Screening for cervical intraepithelial neoplasia in north east Scotland shows fall in incidence and mortality from invasive cancer with concomitant rise in preinvasive disease

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Abstract

***Objective*—To assess the effect of screening for cervical intraepithelial neoplasia on the incidence of and mortality from invasive squamous cell carcinoma of cervix in north east Scotland and to discover why cases of invasive cancer still occur.**

***Design*—(*a*) Analysis of data on cases of cervical intraepithelial neoplasia obtained from the cytology data bank; (*b*) analysis of data on 612 women presenting with invasive squamous cancer during 1968-91, obtained from cancer registry and hospital records; (*c*) analysis of death rates obtained from the registrar general's (Scotland) annual reports, the Information Services Division of the Home and Health Department (Scotland), and local records for 1974-91; (*d*) case-control studies on 282 cases of invasive cancer and 108 deaths which occurred in 1982-91. Cases were matched with two controls both for age and for having a negative smear test result at the time of presentation of the case.**

***Setting*—North east Scotland (Grampian region, Orkney, and Shetland).**

***Subjects*—Women (n=306 608) who had had cervical smear tests between 1960 and 1991.**

***Results*—There had been a substantial increase in cases of cervical intraepithelial neoplasia grade III since 1982. The incidence of invasive cancer has fallen since the start of screening in 1960, the fall occurring mainly in the well screened age group 40-69 years. There was a rise in women aged under 40 and over 70. Women with invasive disease seen between 1982 and 1991 mostly presented at stage I. Of these, half were unscreened, one third were poorly screened, 11% were found in retrospect to have had abnormal cells, 3% had recurrence of disease after treatment for cervical intraepithelial neoplasia grade III, and 3% were lost to follow up. Death rates had fallen, most noticeably in women aged 45-64, who had had the opportunity to be screened and rescreened. There was a disturbing rise in deaths among women under 45. Most deaths (65%) occurred in unscreened women. Case-control studies showed that the longer the time and absence of a smear test before presentation the higher was the risk of invasive cancer and of death.**

***Conclusions*—Screening has been effective in reducing the incidence of and mortality from cervical cancer in north east Scotland. Most cases and deaths occurred in unscreened women or in those who had had few smears at long intervals. An increase in cases of cervical intraepithelial neoplasia grade III in women screened for the first time occurred during 1982-91.**

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Introduction

Deaths from cervical cancer have declined throughout Scotland.[1] The standardised mortality ratio for cervical cancer in the Grampian region (85)[2] is lower than in the rest of Scotland. In England and Wales there has been a fall in death rates in women aged over 45 but a rise in younger women.[3]

Systematic screening for preclinical cervical cancer started in Aberdeen city in 1960[4] with help from general practitioners, practice by practice. It was directed at married women between 25 and 60 years of age—the group at highest risk of invasive disease at that time.[5] Women were identified by surname, maiden name, mother's surname, and date of birth. Since 1989, when computerised call and recall became available, the community health index has been used for identification. Both methods allowed the women screened to be counted, as compared with only numbers of smears. Women who have had first smears outside the area have been readily identifiable since 1989. The contraceptive pill has been widely prescribed in the Grampian region since 1970.

This study was undertaken in north east Scotland because of the highly screened population, length of records, and continual appraisal of efficacy. In 1992 only 8% of women aged 21-60 were unscreened (Grampian Health Board's Northern Computing Services Consortium, unpublished data).

Population and methods

The study population was drawn from all women whose smears were interpreted in the cytology laboratory of Aberdeen University's pathology department between 1960 and 1992. It covered the Grampian region, Orkney, and Shetland. In the study period the female population aged over 15 increased from 192 368 (1961 census) to 227 000 (1989 estimate). The population changed from a predominantly older one to a younger one. Between 1974 and 1989 a boom in the oil industry in the area led to a 28% increase in the female population aged 20-39 years and a 38% increase in the male population in the same age group. There are now more people under 40 than over 40.

