are regularly investigated opportunistically (for gynaecological or screening purposes).[2,4-6] About 55–60% of all cervical smears in Denmark are for screening, while the others are carried out because of gynaecological symptoms or signs.[6,7] The effect of different strategies on the incidence of cervical cancer has been investigated in a case-control study by the same author.[7]

A few Danish regional studies have described the stage distribution of cervical cancer in relation to cervical smears.[8,9] These studies, as well as larger studies abroad, all show that the most advanced stages are diagnosed in women who have never been screened before.

The aim of the present study was to correlate on a nationwide basis the timing, type and number of previous cervical smears, if any, with the stage of cancer among Danish women who received the diagnosis during 1983 and therefore to evaluate the benefit of different preventive strategies on the stage of detection of cervical cancer.

Method

The National Cancer Registry provided the names and personal identity numbers of the 549 women who were diagnosed as having cervical cancer in 1983, and who were on the register by 10 July 1985. After the exclusion of 30 women for various reasons (11 living in Greenland, six not diagnosed in 1983 and 13 on the register by error),[7] standard questionnaires were sent to the general practitioners of the remaining 519 women. The distribution of the different stages of cancer was provided by the registry and by the general practitioners, and it was further checked by comparison with the hospital records.

The questionnaire included information about the number of previous cervical smears each woman had had, as well as the reason for the smear at the time of diagnosis of suspected cancer and the last smear before the diagnosis, together with the date of the diagnosis. Information about smears taken between suspicion and verification of the diagnosis was excluded from this analysis, but has been described elsewhere.[10]

Two methods can be used in the analysis of cervical smear testing. First, screening investigations only, whether systematic or opportunistic, may be considered. The screening investigation is defined as an investigation of a woman without any gynaecological symptoms or signs that could be associated with cervical cancer. Secondly, all prophylactic investigations, whether owing to minor gynaecological symptoms or signs or as part of a screening programme, can be analysed. The data in the present study have been analysed in both ways, as recommended by the health authorities.[2] However, when smears taken for gynaecological reasons were included in the statistical analysis, investigations during the six months before the cancer diagnosis were excluded because smears taken as a part of the diagnostic process cannot have any prophylactic effect.[11]

The statistical analysis included a chi-square test with Yate's correction, as well as Spearman's correlation analysis and a stratified relative risk calculation, as described by Mantel and Haenszel.[12]

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Results

Questionnaires were returned on 428 of the 519 patients (82%). The response rates for cervical cancer stages 1–4 were 86%, 92%, 70% and 81%, respectively. The response rate was more than 75% in all counties, but in the municipalities of Copenhagen and Frederiksberg the overall response rate was 57%.

Details about age distribution, as well as stage distribution according to age and number of previous cervical smears, have been described elsewhere.[4,7] The mean age of the 519 patients was 53.8 years, and for the 428 responders 52.6 years.

In seven cases information was missing about the number and timing of cervical smears, and in one case about the stage of the cancer. These eight cases were excluded, so that the final analysis was performed on 420 patients.

In 32 of the 420 patients with cervical cancer a previous atypical or abnormal cervical smear was later followed by a normal smear; the distribution of these 32 patients by stage 1–4 was as follows: 24, six, two and zero.

The reasons given by the general practitioners for the cervical smears at the time when the diagnosis was suspected were as follows: routine screening of women without symptoms or signs (91), gynaecological symptoms (324), unknown (5). In the routine screening group, 91% of cancers were at stage 1, and the rest at stage 2. In the group with symptoms at the time of diagnosis, the distribution of stages was significantly worse ($P<0.01$, Spearman's test) (Table 1).

Table 1. Percentage stage distribution of cervical cancer in relation to reason for testing and number of previous cervical smears in 420 women who developed cervical cancer during 1983.

	Stage 1	Stage 2	Stage 3	Stage 4
Reason for testing				
Routine screening ($n=91$)	91	9	0	0
Gynaecological symptoms ($n=324$)	46	27	19	7
Number of previous smears				
None ($n=233$)	42	30	18	10
One ($n=79$)	61	19	18	2
At least one ($n=187$)	73	14	11	2
At least two ($n=108$)	81	11	6	2
All women ($n=420$)	56	23	15	6

n = number of women with cervical cancer.

