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Effect of Organized Screening on Incidence and Mortality of Cervical Cancer in Denmark

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ABSTRACT

Pap smears were used only on a limited scale in Denmark until the late 1960s. Since then smears have been taken both in organized screening programs and outside the programs by general practitioners, private gynecologists, and hospital wards. The present smear-taking activity is equivalent to an average of one smear every second year per woman. As the responsibility for health care rests with the counties in Denmark, differences are found between the counties both concerning organization of screening programs, and concerning the overall level of the smear-taking activity. An analysis using multiplicative Poisson models on county-based incidence and mortality data for women aged 30-59 years in 1963-1982 showed a statistically significant effect of organized screening in reducing both the incidence (*RR* = 0.67; 95% CI, 0.61-0.73), and the mortality (*RR* = 0.68; 95% CI, 0.59-0.78) of cervical cancer from 5 years after introduction of an organized screening program. The level of overall smear-taking activity was found to be of limited importance when organized screening was taken into account.

INTRODUCTION

Screening for cervical cancer based on Pap smears is the most widespread cancer preventive measure beside efforts to reduce tobacco smoking. The Pap smear was developed in the 1940s, and it has gradually become an integrated part of most health care systems. The present smear-taking activity in Denmark is equivalent to an average of one smear every second year per woman in the age group 20-59 years (1).

Smears can be taken in organized screening programs where given age groups are invited by personal letters to have a smear taken by their GP[2], or are forwarded cytopipets for self-application. Smears can also be taken in the clinical work, or as a preventive measure on a more individual basis by GPs, private gynecologists or hospital wards. Mass media campaigns may serve as an intermediate between the organized screening program and the spontaneous smear-taking activity.

There are two important parameters in evaluation of the screening activity. The first is the amount of resources used, which can be expressed as the average number of smears taken per woman. The second is the coverage, which can be expressed as the percentage of women screened at least once during a given time period. The relationship between these two parameters is highly dependent on the way in which the screening activity is organized.

Pap smears were used only on a limited scale in Denmark until the late 1960s, when they became generally available in gynecology wards, and when smears taken by GPs started to be covered by the national health insurance. The responsibility for health care rests with the counties in Denmark. An organized screening program was initiated in a small county in 1962, in three main counties in 1967-1968, and in two counties in 1973-1975. The majority of counties has, however, relied only on the spontaneous smear-taking activity. These organizational differences between the counties have resulted in considerable differences both in the number of smears taken per woman and in the percentage of women screened, as illustrated in Table 1.

Computerized data files are available on all incident cancer cases and all deaths in Denmark since 1943. By far the majority of incident cases of cancer uteri notified to the Danish Cancer Registry have been specified by subsite of the uterus, but like in other countries, Denmark had previously a relatively high proportion of death certificates with "cancer uteri unspecified site." Specification of the death certificates by subsite of the uterus is, however, possible by individual record linkage between the two computerized data files.

The natural experiment of different screening strategies adapted over time by the counties in Denmark, and the availability of both incidence and mortality data specified by subsite of the uterus, have allowed estimation of the effect of organized screening on both the incidence and mortality from cervical cancer in a homogeneous population.

MATERIALS AND METHODS

Smear-taking Activity

Up until 1970 Denmark was divided into 22 counties, and the present municipalities can be grouped into equivalent areas. Data are available on the number of smears taken in the organized screening programs, and from 1974/1975 onwards also on the number of smears taken by GPs, private gynecologists and hospital wards outside the organized programs (2).

Population Data. A possible effect of the smear-taking activity on the incidence and mortality of cervical cancer can still not be expected to be seen in older women in Denmark, because the Pap smears were used on only a limited scale before 1970. In the present study, data have therefore been included only for women aged 30-59 years in the period 1943-1982 for all Denmark, and for each of the 22 counties.

Incidence Data. Cases of invasive cancer of the cervicis uteri notified to the Danish Cancer Registry have been tabulated by 5-year age groups and 5-year calendar periods for all Denmark, and for each of the 22 counties.

Mortality Data. Death certificates with the primary cause of death specified as cancer cervicis uteri, cancer uteri unspecified site, and related or uncertain cancer diagnoses, were linked automatically to the Cancer Registry file based on date of birth, date of death, marital status, primary cause of death, and from 1970 onwards on municipality code. The linkage was supplemented with a manual search on microfilms of original notification forms and death certificates. The Cancer Registry diagnosis was transferred to the death certificate file for all matched cases.

