Cervical smear histories of 500 women with invasive cervical cancer in Yorkshire

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Abstract

The smear histories of 312 women with cancer of the cervix have been determined. Eighty nine women had had at least one negative smear reported in the 10 years before a diagnosis of cancer and 14 had had more than one negative smear. Fifty six of the 89 women had had a negative smear in the three years preceding the diagnosis of cancer. The highest number of negative smears (61) reported was among the 115 women aged under 45. Fifty eight slides reported as negative were submitted to independent review; 13 were subsequently reported as negative, 11 as unsatisfactory, and 34 as abnormal.

These findings may in part explain why in this region there has been a disappointing reduction in the incidence of clinically invasive cervix cancer, and our findings may also apply elsewhere. Nevertheless, the confirmed negative smears chiefly occurred within three years of clinical cancer, particularly in the younger women, and this finding suggests that these women may have a short preinvasive phase.

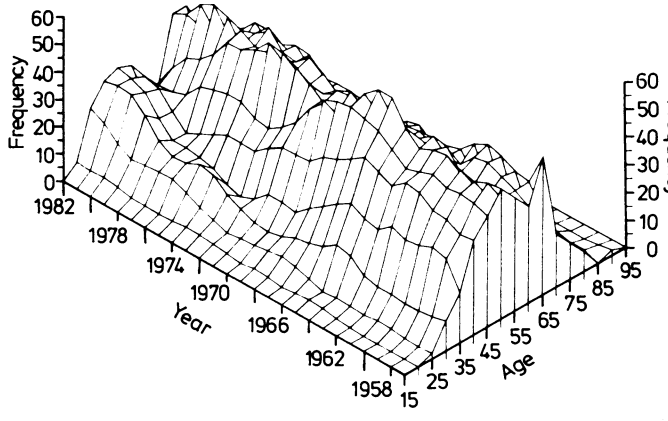
Introduction

The relation between cervical intraepithelial neoplasia and invasive cancer continues to cause controversy, although the bulk of cytological and epidemiological evidence suggests that progression from grade 3 cervical intraepithelial neoplasia (CIN III) to clinically invasive cancer takes over 10 years.[1,2] The overall incidence of invasive cervical cancer in England and Wales has altered little between 1974 and 1980, although there has been some reduction in the number of deaths.[3] In reviewing the results for Yorkshire from 1957 to 1982 we found that a change in the age distribution of cases had occurred (see figure). Women aged under 35 are now at greater risk of developing invasive cancer than ever before. Death rates also indicate a change in pattern, with more women dying in the younger age groups compared with women aged over 40 (table I).

Currently 3 million cervical smears are performed in England and Wales each year, yet over 2000 women still die from cancer of the cervix. Unfortunately there is little evidence on the accuracy of smear reports; nor do we know how often smears should be repeated in younger women. In an attempt to establish any possible relationships we decided to review 500 patients with clinically invasive cancer of the cervix, treated by two of us, to determine how many had had a cervical smear in the 10 years preceding the diagnosis of invasive cancer.

Patients and methods

All those women with cancer of the cervix treated by two of us (CAJ and KRP) between 1968 and 1980 were included in the study. A detailed inquiry was made to determine the smear histories of these women; these were obtained from the patients' general practitioners, hospital case records, the records of the relevant cytology laboratories, and in some cases from the patients themselves. Permission was requested to obtain from the appropriate pathologist as many relevant negative smears as were available. These were submitted to a highly qualified cytologist from another region for anonymous review.



Three dimensional representation relating frequency of cervical cancer to age from 1957 to 1982.

TABLE I—*Mortality figures for cancer of the cervix from the Office of Population Censuses and Surveys*

Year	Age											Total
	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	≥70	
1978	1	34	59	81	82	125	233	306	266	302	664	2153
1977	2	18	53	74	92	126	270	262	308	277	663	2145
1976	7	20	40	61	67	139	286	326	343	244	671	2206
1975	9	22	46	58	78	154	258	292	305	276	645	2143
1974	5	19	31	50	72	157	286	243	281	260	664	2068
1973	7	15	24	54	83	211	331	305	300	263	656	2249
1972	4	20	26	50	114	218	292	299	305	252	638	2218
1971	2	10	31	52	132	239	341	291	303	271	653	2315
1970	5	12	22	49	121	276	290	336	289	268	675	2343
1969	5	8	24	57	148	291	273	326	281	287	716	2417
1968	3	8	24	67	159	304	326	313	305	255	670	2434
1967	1	13	19	66	175	296	332	297	277	286	685	2449
1966	0	8	19	74	206	257	298	319	280	307	714	2472
1965	3	4	29	96	234	262	334	289	315	233	654	2453
1964	3	8	24	98	239	312	315	287	274	293	724	2577

Results

The smear histories of 312 of the 500 patients were obtained. Of these, 268 were living and 44 had died. The patients for whom smear histories

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could not be obtained included 57 living and 131 who had died. Of the 268 women still alive, 68 (26%) had had a negative smear reported in the five years preceding a clinical diagnosis compared with three (7%) of the women who had died.