One hundred and eighty seven patients (45%) had undergone at least one previous cervical smear. In these patients, the reason for the last smear was routine screening (systematic or opportunistic) in 52%, gynaecological symptoms in 42%, and unknown in 7%. There was an insignificant trend towards earlier stages among patients in the routine screening group.

Table 1 shows the distribution of stages of cervical cancer in relation to the number of previous smears, regardless of the reason for the smear and timing with respect to final diagnosis. Those who had never had a smear (233 women, 56%) were diagnosed at considerably later stages than those examined once, and the stage distribution was earlier among those examined at least twice compared with those examined only once. The difference in the stage distribution between those never examined, those examined once, and those examined at least twice was highly significant (Spearman's test, $P<0.001$).

Figure 1 shows the stage distribution of patients previously and not previously examined.

Table 2 gives the timing of the last cervical smear, regardless of the reason for it, in 187 patients with at least one previous

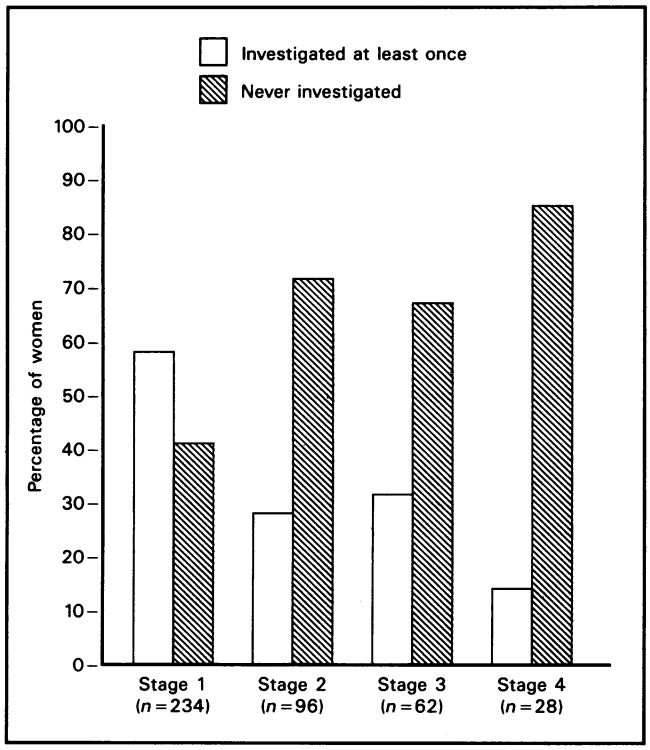

Figure 1. *Relative stage distribution of cervical cancer for women never investigated compared with women investigated at least once (n = total number of cases diagnosed at each stage).*

smear. For those who had a smear within six months of the first suspicion of cancer, the stage distribution was worse than in the group examined between six and 36 months or six and 60 months previously. The stage distribution was even worse when the last cervical smear was performed more than 60 months previously. These differences were significant (Spearman's test, $P<0.05$). It can be concluded that at least 80% of cervical cancers will be at stage 1 if the patient has been examined within the last six months to five years, regardless of the reason for the last examination.

One hundred and eight of the 187 patients in Table 2 had been examined at least twice. The stage distribution of these is given in Table 3 in the same way as in Table 2; 88 and 91% were at stage 1, with maximum intervals of five and three years respectively between the last cervical smear and the last but one.

Looking only at those symptomless patients with cancer diagnosed at routine screening, 74 patients had been examined at least once within the previous five years, whereas 58 had been examined within the last three years. In both these groups, 81% were diagnosed at stage 1. Only 30 patients had been examined at least twice at intervals of not more than five years: 90% of them were diagnosed at stage 1, and the rest at stage 2; 24 patients had been examined in the same way, but at intervals of

Table 2. Percentage stage distribution of cervical cancer in relation to the timing of the preceding cervical smear in 187 women who had had at least one cervical smear.

Time elapsed from last smear (months)	Stage 1	Stage 2	Stage 3	Stage 4
0–6 ($n=36$)	61	19	14	6
6–36 ($n=82$)	83	9	7	1
6–60 ($n=114$)	82	8	9	1
> 36 ($n=69$)	67	19	13	1
> 60 ($n=37$)	54	30	14	3

n = number of women with cervical cancer who had had at least one smear.