CERVICAL INTRAEPITHELIAL NEOPLASIA

Detection rates of cervical intraepithelial neoplasia grade III in women screened for the first time (see fig 1) were calculated as a percentage of all women screened for the first time in each year.

INVASIVE SQUAMOUS CANCER

The incidence of invasive squamous cell carcinoma

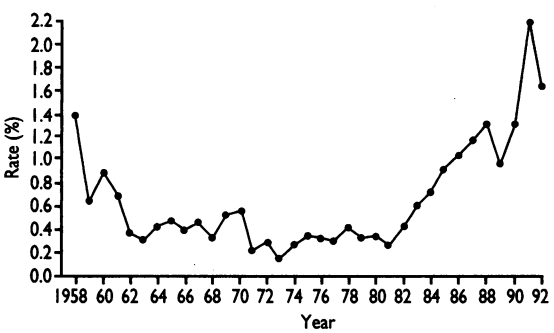

FIG 1—*Detection rates of cervical intraepithelial neoplasia grade III in Grampian region during 1958-92. Plots are percentages of women having first smear tests in each year*

of the cervix was calculated per 100 000 women aged over 20 between 1968 and 1991 by using the nearest census figures and, after 1975, the annual figures of population by age from the Information Services Division of the Scottish Health Service. To assess the change in presentation over time 612 cases (1968-91) were divided into two 11 year periods and rates of presentation calculated by age (see fig 2).

To assess the screening history and disease stage the records of 282 cases that presented in 1982-91 were obtained from hospital records and the cytopathology database. Previous cervical smears were available for review. The 282 patients were divided into screened, screen detected cases, and unscreened (see table I).

Screened women were those who had had one or more previously negative smears but not including the smear at the time of presentation with symptoms.

Screen detected women were those who had no known signs or symptoms of the disease when the current routine smear was taken and found to be abnormal. In these women invasive disease was found on biopsy. Patients may have had previous smears or may not; if they had they were negative on review. These were invasive cases detected by screening.

Unscreened women were those who had never had a smear taken before the current one at the time of presentation with the disease.

The three groups are presented by disease stage. The previous screening history of all 282 cases was examined. Reasons for being unscreened were identified and, if screened, for the disease developing. Age at presentation was related to disease stage and expressed as a percentage of the total 282 cases (see fig 3).

To ascertain why so many cases in this well screened area were completely unscreened, 26 women were selected because they were well after treatment and their general practitioners thought it was appropriate to speak to them.

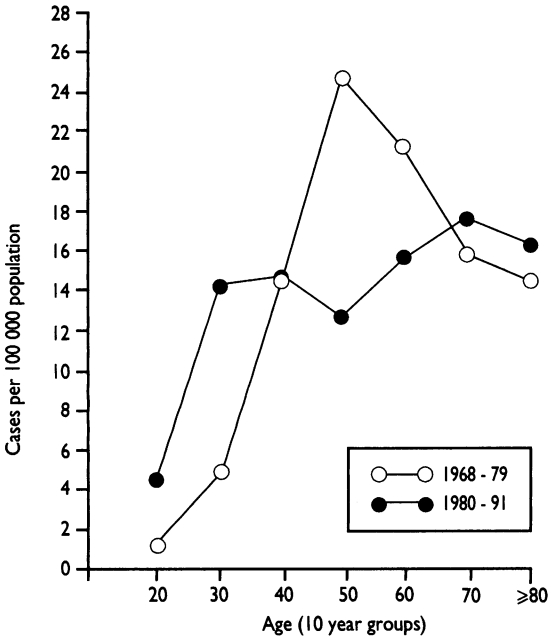

FIG 2—*Ages of women presenting with invasive squamous cell carcinoma of cervix in north east Scotland plus Orkney and Shetland in 1968-79 and 1980-91 (612 cases)*

