ORIGINAL ARTICLE

What happens when organization of cervical cancer screening is delayed or stopped?

Elsebeth Lynge, Lene Bjørk Clausen, Romain Guignard and Paul Poll

J Med Screen 2006;**13**:41–46

Objectives Many countries rely on opportunistic screening, and data on its effectiveness are asked for. We assessed the impact on cervical cancer incidence and mortality of opportunistic screening compared with organized screening.

Setting Women aged 30–64 in Denmark, 1973–2002; 16 counties with different screening strategies.

Methods Cumulative incidence and mortality rates for women aged 30–64 by county. Poisson regression of incidence and mortality rates by age, calendar period and county. Interaction between type of county and calendar period measured the difference between counties with screening organized early versus late in time.

Results A statistically significant interaction was found between type of county and calendar period ($P=0.0151$) for cervical cancer incidence, but not for cervical cancer mortality ($P=0.9593$). The interaction terms were not statistically significant when a comparison was made between a single county in which an organized programme was interrupted for an 11-year period and other counties. There was, however, a statistically significant increased incidence and mortality rates at the restart of the organized programme.

Conclusion Organization of cervical cancer screening accelerated the decline in cervical cancer incidence, compared with the trend in areas relying on opportunistic screening. No impact could be measured of the screening organization on cervical cancer mortality. A decade long stop of an organized screening programme was associated with a temporary increase in cervical cancer incidence and mortality. Coverage remains a key quality indicator in the ongoing modernization of screening technology.

See end of article for authors' affiliations

Correspondence to: Professor E Lynge, Institute of Public Health, University of Copenhagen, Øster Farigmagsgade 5, opg. B, Postboks 2099, DK 1014 København K, Denmark; elsebeth@pubhealth.ku.dk

Accepted for publication 10 January 2006

INTRODUCTION

Many countries rely on opportunistic screening for control of cervical cancer, and further investigation of the effectiveness of opportunistic screening is warranted.[1] Denmark is a small and homogeneous country with a total population of 5.4 million. Pap smears started to be used in the late 1950s, and Denmark has experienced a decline over time in both cervical cancer incidence and mortality (Figure 1). Considerable differences have nevertheless existed across Denmark in the organization of cervical cancer screening, as health care is the responsibility of 16 counties. The term 'an organized screening programme' is used in the following for a set-up with personal invitation to screening of all women in the target age groups at regular time intervals and with all services provided free of charge. The term 'opportunistic screening' covers use of Pap smears in asymptomatic women outside the schedule of an organized programme, for example as part of a consultation for prescription of oral contraceptives. The early programmes targeted women aged 30–50 years, every fifth year. Over time, the age range was expanded and the screening interval shortened. National guidelines were issued in 1986 recommending screening of women aged 23–59 years, every third year.[2]

The first cervical cancer screening pilot programme was set up in a small county in 1962, followed by the implementation of programmes in three larger counties in 1967/68. However, 30 years passed before screening was organized in the last county in 1996[3–6] (Figure 2). The counties gradually adopted the recommended age range of 23–59 years, but even today one county still only invites women aged 25–45. In addition to the organized programmes, opportunistic screening activity expanded after 1969 when all smears started to be provided free of charge.[4] The screening coverage varied considerably between counties with organized programmes and counties with opportunistic screening, as illustrated with data from the mid-1980s from Bornholm and Vestsjælland counties, respectively,[7] (Table 1). Organized screening ensured a high coverage of women aged 30–50, whereas opportunistic screening lead to a high coverage of women aged 15–22, which was actually below the age range recommended for screening in the national guidelines. An effort was made in the 1990s to integrate the opportunistic smears into the organized programmes.[8]

A particular development took place in Storstrøm county. An organized programme targeting women aged 30–50 started here in 1967 in the southern part of the canty, and in 1972 in the northern part of the county. The programme was, however, stopped by the end of 1982, and it took another 11 years before the programme was restarted in 1994. Stopping the organized programme had little impact on the number of smears used in the county. It had, however, a considerable impact on the screening coverage in the different age groups, where an opportunistic pattern developed after the organized programme stopped (Table 1).