Table 3. Percentage stage distribution of cervical cancer in relation to the timing of the preceding cervical smears in 108 women who had had at least two cervical smears.

Time elapsed from:					
Last smear (months)	Last smear but one (months)	Stage 1	Stage 2	Stage 3	Stage 4
0–6	>6 (*n* = 20)	*70*	*15*	*5*	*10*
6–36	>6 (*n* = 63)	*89*	*6*	*5*	*0*
6–60	>6 (*n* = 75)	*88*	*7*	*5*	*0*
6–36	<72 (*n* = 58)	*91*	*7*	*2*	*0*
6–60	<120 (*n* = 74)	*88*	*7*	*5*	*0*

n = number of women with cervical cancer who had had at least two smears.

Table 4. Relative chance, corrected for age, of being diagnosed in stage 1 for 420 women with cervical cancer, in relation to number and timing of previous cervical smears.

Number and timing of previous smear	Odds ratio	95% confidence limits	*P*
Examined once, regardless of timing of preceding smear	1.5	0.8– 2.9	>0.05
Examined at least twice, regardless of timing of preceding smear	3.8	2.0– 7.4	<0.01
Examined at least twice, with last smear 6–60 months before suspicion of cervical cancer	7.2	3.2–16.3	<0.01
Examined at least twice, with last smear 6–36 months before suspicion of cervical cancer	7.1	3.2–16.0	<0.01

not more than three years: 92% were diagnosed at stage 1, the rest at stage 2.

The relative risk of a woman being diagnosed at stage 1, should she develop cancer, was calculated by odds ratio analysis, stratified by age according to the method of Mantel and Haenszel. Table 4 shows that the patients' chances, corrected for age, of a stage 1 diagnosis were increased by a factor of between four and seven, according to the number and timing of previous cervical smears. Shortening the interval between two investigations from five years to three years did not improve the stage distribution.

Eight counties in Denmark had introduced systematized routine cervical screening before 1980. In the eight other counties screening is performed opportunistically. Table 5 shows that fewer women had never been examined and more had been examined at least twice in counties with routine screening. This holds particularly for patients at stage 1, where the difference was statistically significant (Spearman's test, $P<0.01$). As seen in Table 6, however, there was no difference in the distribution of stages of cancer at the time of diagnosis between counties with and without routine screening.

Table 6. Percentage stage distribution in 420 women with cervical cancer in relation to residency in counties with or without routine cervical screening.

Women resident in counties with:	Stage 1	Stage 2	Stage 3	Stage 4
Routine screening (*n* = 170)	*55*	*21*	*16*	*8*
No routine screening (*n* = 250)	*56*	*24*	*14*	*6*

n = number of women with cervical cancer.

Three hundred and sixty five patients (87%) had a squamous cell carcinoma and 56% of them were diagnosed at stage 1. Among non-squamous cell carcinoma fewer (54%) were at stage 1. Among the patients examined six to 60 months before the diagnosis, the corresponding figures were 83 and 78%. This difference was not significant.

Discussion

The Danish cancer register is well established and nationwide, and it records almost 100% of all cases of cancer in Denmark. Since the study was based on information from both the cancer register and hospital and general practice records, the data should be reliable, as well as representative for Denmark because of the high response rate and the distribution by county, age and stage of cancer. However, the possible loss of information about the result and timing of previous cervical smears should not be overlooked. In previous studies such loss has been considered of little importance,[5-7] especially since it can be expected to be equally distributed among the patients. On the other hand, loss of data might cause an overestimation of the number of women never examined.

The study has shown that cervical cancer is detected at an earlier stage in women who have been tested previously. Regardless of whether all cervical smears are taken into con-

Table 5. Percentage stage distribution in 420 women with cervical cancer in relation to number of previous cancer smears, and to residency in counties with or without routine cervical screening.