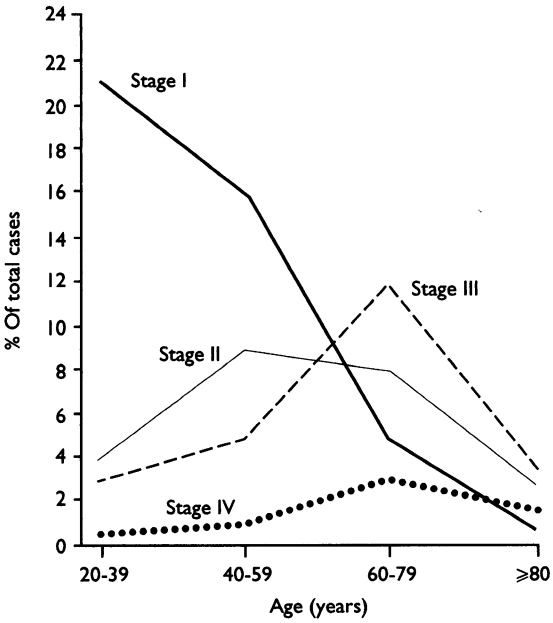

FIG 3—*Distribution of disease stages at various ages among women who presented with invasive squamous cell carcinoma of cervix in 1982-91 (282 cases)*

TABLE I—*Screening status of 282 patients who presented with invasive squamous cell carcinoma of cervix in 1982-91. Figures are numbers (percentages) of patients*

Screening status at presentation	Disease stage				Total
	I	II	III	IV	
Screened	45 (36)	24 (35)	22 (31)	3 (18)	94 (33)
Screen detected	52 (42)	7 (10)	3 (4)	1 (6)	63 (22)
Unscreened	27 (22)	38 (55)	47 (65)	13 (76)	125 (44)
Total	124 (44)	69 (24)	72 (26)	17 (6)	282 (100)

Trend: $\chi^2_1 = 21{\cdot}01$; $P < 0{\cdot}001$.

TABLE II—*Case-control study of time from last negative smear test result to date of presentation with invasive squamous cell carcinoma of cervix during 1982-91. Figures are numbers (percentages) of women*

	Time interval (months)				No previous negative smear
	≤36	37-72	73-108	≥109	
Cases (n=282)	40 (14)	37 (13)	8 (3)	42 (15)	155 (55)
Controls (n=564)	130 (23)	180 (32)	34 (6)	68 (12)	152 (27)
Odds ratio (95% confidence interval)	1·00	0·67 (0·39 to 1·14)	0·60 (0·24 to 1·48)	2·01 (1·15 to 3·50)	3·31 (2·14 to 5·18)

TABLE III—*Case control study of number of smear tests before presentation with invasive squamous cell carcinoma of cervix during 1982-91. Figures are numbers (percentages) of women*

	No of smears				
	1-3	4-6	7-9	≥10	0
Cases (n=282)	96 (34)	28 (10)	14 (5)	6 (2)	138 (49)
Controls (n=564)	243 (43)	130 (23)	51 (9)	17 (3)	123 (22)
Odds ratio (95% confidence interval)	1·00	0·55 (0·33 to 0·90)	0·69 (0·35 to 1·37)	0·89 (0·28 to 2·47)	2·84 (2·00 to 4·05)

MORTALITY

Between 1974 and 1991, 308 women died of squamous cell carcinoma of the cervix. The fall in

TABLE IV—*Case-control study of parity among women presenting with squamous cell carcinoma of cervix during 1982-91. Figures are numbers (percentages) of women*

	No of pregnancies						
	0	1	2	3	4	≥5	Not known
Cases (n=282)	23 (8)	51 (18)	59 (21)	56 (20)	31 (11)	59 (21)	3 (1)
Controls (n=564)	73 (13)	85 (15)	175 (31)	113 (20)	56 (10)	39 (7)	23 (4)
Odds ratio (95% confidence interval)	1·00	1·90 (1·02 to 3·56)	1·07 (0·59 to 1·93)	1·57 (0·86 to 2·89)	1·76 (0·88 to 3·51)	4·80 (0·88 to 3·51)	0·41 (0·07 to 1·58)

mortality (see fig 4) was calculated by age and year of presentation per 100 000 women aged over 20. We obtained the case notes and full screening histories of 108 women out of 159 who died in 1982-91 (see table V). The cervical smears were reviewed and management assessed.