The purpose of cervical cancer screening is to reduce the mortality from the disease and to reduce the incidence of invasive cancer. Given the wide variation in the implementation of organized screening across Danish counties, we have therefore tested the following hypotheses. First, during the past 30 years the incidence and mortality from cervical cancer decreased more in counties where screening was organized early than in counties where screening was organized late. Second, the 11 years' gap in the organized screening programme in Storstrøm county affected the trend in both incidence and mortality. To test these hypotheses, we have taken advantage of the nationwide cancer registration in Denmark.

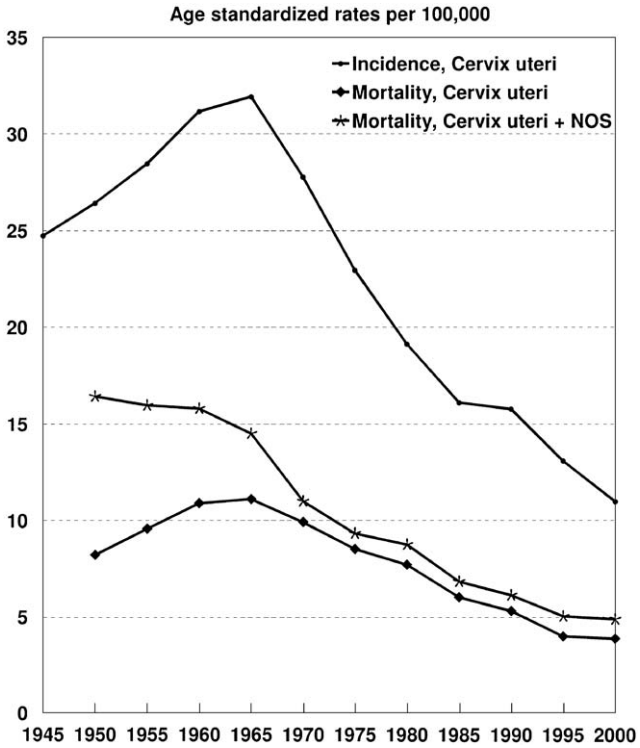

Figure 1 Age standardized rates per 100,000 (World Standard Population) for cervical cancer incidence and mortality in Denmark, 1943–2002. NOS 'not otherwise specified'

MATERIALS AND METHODS

A nationwide registration of both incident cancer cases and causes of death started in Denmark in 1943. Incident cancer cases have been coded with a modified version of International Classification of Disease (ICD)-7, where cancer of the cervix uteri is 171. Causes of death have from 1969–93 been coded according to ICD-8 where cancer of the cervix uteri is 180, and from 1994 onwards according to ICD-10 where cancer of the cervix uteri is C53. In 1970 Denmark was divided into 16 administrative areas, the municipalities of Copenhagen and Frederiksberg, and 14 counties. We have used the term 'county' for all 16 areas in this paper, calling the municipality of Copenhagen 'Copenhagen m' and the county of Copenhagen 'Copenhagen c'. For each county we retrieved from the two registers the number of cases by five-year age groups (30–34, 35–39, … 60–64), and five-year calendar periods (1973–77, 1978–82, … 1998–2002); mortality data only through 1999. Person years at risk were estimated from the population data

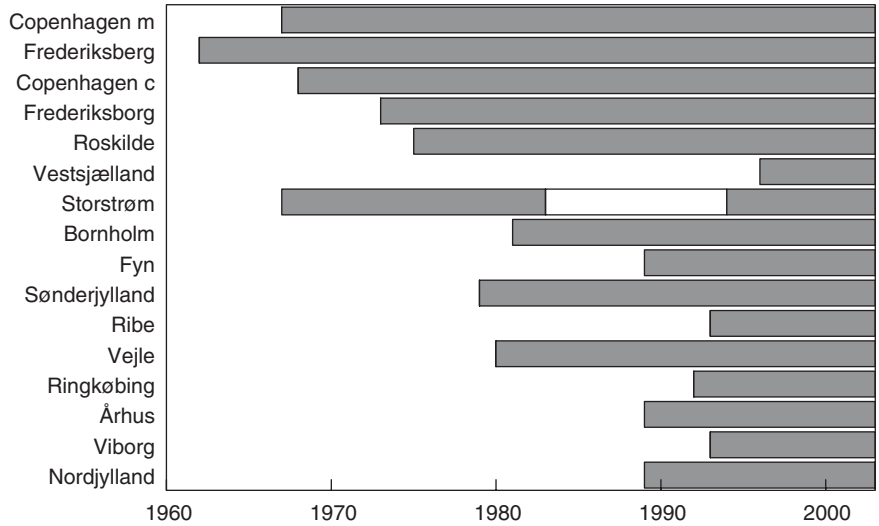

Figure 2 Year for start of organized cervical cancer screening in counties in Denmark