	Stage 1		Stages 2–4		Total	
Number of previous smears	Routine screening[a] (*n* = 94)	No routine screening[b] (*n* = 140)	Routine screening (*n* = 76)	No routine screening (*n* = 110)	Routine screening (*n* = 170)	No routine screening (*n* = 250)
None	*33*	*48*	*71*	*74*	*50*	*59*
One	*18*	*22*	*20*	*14*	*19*	*19*
Two or more	*49*	*30*	*9*	*12*	*31*	*22*
Total	*100*	*100*	*100*	*100*	*100*	*100*

n = number of women with cervical cancer.
[a] Women resident in counties with systematized routine cancer smear testing introduced before 1980. [b] Women resident in counties without systematized routine testing introduced before 1980.

sideration (excluding only examinations performed during the six months preceding the diagnosis[11]) or whether only routine screenings are considered, about 90% of the patients were diagnosed at stage 1 when examined at least twice at intervals of not more than three to five years, as is now recommended in most countries.[1,2] Routine investigation more often than every fifth year did not significantly alter the stage distribution. The improvement in the stage distribution shown here is in agreement with two regional Danish studies[8,9] as well as with studies in England and Canada.[13,14]

The stage distribution was not uniform in different age groups, nor were the number of times the women had been tested.[10] This is described in detail in another article,[4] but briefly, there were more cancers at later stages and more cases which had never been investigated among older women. Age-dependent differences in the threshold for the patients' attendances at the general practitioner and in the natural history of the cervical cancer might influence the stage distribution. However, the possible confounding effect of age was eliminated in Table 4, which clearly showed a better chance of a stage 1 diagnosis in patients previously investigated compared with those never investigated.

Improving the stage of detection of cancer should reduce the case fatality rate, because lower stages have a better prognosis. Thus, a Norwegian study, which covered the period 1968–75, showed that the five-year survival for stage 1 was 89%, while it was only 11% for stage 4.[15] It also showed that improvement in the prognosis of cervical cancer over the last decades was largely the result of detecting it at an earlier stage, while a change in age distribution and in treatment did not contribute significantly to the reduced case fatality rate.

An improved case fatality rate does not necessarily alter the mortality rate when the incidence of the disease is unchanged.[12] Misinterpretations are possible if routine screening reveals diseases which would have resolved spontaneously or which would not have become manifest before the death of the patient from other causes (length biased sampling). The same holds if the prognosis of each single stage becomes worse because biologically serious forms of cancer are being diagnosed at an early stage (lead time bias). Regarding cervical screening there are no indications that these types of bias influence the relation between case fatality rate and mortality rate.[15] Furthermore, there are strong indications that the incidence of invasive cervical cancer is reduced through prophylactic examinations.[16] In an ongoing analysis of the present data, the case fatality rate of stage 1 in previously screened and unscreened patients reveals no difference three years after the diagnosis of cervical cancer.

The present study showed a difference in the proportion of women never tested between counties with and without routine screening, just as the proportion of women examined more than twice was higher in counties with routine screening. However, it is interesting that this did not cause a skewness to the left in the distribution of cancer stages in counties with routine screening, although the incidence of cervical cancer had fallen faster in these counties than in others.[2,16] The unchanged stage distribution may be explained by the fact that the routine screening programmes mainly aim at the target group under 50 years old, while the most severe cases are found in those aged over 50 years.

Another study using the same material[7] showed that cervical screening was probably more effective in preventing the development of invasive squamous cell carcinomas than of adenocarcinomas or mixed tumours. In agreement with this the present study found a rather worse stage distribution among the non-squamous cell carcinomas. This trend, however, was not significant.

It is reasonable to conclude that regular cervical smear testing, whether done for minor gynaecological problems or screening purposes, reduces the number of severe cases of cervical cancer considerably, so that at least 80–90% of cases occurring among previously examined women are diagnosed in stage 1. This contrasts with the present situation, in which an average of 56% of cases (42% of women never screened) are in stage 1 when diagnosed.

As organized preventive programmes have fewer women never investigated and higher participation rates than unorganized programmes, there is a strong argument for introducing organized preventive programmes for cervical screening.[1,5,6]

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Acknowledgements

General practitioners participating in data collection, the Danish cancer register, and the national health service are acknowledged for their kind assistance. The investigation was funded by the Danish National Cancer Society and by the Sara Krabbes foundation.

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