CASE-CONTROL STUDIES

A case-control study was carried out on both the 282 cases of invasive disease and the 108 deaths occurring in 1982-91. Each was matched for two controls, both for age and for having had a negative smear test result at the date of presentation of the case (see tables II-IV and VI-VIII).

Results

The detection rate of cervical intraepithelial neoplasia grade III in women screened for the first time (fig 1) rose dramatically from 1983 (from 0·4% to 1·6%). The overall percentage of biopsies in relation to all smears in this laboratory between 1985 and 1992 was 1·4%. Of those biopsies, 74% showed cervical intraepithelial neoplasia grade II or grade III.

INVASIVE CANCER

Comparing the incidence of invasive cancer between the 1970s and 1980s showed a sharp fall in women aged 40-69, the group (fig 2) who had been well screened and had the opportunity to be rescreened (z test for proportion, $P < 0·001$). There was a rise in incidence in women under 40 (test for proportion, $P < 0·001$) and in those over 70, though in this age group the difference did not reach significance.

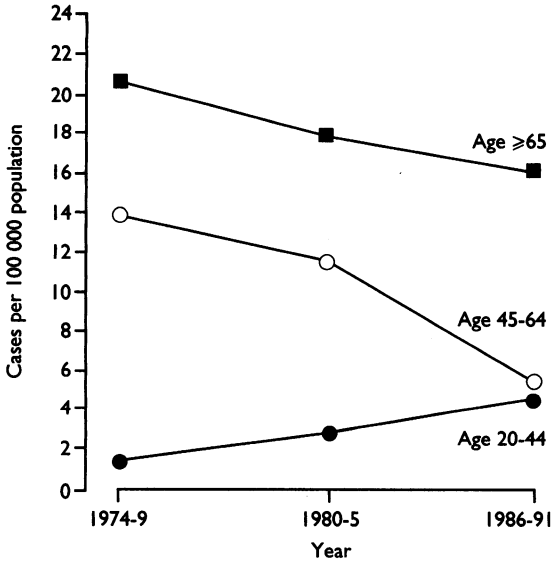

FIG 4—*Mortality from squamous cell carcinoma of cervix at various ages in north east Scotland plus Orkney and Shetland in five year periods during 1974-91 (308 deaths)*

TABLE V—*Distribution of 108 deaths among women who presented with invasive squamous cell carcinoma of cervix at various ages during 1982-91. Figures are numbers (percentages) of patients*

Screening status at presentation	Age (years)			
	<45	45-64	≥65	Total
Screened	20 (63)	10 (36)	8 (17)	38 (35)
Unscreened	12 (38)	18 (64)	40 (83)	70 (65)
Total	32 (30)	28 (26)	48 (44)	108 (100)

TABLE VI—*Case-control study of numbers of smear tests before presentation among women who died of squamous cell carcinoma of cervix during 1982-91. Figures are numbers (percentages) of women*

	No of smears				
	1 or 2	3 or 4	5 or 6	≥7	0
Cases (n=108)	21 (19)	10 (9)	6 (6)	1 (1)	70 (65)
Controls (n=216)	70 (32)	49 (23)	18 (8)	20 (9)	59 (27)
Odds ratio (95% confidence interval)	1·00	0·68 (0·27 to 1·69)	1·11 (0·32 to 3·42)	0·17 (0·00 to 1·19)	3·95 (2·09 to 8·53)