Table 1 Cervical smear coverage* of women by age and screening organization in selected Danish counties

Type of screening	County	Period†	Coverage (%) 15–22 years	23–30 years	30–50 years	50–60 years	% Women with >1 smear	Number of smears
Organized	Bornholm	1985–89	23%	83%	88%	59%	16%	13,716
Opportunistic	Vestsjælland	1985–89	53%	83%	69%	38%	24%	95,371
Organized	Storstrøm	1979–82	21%	54%	91%	22%	16%	70,492
Opportunistic	Storstrøm	1985–89	57%	82%	66%	33%	17%	72,437

*Coverage is a percentage of women in the target population with at least one smear during the studied period
†All periods of similar length, 3.6 years

available by sex, age and county from Statistics Denmark (Table 2).

To test the first hypothesis, we grouped together the five counties with organized screening programmes starting early in our observation period 1973–2002. These counties were Frederiksborg, Roskilde, Bornholm, Sønderjylland and Vejle. Similarly we grouped together the seven countries with organized screening programmes starting late in the period. These were Vestsjælland, Fyn, Ribe, Ringkøbing, Århus, Viborg and Nordjylland. We used Poisson regression with log-linear link function to test for an interaction between county type and calendar period. A statistically significant interaction term means that the two types of counties have experienced different trends over time. Poisson regression was also used to estimate the relative risks for late versus early starting counties for each five-year period. We finally calculated the expected number of cervical cancer cases in the late starting counties, given that the population here had been under the risk of the early starting counties.

To test the second hypothesis, we compared the trends in incidence and mortality in Storstrøm after 1983, where the programme was stopped, with the trends in counties with ongoing programmes also started well before 1983. These counties were Copenhagen m, Frederiksberg, Copenhagen c, Frederiksborg and Roskilde. We used Poisson regression analysis to test for an interaction between county type and calendar period. We also used Poisson regression to estimate the relative risks for Storstrøm versus continuing programmes for each five-year period.

RESULTS

The counties with an organized screening programme starting in 1973 or early thereafter had a rapid decline in the cumulative incidence rate for women aged 30–64 in the beginning of the period and a stabilization thereafter. The counties starting late had an almost linear decline in the cumulative incidence rate throughout the 30-year period (Figure 3). For the incidence data, the Poisson regression analysis showed a statistically significant interaction term between type of county and calendar period ($P=0.0151$). The interaction term was, however, not statistically significant for the mortality data ($P=0.9593$). The relative risks for each five-year period showed a similar pattern, (Table 3). During the years 1973–2002, in total 5501 cases of cervical cancer were diagnosed in women aged 30–64 in the late starting counties. If women in the late starting counties had been under the same risk as women in the early starting counties, only 4718 cases of cervical cancer would have occurred.

The cumulative incidence rate for the counties with programmes well established before 1982 and uninterrupted until 2002 showed a rapid decline up until the early 1980s, followed by a relatively stable level. In Storstrøm county, on the other hand, the decline in cumulative incidence stopped with the interruption of the organized programme and was followed by an increase with the restart of the programme in 1994 (Figure 4). The interaction term for the period 1983–2002 between type of county and calendar period in the Poisson regression analysis was not statistically significant for incidence ($P=0.3749$) as well as for mortality