Deaths were tabulated by 5-year age groups and 5-year calendar periods for all Denmark and for each of the 22 counties based on three definitions for number of deaths: (*a*) primary cause of death coded as cancer cervicis uteri, (*b*) primary cause of death either coded as cancer cervicis uteri, or coded as cancer uteri unspecified site with the Cancer Registry diagnosis being cancer cervicis uteri, or (*c*) primary cause of death either coded as cancer cervicis uteri, or as any of the other selected causes of death and the Cancer Registry diagnosis being cancer

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[2] The abbreviations used are: RR, relative risk; ICD, International classification of diseases; GP, general practitioner.

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Table 1 *Annual number of smears per women and percentage of women with at least one smear taken in a 3-year period in selected counties in Denmark around 1975 (2)*

County		Smear per women[a]	Percentage with at least one smear
Frederiksborg	Organized program, not coordinated with spontaneous activity	0.56	>72%[b]
Storstrøm	Organized program, coordinated with spontaneous activity	0.25	>81%[c]
Fyn	Only spontaneous activity	0.19	44%[d]

[a] Aged 20–59 years.
[b] Aged 25–54 years.
[c] Aged 30–50 years.
[d] Aged 25–49 years.

Table 2 *Average annual number of smears per woman aged 20–59 years in 1974/1975, percentage of economically active woman aged 20–59 years in 1976, and percentage of blue collar workers for the three areas defined by smear taking activity (2, 4)*

	Average annual number of smears per women aged 20–59 in 1974/1975	Percentage of economically active women aged 20–59 in 1976	Blue collar workers as percentage economically active women
Copenhagen	High[a]	70%	43%
High activity	0.31	68%	42%
Low activity	0.20	65%	43%

[a] Accurate figure not available due to special agreement for GPs in the Copenhagen municipality.

cervicis uteri, or as cancer uteri unspecified site with no diagnosis found in the Cancer Registry.

Cumulative Rates

Cumulative incidence rates per 1000 and mortality rates for each of the three definitions have been calculated for women aged 30–59 years for each of the 5-year periods 1943–1947, ... 1978–1982.

Multiplicative Poisson Models. Multiplicative Poisson models were used to estimate the effect of the organized screening programs. The models were fitted to the county-based data for the period 1963–1982, where both the incidence and mortality trends were decreasing for the country as such.

It is assumed in the Poisson model, that the observed number of cases d_{ij} in the subgroup ij (i = age, j = other factors to be studied in the analysis) follows a Poisson distribution with the expected number of cases $E(d_{ij}) = N_{ij}\,\lambda_{ij}$, where N_{ij} is the person years at risk experienced in the subgroup, and λ_{ij} is the age specific incidence in the subgroup. The models were fitted using GENSTAT (3). Excluded from this analysis were a small county with an organized program initiated already in 1962, and two counties which could not be classified by smear-taking activity in 1974/1975.

To estimate the effect of organized screening, each of the 456 cells defined by combinations of the six 5-year age groups 30–59 years, the four 5-year calendar periods 1963–1982, and the 19 counties was classified according to whether the women belonging to the cell: (*a*) had not been offered organized screening, (*b*) had been offered organized screening for the first time during the last 5 years, or (*c*) had been offered organized screening more than 5 years ago.

To control for the effect of the overall smear-taking activity, the 19 counties were furthermore classified into areas with: (*a*) high smear-taking activity (12 counties), (*b*) low smear-taking activity (six counties), or (*c*) the Copenhagen municipality (this area was put into a separate category due to initially high levels of both incidence and mortality). The grouping was based on the average number of smears per women aged 20–59 years in 1974/1975, as showed in Table 2.

The analysis was made for the incidence data and for the mortality data following definition 2.

RESULTS

Table 3 shows the number of incident cancer cases and the number of deaths following the three definitions given above. The true number of cases is expected to lie between the numbers estimated from definitions 2 and 3, respectively. The differences between these numbers are small after 1963, and only definition 2 has therefore been used in the further analysis. The cumulative rates for all Denmark are given in Fig. 1. The incidence of cervical cancer for women aged 30–59 years increased from 1943–1947 to 1958–1967 and decreased afterwards. A similar pattern is seen for the mortality data.