TABLE VII—*Case-control study of time from last negative smear test result to date of presentation with squamous cell carcinoma of cervix among women who died during 1982-91. Figures are numbers (percentages) of women*

	Time interval (months)			
	1-59	60-119	≥120	0
Cases (n=108)	16 (15)	10 (9)	12 (11)	70 (65)
Controls (n=216)	91 (42)	35 (16)	31 (14)	59 (27)
Odds ratio (95% confidence interval)	1·00	1·63 (0·62 to 4·25)	2·20 (0·86 to 5·60)	6·75 (3·43 to 13·41)

The screening history of 282 cases presenting during 1982-91 (table I) showed that women who had never had a smear test accounted for almost half (125 cases; 44%) of the total. One third (94; 33%) had been screened, and 63 cases (22%) were detected on screening. The largest single group of patients (124; 44%) presented with stage I disease. Only 17 (6%) of all cancers were at stage IV. Unscreened women had a significantly higher risk of presenting with a more severe stage of disease ($P < 0·001$).

The reasons for the 282 cases of invasive cancer occurring were examined. One hundred and thirty six (48%) of the patients (including 11 unscreened but screen detected cases) were unscreened for no obvious reason, were too old, or had moved. Poorly screened women—those with one or only a few smear tests at long intervals—accounted for 57 cases (20%). A further 41 (15%) had truly negative smears less than five years before presenting with invasive cancer, suggesting cell sampling which did not reflect the cell changes in the cervix. Thus 83% of invasive cancers (234/282) occurred in unscreened or inadequately screened women. Abnormal cells were found on review of the previous slides in 32 (11%) of the 282 cases. Some smears had only a few abnormal cells, others had more. Recurrence after treatment at colposcopy occurred in eight women (3%). A further nine (3%) of the cases were lost to detailed follow up.

Relating the age at presentation to disease stage in the 282 cases (fig 3) showed that most women presenting with invasive cancer were under 40 and had stage I disease.

Case-control study (tables II-IV) found from the odds ratio that the longer the time since the last negative smear the higher was the risk of invasive

TABLE VIII—*Case-control study of parity among women who died of squamous cell carcinoma of cervix during 1982-91. Figures are numbers (percentages) of women*

	No of pregnancies						
	0	1	2	3	4	≥5	Not known
Cases (n=108)	6 (6)	22 (20)	19 (18)	25 (23)	10 (9)	24 (22)	2 (2)
Controls (n=216)	21 (10)	31 (14)	63 (29)	46 (21)	19 (9)	16 (7)	20 (9)
Odds ratio (95% confidence interval)	1·00	2·48 (0·79 to 8·70)	0·56 (0·16 to 2·11)	1·90 (0·63 to 6·49)	1·84 (0·49 to 7·14)	5·25 (1·55 to 18·61)	0·35 (0·03 to 2·31)

cancer. Similarly, the absence of a smear test before presentation was associated with a higher risk of invasive cancer, and also the higher the parity the higher was the risk.

To ascertain why women in this highly screened region were completely unscreened for no obvious reason, 26 of the patients were asked (with the help of their general practitioners) about their screening history. The main reason given for not being screened was that they had never specifically been invited for screening. If they did not have a smear test at time of pregnancy they did not think it concerned them later. Only one woman definitely refused; she also refused breast screening. Other reasons included: "won't happen to me," recently moved to area, physical handicap, alcoholism, and "already attending gynaecological outpatients" but had not had a smear.

MORTALITY

Grampian Health Board figures show a fall in death rates from invasive cancer of the cervix (standardised mortality ratio 85) compared with the rest of Scotland.[1,2] Analysis of 308 deaths during 1974-91 showed that the fall was most pronounced in women aged 45-64 years, the age group who had the greatest opportunity to be screened and rescreened (fig 4). The fall was less in women over 65, and there was a rise in women under 45.