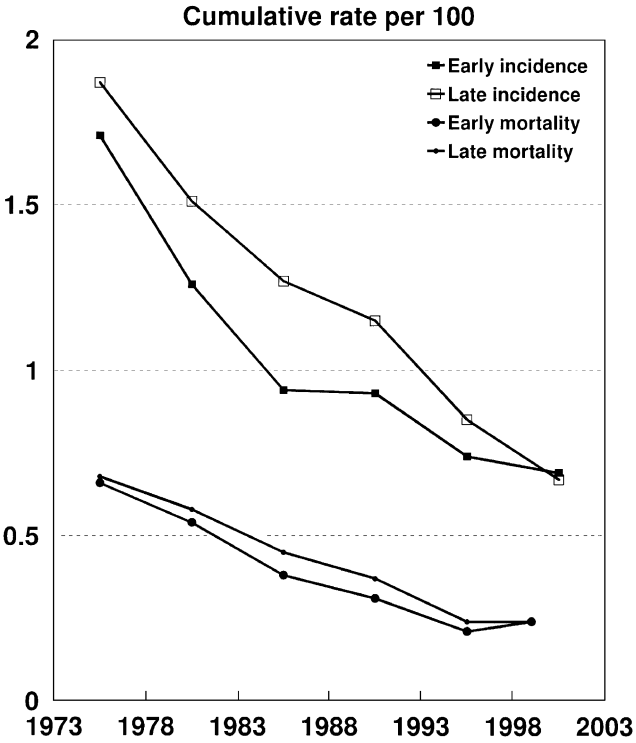

Figure 3 Cumulative rates per 100 of cervical cancer incidence in 1973–2002 for women aged 30–64 for counties starting organized screening in 1973 or shortly thereafter (early) and for counties starting organized screening later (late)

Table 2 Number of women aged 30–64 in 1990, person years at risk 1973–2002, incident cases of cervical cancer 1973–2002, and deaths from cervical cancer 1973–1999 by county in Denmark

County	Number of women (1990)	Person years at risk 1973–2002	Incident cases 1973–2002	Deaths 1973–1999
Copenhagen m	89,380	3,019,454	1157	436
Frederiksberg	18,470	606,584	224	75
Copenhagen c	146,999	4,466,130	1229	336
Frederiksborg	83,441	2,424,184	587	149
Roskilde	52,995	1,517,185	431	128
Vestsjælland	63,198	1,873,667	651	224
Storstrøms	58,209	1,740,100	526	173
Bornholm	10,101	304,069	93	36
Fyns	101,206	3,018,627	1118	320
Sønderjylland	55,282	1,628,566	484	178
Ribe	47,073	1,379,752	455	135
Vejle	72,566	2,172,123	652	222
Ringkøbing	57,328	1,680,861	429	136
Århus	130,840	3,876,693	1348	375
Viborg	49,140	1,466,974	463	163
Nordjylland	105,424	3,146,076	1037	344

Table 3 Cumulative rates for women aged 30–64 for cervical cancer incidence and mortality in Denmark 1973–2002 for groups of counties starting organized screening programmes either late or early in this period, and relative risks for late versus early

		Counties with organized screening started		Relative risk late/early: Poisson regression	
	Period	Late	Early	RR	95%CI
Incidence					
	1973–77	1.87	1.71	1.10	0.99–1.22
	1978–82	1.51	1.26	1.21	1.08–1.35
	1983–87	1.27	0.94	1.35	1.19–1.52
	1988–92	1.15	0.93	1.23	1.09–1.39
	1993–97	0.85	0.74	1.16	1.01–1.33
	1998–02	0.67	0.69	0.98	0.85–1.12
Mortality					
	1973–77	0.68	0.66	1.05	0.88–1.24
	1978–82	0.58	0.54	1.09	0.91–1.30
	1983–87	0.45	0.38	1.16	0.94–1.43
	1988–92	0.37	0.31	1.15	0.92–1.43
	1993–97	0.24	0.21	1.15	0.89–1.49
	1998–99	0.24	0.24	1.05	0.71–1.53

Table 4 Cumulative rates for women aged 30–64 for cervical cancer incidence and mortality in Denmark 1973–2002 for Storstrøm county and for counties with continued organized screening programmes, and relative risks for Storstrøm versus continued screening