The final multiplicative Poisson model was for both the incidence and the mortality data:

$$\log \lambda_{ijke} = \alpha_{ij} + \beta_k + \gamma_e$$

where i = age (six groups), j = period (four groups), k = smear-taking activity (three groups), and e = offered screening (three groups). Table 4 shows the goodness of fit for the final model,

Table 3 *Annual number of incident cases and deaths from cervical cancer in Denmark for women aged 30–59 years*

	Incident cancer cases	Deaths Definition 1	Definition 2	Definition 3
1943–1947	450		180	222
1948–1952	505	142[a]	205	216
1953–1957	574	175	227	239
1958–1962	658	206	243	249
1963–1967	667	217	239	241
1968–1972	562	189	199	203
1973–1977	434	144	152	157
1978–1982	335	120	124	127

[a] 1951–1952 only.

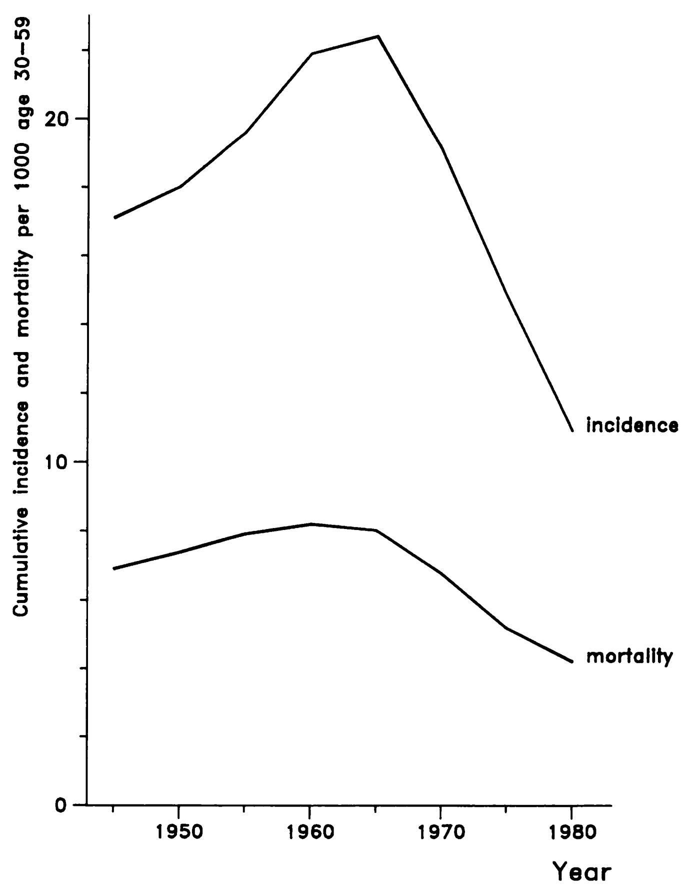

Fig. 1. Cumulative incidence and mortality per 1000 from cervical cancer for women aged 30–59 years in Denmark.

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Table 4 *Effect of organized screening programs and of smear-taking activity on incidence and mortality of cervical cancer as estimated in multiplicative Poisson models*

	Incidence	Mortality
Goodness of fit of final model		
Deviance[a]	65.8	75.3
DF	67	67
P	0.5	0.2
Test for exclusion of organized screening		
Deviance	87.9	33.0
DF	2	2
P	<0.001	<0.001
Relative risks and 95% confidence intervals		
No organized screening	1	1
Organized screening for 0–4 years	0.97 (0.89–1.05)	0.82 (0.70–0.95)
Organized screening for 5 or more years	0.67 (0.61–0.73)	0.68 (0.59–0.78)
Test for exclusion of smear-taking activity		
Deviance	206.6	83.6
DF	2	2
P	<0.001	<0.001
Relative risks and 95% confidence intervals		
Copenhagen	1	1
High activity	0.64 (0.61–0.68)	0.63 (0.57–0.69)
Low activity	0.70 (0.66–0.75)	0.66 (0.59–0.74)

[a] Deviance = −2 (log likelihood ratio).

the tests for the effect of organized screening and for the effect of smear-taking activity, and the estimated relative risks. The goodness of fit tests show that the model was well accepted for the incidence data with a *P* value of 0.5, and for the mortality data, where the *P* value was 0.2. There is an interaction between age and period in the final model because the declining trends in incidence and mortality have varied between the age groups.