Of 108 deaths that occurred during 1982-91, 70 (65%) were in unscreened women and 38 (35%) were in women who had been screened (table V). Of the 38 screened cases, six had cells which on review of the slide had been missed on interpretation three to 12 years before presentation; in two of these cases these had been followed by negative smears. One woman had an abnormal smear followed by three negative smears. Two cases recurred after treatment for cervical intraepithelial neoplasia grade III. There were no cases of known mild cell changes occurring without action being taken.

The case-control study (tables VI-VIII) found from the odds ratio that the absence of a smear test before presentation was associated with a risk of death. The time since last negative smear further highlighted evidence of a trend—that is, the risk of death increased with the time since last negative smear. Only 16 (15%) of 108 patients who died had had a smear test within five years of presenting with invasive disease, whereas 91 (42%) of 216 controls had. The screening interval at the time was five years. Strong evidence was found that the higher the parity the higher was the risk of death.

Discussion

There is little doubt that cervical intraepithelial neoplasia grade III if left untreated[6] will progress to invasive disease. If allowed to do so the resulting number of invasive cancers in the United Kingdom would be roughly compatible with the expected incidence of the invasive disease—but not so if cases of cervical intraepithelial neoplasia grades I and II are included.[7] The dramatic rise in cases of cervical intraepithelial neoplasia grade III over the past 10 years may reflect social changes[8] such as the increase in smoking in young women, greater sexual freedom, and early age at first intercourse.[9] A study in 1985 of 203 primigravidas in the Grampian region found that 144 (91%) of 158 women interviewed had used the pill.[10] Unless a rigorous screening policy is maintained a rise in cases of invasive cancer may be expected. Cancer at a young age may be associated with a change in the pattern of presentation of the disease,[11] but none of the cancers in this study was adenosquamous.

Cohort effects of incidence and mortality from squamous cancer of the cervix have been described.[12,13] Nordic countries find that whereas countries with screening programmes have reduced mortality by 50%, those with no organised programmes have reduced mortality by only 10%.[14] The fall in incidence in north east Scotland is roughly 63% after 25 years of screening.[5,15]

Incidence rates in England and Wales in 1984 showed two peaks, an increase in young women in their 30s and in older women over 60,[16] similar to that found in north east Scotland.

Though we agree in principle that screening can stop at 50 years of age[17] in women who have been well screened, caution would be advisable until the national screening programme can say confidently how many of these older women have been screened and rescreened.

That 44% (125/282) of clinically invasive cancers that occurred in north east Scotland during 1982-91 were in completely unscreened women (who represent less than 10% of the female population aged 21-60) is highly relevant. When specifically invited, women did attend. The now established national network for call and recall should improve efficiency in detecting cases before they become invasive. A small residual group may always refuse the test.

Invasive cases were detected by the screening programme in women who had no known symptoms (n=63; 22%). They were mainly at stage I, when the prognosis should be good. A study from the Netherlands showed that screen detected cases had a better prognosis than clinically diagnosed cancer.[18] Though this is not the prime intention of the screening programme, it must contribute substantially to the fall in mortality from the disease.

IMPROVING INTERPRETATION OF SMEARS

Adding inadequately screened to unscreened women accounted for 83% of women (234/282) with invasive disease in this study. Some women with invasive disease had been screened and misinterpretation of cervical smears had occurred.