		County		Relative risk Storstrøm/Continued screening: Poisson regression	
	Period	Storstrøm	Continued	RR	95%CI
Incidence					
	1973–77	1.53	1.68	0.90	0.75–1.10
	1978–82	0.98	1.23	0.80	0.63–1.01
	1983–87	0.97	0.89	1.07	0.84–1.36
	1988–92	1.01	1.00	1.05	0.84–1.32
	1993–97	1.13	0.87	1.31	1.05–1.62
	1998–02	0.78	0.80	0.97	0.76–1.25
Mortality					
	1973–77	0.48	0.61	0.79	0.56–1.11
	1978–82	0.46	0.54	0.85	0.60–1.21
	1983–87	0.41	0.36	1.12	0.77–1.63
	1988–92	0.35	0.30	1.21	0.81–1.82
	1993–97	0.38	0.25	1.50	1.02–2.22
	1998–99	0.27	0.20	1.88	0.93–3.82

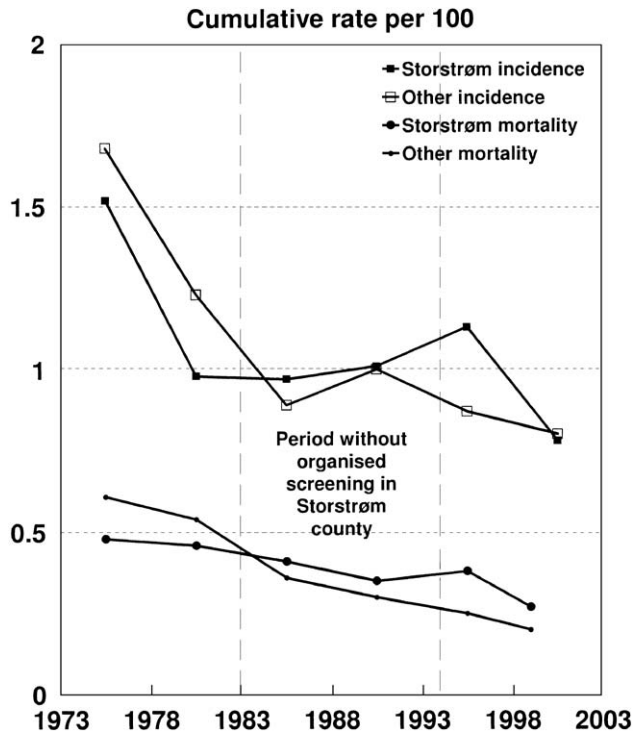

Figure 4 Cumulative rates per 100 for cervical cancer incidence and mortality 1973–2002 for women aged 30–64 for Storstrøm county and for other counties with long-term operating organized screening programmes in 1982

(*P* = 0.6786). This is hardly surprising as only the rate for one of the four time periods in Storstrøm county differed from the general pattern. The relative risks for each five-year period showed, however, statistically significant elevated risks for Storstrøm county coinciding with the restart of the programme in 1994 (Table 4). Women aged 30–34 and 35–39 years in 1993–97 in Storstrøm county came mainly from the generations first targeted by organized screening when the programme restarted in 1994. This was reflected in the number of incident cases, which in these ages increased from 22 in 1988–92 to 40 in 1993–98 and decreased again to 21 in 1998–2002. The deaths occurred primarily in the older ages both before, during and after the stop of the organized programme.

DISCUSSION

We found that organization of cervical cancer screening accelerated the decline in cervical cancer incidence compared with the trend in areas relying on opportunistic screening. We found no impact of the screening organization on cervical cancer mortality, but it should be taken into account that the numbers were small and that the five-year survival rate for cervical cancer patients is 70%.[9] We also found that a decade long gap in an organized screening programme was associated with a temporary increase in cervical cancer incidence and mortality.

It is important to note that opportunistic screening was not cheaper than organized screening. In total, 70,492 smears were taken in one round of the organized screening programme in Storstrøm county in 1979–82. Some years after the stop of the organized programme, 72,437 smears were taken during a period of similar length. The coverage in Vestsjælland county in 1985–89, where screening had never been organized, was very similar to the coverage in Storstrøm county after the organized programme was stopped, while the proportion of women with more than one smear was higher. This shows that opportunistic screening was more expensive to run than organized screening. The fact that the coverage pattern in Storstrøm county 3–6 years after the stop of the organized programme resembled the coverage pattern in Vestsjælland county shows that 16 years of practice with an organized screening programme had long-term educational impact neither on the targeted women nor on their general practitioners. Organization of screening should therefore be a continuous activity.