The relative risk estimated in the model for the incidence of cervical cancer was 0.67 (95% CI, 0.61–0.73) for women who were offered organized screening more than 5 years ago compared to women not offered screening. The equivalently estimated relative risk for the mortality from cervical cancer was 0.68 (95% CI, 0.59–0.78). As expected, the relative risks for both the area with a high and for the area with a low overall smear-taking activity in 1974/1975 were below that of Copenhagen. Of importance is, however, that there was little difference between the areas with a high and the areas with a low overall smear-taking activity. The relative risks for the incidence were 0.64 and 0.70, respectively. The results of the analysis of incidence data are illustrated in Fig. 2, which shows the expected incidence 1963–1967, and the expected incidence 1978–1982 without and with organized screening, for the areas with a high overall smear-taking activity. The results of the analysis of mortality data are illustrated in Fig. 3 in the same way.

The analysis was redone with no grouping of the counties according to smear-taking activity, but with each of the 19 counties as a separate category. This analysis gave the same estimates for the effect of organized screening programs, as found in the earlier analysis.

DISCUSSION

The gradual incorporation of Pap smears into the health care systems has resulted in a high and predominantly spontaneous smear-taking activity in developed countries. We are therefore left with a widely used technology for which the benefits can be

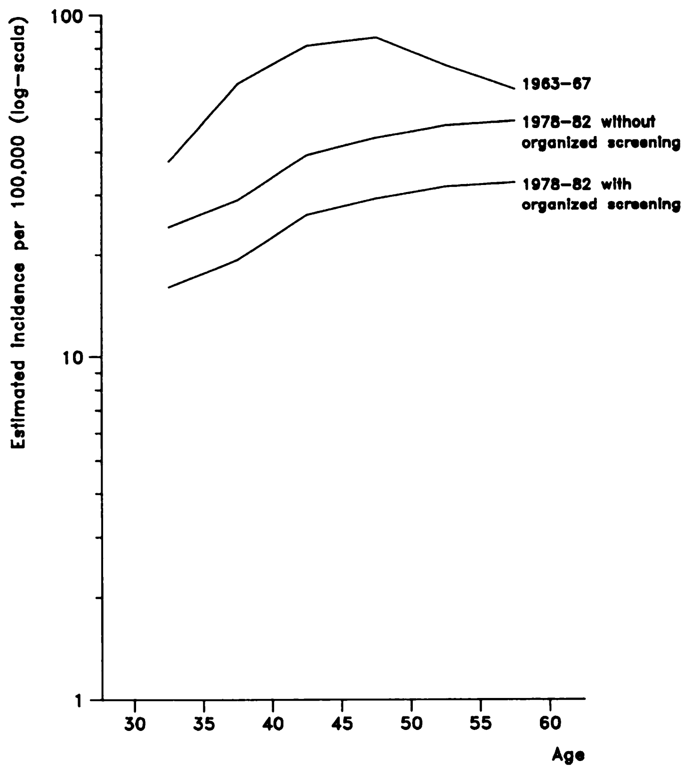

Fig. 2. Expected incidence of cervical cancer 1963–1967, and expected incidence of cervical cancer 1978–1982 without and with organized screening, in the areas with a high overall smear-taking activity, as estimated in the multiplicative Poisson model.