The National Coordinating Network emphasises the need for improvement both in training and in quality assurance schemes to reduce the number of false negative smears.[19,20] As yet no new techniques are available to replace the cervical smear. Recent research suggests a possible serological test[21] or virological assessment,[22] which could be more reliable than smears. Studies on oncogenes continue.[23]

The option for earlier referral for colposcopy[24] did not arise in the 32 (11%) cases found on review of their smears, as they were not known originally to have had abnormal cells, nor in the 41 (15%) of women with no abnormal cells found within five years of presenting with invasive disease. Suggestions of a rapidly progressing disease are not supported.[25] Clinical cancers have been known to give negative smears.[26-28] Diagnosing an early clinical invasive lesion is not easy. Taking good cervical smears from within the endo-

Epidemiological implications

- Screening for preclinical cervical cancer has reduced the incidence of and mortality from invasive cancer in north east Scotland
- Case-control studies show that the longer the time and the absence of a smear test before presentation the higher is the risk of invasive cancer and death
- There has been a substantial and worrying rise in invasive cancers in women under 40
- A substantial rise in cases of cervical intraepithelial neoplasia grade III has occurred in women screened for the first time since 1983
- The national network for call and recall to screening will be the main factor in preventing invasive cervical disease

cervical canal and from around the external os is paramount.[29]

The correlation between cytology and histology—both of which are subjective—leaves much to be desired,[30 31] yet smear surveillance has worked well to date. Women who have even one abnormal smear[32] are at greater risk of having some grade of cervical intraepithelial neoplasia than women who have normal smears. They require rigorous smear surveillance, which will allow at least one third of patients to return to normal and avoid unnecessary treatment. In this study there was no evidence that cases occurred owing to lack of follow up once abnormal cells were recognised.

The main reason for cases occurring is failure to attend for screening. Recognition as a priority in the *Health of the Nation* has given a welcome boost to the screening programme. The now established national network for screening and rescreening will contribute more than any other factor in preventing invasive disease, which is increasing in young women.

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Breast feeding and multiple sclerosis

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Several studies indicate that multiple sclerosis might be a rare result of delayed exposure to a common infectious agent,[1] but some authors have suggested a "geographical predisposing factor" that could be associated with the diet in industrialised countries.[2] We investigated the association between multiple sclerosis and breast feeding in a case-control study.

Patients, methods, and results

Cases and controls were selected from the patients attending the neurological outpatient department of Cardarelli General Hospital, Naples, where neurologists from the Italian association for multiple sclerosis follow up about 300 patients with this disease. Cases were all the patients observed between 1 March and 31 May 1993 who had a definite diagnosis of multiple sclerosis according to the criteria of Poser *et al.*[3] Controls were the first patients observed in the same department during the same period who matched the cases in terms of age (plus or minus five years) and sex. Patients who declined to be interviewed or could not provide reliable information about their feeding during infancy were excluded.

The groups were contacted by two interviewers, who were blind to the objectives of the study and interviewed the same number of patients from each group. Whenever possible the mothers of the patients were interviewed, otherwise the patients provided the information, usually quoting their mothers. Relative risk was calculated by odds ratios with confidence intervals by Cornfield's method. Confounding and effect modification were investigated by stratified analysis. Ninety three cases and 93 controls were enrolled in the study. The diagnoses of controls were back pain and sciatic nerve injury (56), hemicrania (19), polyneuropathies (15), and other (four). The information was provided by the mothers for 56 (60%) cases and 54 (58%) controls.

The table shows characteristics of the groups. The mean (SD) duration of breast feeding was 8·4 (6·9) months for cases and 12·5 (7·5) months for controls

Characteristics of patients with multiple sclerosis according to case-control status

Characteristic	Cases (n=93)	Controls (n=93)	P value
Sex (M/F)	47/46	47/46	
Mean (SD) age (years)	37·7 (9·5)	37·1 (10·2)	
Low birth weight (<2500 g)	3	3	
Type of birth (vaginal/caesarean section)	90/3	92/1	
Social class (I, II, III/IV, V, VI)	14/79	5/88	0·052
No (%) who did not breast feed	13 (14)	8 (8·6)	0·3
No (%) who breast fed:			
For 0-6 months	29 (31)	14 (15)	0·015
For ≥7 months	51 (55)	71 (76·4)*	<0·01

*Odds ratio=0·38, 95% confidence interval 0·19 to 0·74; χ^2 for trend P<0·01.