The restart of the programme in Storstrøm county was associated with a prevalence peak concentrated to the

generations entering the programme for the first time at the age of 30–39 years. The increase in mortality was concentrated in the older age groups, and it started at the end of the programme-free period, although not reaching statistical significance at that time.

Even within an organized programme, a certain proportion of smears will be taken outside the recommended age group and screening interval. In 2000 these excess smears were estimated for a three-year period per 1000 women to be 140 in Sweden, 205 in Denmark, and 228 in Finland.[10] In Denmark, invitation to screening is postponed if a smear is already registered in the pathology system.[8] In Copenhagen in 2000, smears taken at a shorter interval than three years in the target age group 23–59 years in women without an abnormal smear during the past 10 years constituted 34% of all smears in this age group. The programme manager then started to send lists of these excess smears to general practitioners, and the percentage had decreased to 22% in 2004.[11]

The common nationwide cancer registration in Denmark made this study possible, and the comparison of outcome of different screening policies within an otherwise homogenous country was a strength of this study. A disadvantage was the relatively small number of deaths from cervical cancer within each county.

Data from Sweden showed that the probability of detecting carcinoma *in situ* was slightly higher for opportunistic smears than that for smears taken in organized programmes, and it was claimed that the dogma that organized screening is more efficient than opportunistic screening needed to be reconsidered.[12] However, not all cases of carcinoma *in situ* progress to invasive cancer, and finding more carcinoma *in situ* lesions therefore does not necessarily lead to a reduction in the incidence of invasive cervical cancer and in the mortality from the disease. Data from Finland showed that women with a previous smear in the organized screening programme had an odds ratio of 0.38 for later development of invasive cervical cancer compared with unscreened women, whereas women with a previous spontaneous smear had a higher odds ratio of 0.82.[13]

In Denmark, by far the majority of both opportunistic smears and smears in organized programmes are taken by general practitioners. Many of the opportunistic smears have furthermore been examined under the responsibility of the same pathologists responsible for the organized smears. It is therefore unlikely that the quality of the two types of smears have differed. Thus the reason for the more rapid decline in the incidence of cervical cancer under the organized than under the opportunistic regime is primarily the difference in coverage. About 90% of 30–50 years old women have been covered in the organized programmes, compared with only about 66% in the opportunistic setting. This pattern started to emerge early after organization of screening in Denmark.[14] The importance of coverage is also clearly illustrated in the drastic decline seen in the incidence of invasive cervical cancer in England after introduction of the national call–recall system in 1987.[15,16]

Cervical cancer screening is at present undergoing technical improvements. The proportion of unsatisfactory smears is reduced by the use of liquid-based cytology.[17] Many women with atypical smears can be spared colposcopy by the use of supplementary human papilloma virus (HPV)-DNA testing.[18] Studies are ongoing to determine whether testing for high-risk HPV types should supplement conventional cytology,[19] or replace it as the primary test.[20] The present study shows that whatever the test being used, a key factor in the improvement of cervical cancer screening is the coverage of the high-risk age groups, and this indicator should be monitored in all screening programmes.[8]

In parts of Denmark, opportunistic screening was for a long time the preferred approach to cervical cancer control. But the number of smears used in the opportunistic setting exceeded the number of smears needed for an organized programme, and close to 800 Danish women could have been spared the fate of becoming cervical cancer patients had organized screening programmes been implemented nationwide at an earlier point in time. Denmark learned the lesson slowly, but the visibility of the costs should enable other countries to avoid similar mistakes.

ACKNOWLEDGEMENTS

Romain Guignard spent an internship at the University of Copenhagen, financially supported by INSERM, France. Christian Pipper gave valuable advice on the analysis.

Authors' affiliations
Elsebeth Lynge, *Professor*, Institute of Public Health, University of Copenhagen, Denmark.
Lene Bjørk Clausen, *Data Manager*, Institute of Public Health, University of Copenhagen, Denmark.
Romain Guignard, *Statistician*, Institute of Public Health, University of Copenhagen, Denmark.
Paul Poll, *MD*, Institute of Public Health, University of Copenhagen, Denmark.