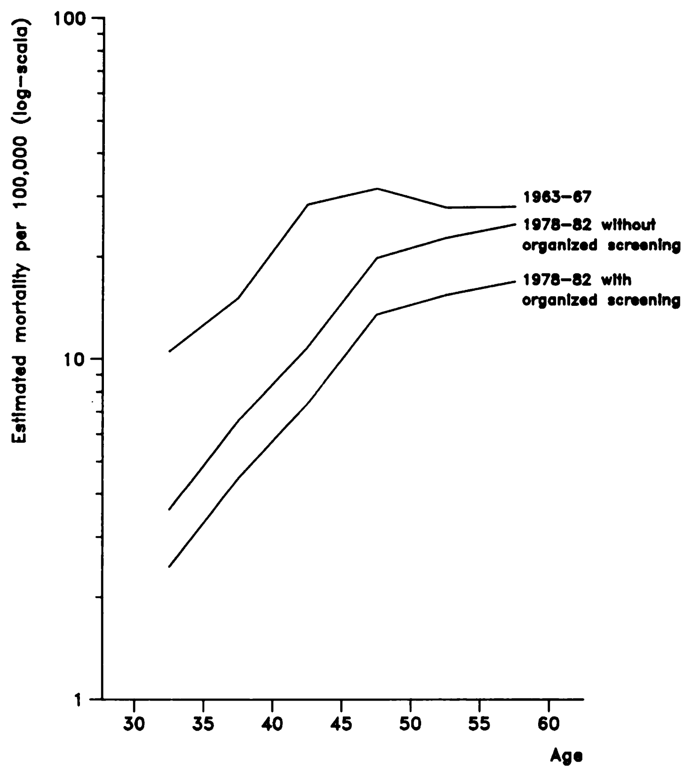

Fig. 3. Expected mortality of cervical cancer 1963–1967, and expected mortality of cervical cancer 1978–1982 without and with organized screening, in the areas with a high overall smear taking activity, as estimated in the multiplicative Poisson model.

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assessed only indirectly. Comparison of regional trends has been a main approach in these efforts (5).

From the mid 1960s to the late 1970s Hakama (6) found a rapid decrease in the incidence of cervical cancer in Iceland, Finland, and Sweden, where all women had been covered by organized screening programs; a less steep decrease in Denmark, where approximately 40% of women had been covered by organized programs, and an increasing trend in Norway, where only 5% of women had been covered by a program. An update of the Norwegian data (7) showed a slight decrease in the incidence of cervical cancer since 1974. Analyzing the mortality data on cervical cancer from the Nordic countries, Laara *et al.* (8) found the cumulative rates to have decreased by 84% between 1965 and 1982 in Iceland, and by only 11% in Norway.

In the present study, the approach for regional comparisons has been applied to county-specific incidence and mortality data. Advantage was taken of the fact that the available data allowed a separate characterization to be made of the screening situation in each individual cell of observations defined by age group, time period, and county. Furthermore, individual record linkage was used to overcome the incompleteness of mortality data, and the analysis covered a homogenous population as there are relatively small differences between regions in Denmark in the women's labour market participation and socioeconomic status, as seen in Table 2. Finally, incidence and mortality rates in Denmark are influenced only to a limited extent by the prevalence of hysterectomy (9).

For the incidence data, the study showed the relative risk of cervical cancer during the first 5 years after a screening program was introduced to be close to unity, $RR = 0.97$, when the base line was defined as women not offered organized screening. The lack of effect could be the result of two counteracting processes: treatment of precancerous lesions would reduce the number of invasive cancers, but the screening may itself increase the number of preclinical microinvasive lesions detected. The full effect of a screening program on the incidence is expected only to be seen after a certain latency period, here specified as 5 years or more, for which a statistically significant deficit was found with a relative risk of 0.67 (95% CI, 0.61–0.73).

For the mortality data, the risk was slightly reduced already during the first 5 years after introduction of a screening program, $RR = 0.82$, and after 5 years to the same level as for the incidence data, with a relative risk of 0.68 (95% CI, 0.59–0.78). The average 5-year survival rate for cervical cancer patients in the Nordic countries is close to 70% (10), and it is thus puzzling that the estimated effect of organized screening from 5 years after introduction of a program is found to be of the same order for the mortality data as for the incidence data. The final model does not, however, fit as well for the mortality data as for the incidence data, and the confidence interval for the estimated relative risk is broader.

Almost no differences were found in the relative risks for cervical cancer between areas with a high and a low overall smear-taking activity, when the existence of organized screening programs was included as a variable in the analysis. This is not surprising, as the same overall activity level is found in counties with very different percentages of women screened, as illustrated in Table 1.

The study thus showed a statistically significant effect of organized screening in reducing both the incidence and the mortality of cervical cancer. The level of overall smear-taking activity was found to be of limited importance, when organized screening was taken into account. The efficiency of the prevention against cervical cancer is thus indicated to be improved by introduction of organized screening with personal invitations, whereas the efficiency is not necessarily improved by adding more resources.

It was demonstrated by the International Agency for Research on Cancer working group (11), that the protection against cervical cancer remains high for the first 3 years after the last negative smear, and 3 year rounds are thus acceptable from the point of view of the individual woman. At present, organized screening programs only exist in 6 out of the 22 counties in Denmark. Nevertheless, a total of 631,000 Pap smears are taken per year, where only 523,000 Pap smears would be needed to run an organized screening program covering all women in the age-group 23–75 years every third year (1). Less resources are therefore required when the smear taking activity is organized. Computerized pathology registration systems offer a tool for integration of an organized screening program with the ongoing spontaneous smear-taking activity. Using such systems, participation rates above 90% have been obtained by some counties in Denmark (12).

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