REFERENCES

1 Bray F, Loos AH, McCarron P, *et al.* Trends in cervical squamous cell carcinoma incidence in 13 European countries: changing risk and the effects of screening. *Cancer Epidemiol Biomarkers Prev* 2005;**14**:677–86
2 Sundhedsstyrelsen. *Prophylactic Examinations of the Cervix Uteri*. København: Sundhedsstyrelsen, 1986 (in Danish)
3 Lynge E. Regional differences in smear-taking and cervical cancer incidence in Denmark 1943–1982. *Ugeskr Læger* 1984;**146**: 3477–3482 (in Danish, abstract in English)
4 Lynge E, Arffmann E, Hansen KC, *et al.* The status for prophylactic examinations for cancer of the uterine cervix in Denmark in 1991. *Ugeskr Læger* 1992;**154**:1339–42 (in Danish, abstract in English)
5 Lynge E, Arffmann A, Erbs K, *et al.* Cervical cancer screening in Denmark: status. *Ugeskr Læger* 1994;**156**:471–3 (in Danish, abstract in English)
6 Lynge E, Arffmann A, Behnfeld L, *et al.* Cervical cancer screening in Denmark: status in 1995 and plans for 1996. *Ugeskr Læger* 1996;**158**:4916–19 (in Danish)
7 Lynge E, Poll P, Larsen J, *et al.* Screening for cancer of the uterine cervix in three Danish counties during the period 1979–1989. *Ugeskr Læger* 1992;**154**:1335–8 (in Danish, abstract in English)
8 Coleman D, Day N, Douglas G, *et al.* European guidelines for quality assurance in cervical cancer screening. *Eur J Cancer* 1993;**29A**(Suppl. 4):1–38
9 Sundhedsstyrelsen. *Cancer in Denmark*. København: Sundhedsstyrelsen, 2005 (in Danish)
10 van Ballegooijen M, van den Akker-van Merle E, Parnick J, *et al.* Overview of important cervical cancer screening process values in European Union (EU) countries, and tentative predictions of the corresponding effectiveness and cost-effectiveness. *Eur J Cancer* 2000;**36**:2177–88
11 Junge J. *Cervical cancer screening in Copenhagen and Frederiksberg*. København: H:S Hvidovre Hospital, 2005 (in Danish)
12 Gustafsson L, Sparén P, Gustafsson M, *et al.* Efficiency of organised and opportunistic cytological screening for cancer *in situ* of the cervix. *Br J Cancer* 1995;**72**:498–505
13 Nieminen P, Kallio M, Antilla A, Hakama M. Organised vs. spontaneous pap-smear screening for cervical cancer: a case-control study. *Int J Cancer* 1999;**83**:55–8
14 Lynge E. Regional trends in incidence of cervical cancer in Denmark in relation to local smear-taking activity. *Int J Epidemiol* 1983;**12**: 405–13

15 Quinn M, Babb P, Jones J, Allen E. Effect of screening on incidence of and mortality from cancer of cervix in England: evaluation based on routinely collected statistics. *BMJ* 1999;**318**:904–8
16 Peto J, Gilham C, Fletcher O, Matthews FE. The cervical cancer epidemic that screening had prevented in the UK. *Lancet* 2004; **364**:249–56
17 Karnon J, Peters J, Platt J, *et al.* Liquid-based cytology in cervical screening: an updated rapid and systematic review and economic analysis. *Health Technol Assess* 2004;**8**:1–78
18 Schiffmann M, Solomon D. Findings to date from the ASCUS-LSIL Triage Study (ALTS). *Arch Pathol Lab Med* 2003;**127**:946–9
19 Bulkmans NW, Rozendaal L, Snijders PJ, *et al.* POBASCAM, a population-based randomised controlled trial for implementation of high-risk HPV testing in cervical screening: design, methods and baseline data of 44,102 women. *Int J Cancer* 2004;**110**:94–101
20 Kotaniemi-Talonen L, Nieminen P, Anttila A, *et al.* Routine cervical screening with primary HPV testing and cytology triage protocol in a randomised setting. *Br J Cancer* 2005;**93**:862–7