A total of 89 women had had at least one reported negative smear during the 10 years preceding the diagnosis of invasive cancer. Table II shows the relation between patient's age and the time interval between the most recent smear and the diagnosis of invasive cancer. This indicates that roughly one in two of women aged under 35 had had a negative smear reported at least once during the 10 years preceding the diagnosis of cancer compared with one in 13 of the women over 65. Of the 89 women, 71 negative smears had been reported in the five years before a diagnosis of invasive cancer and again the numbers were greater for the younger women. Moreover, 56 negative smears were reported within three years of invasive cancer being diagnosed.

Table III shows the relationship between clinical stage of disease and the interval between the most recent negative smear and a diagnosis of invasive cancer. Some 41% of women with stage I disease had had a negative smear compared with 11% of women with stage III disease. Nevertheless, most women with stage I disease were younger. Of 71 women who had had negative smears in the five years before the diagnosis of carcinoma, nine had had two negative smears, one three, two four, and one six, although the last followed a cone biopsy six years before the diagnosis of invasive cancer.

TABLE II—*Relation between age and the number of years between the most recent negative smear and the diagnosis of invasive cancer*

Age	No of years since last negative smear										Total reported as smear negative	No of women available	% With negative cytology
	1	2	3	4	5	6	7	8	9	10			
35	5	4	11	1	3	1	0	2	2	0	29	55	53
36-45	7	6	4	3	4	1	1	3	2	1	32	60	53
46-55	7	0	4	0	2	1	0	1	1	0	16	71	23
56-65	3	2	0	1	1	0	0	2	0	0	9	82	11
≥65	3	0	0	0	0	0	0	0	0	0	3	44	7
Total	25	12	19	5	10	3	1	8	5	1	89	312	29

TABLE III—*Relation between clinical staging (FIGO) and the number of years between the most recent negative smear and the diagnosis of invasive cancer*

Stage (FIGO)	No of years since last negative smear										Total	No of women in study
	1	2	3	4	5	6	7	8	9	10		
I	15	10	16	4	10	3	0	7	4	1	70	169
II	6	2	2	1	0	0	1	1	1	0	14	95
III	4	0	1	0	0	0	0	0	0	0	5	44
IV	0	0	0	0	0	0	0	0	0	0	0	4
Total	25	12	19	5	10	3	1	8	5	1	89	312

Fifty eight of the reported smears taken from 42 of the 89 women were sent for anonymous review. Unfortunately these were the only slides available despite a most diligent search and help from the various laboratories. (In some laboratories negative smears are destroyed after two to three years because of lack of storage facilities.) The independent review reported 14 smears as positive (the presence of definite malignant cells); 10 as showing severe dyskaryosis (probably malignant, but not sufficient evidence); 10 as suspicious of malignancy; 13 as negative; and 11 unsatisfactory for diagnosis. Analysis of the relation between the review cytology and time before the diagnosis of invasive cancer (table IV) shows that most positive lesions were detectable up to three years before a clinical diagnosis of invasive cancer.

Discussion

Various investigations have shown the place of cervical cytology in reducing mortality from cancer of the cervix—particularly in British Columbia,[4] Iceland,[5] and Finland.[6] Nevertheless, in England and Wales between 1974 and 1980 the number of women dying from cancer of the cervix was unchanged for the older age groups, reduced for the middle age groups, but increased for the younger age groups (table I).

The results of our study indicate that several women had had a negative smear reported at least once during the ten years before a clinical diagnosis of cancer. Great difficulty was experienced in obtaining smear histories of the women who had died, but just over a quarter of women who were alive had had a negative smear reported during the five years preceding a clinical diagnosis of cancer. Table II indicates that the younger women had the highest chance of a negative smear being reported, which is to be expected since over 70% of all smears in Yorkshire are from women under the age of 50.[7] Fifty three per cent of women aged 45 or under had had a negative smear reported in the 10 years before a diagnosis of cervical cancer and most (61%) were within three years of diagnosis.

Nevertheless, because of the higher number of smears done in the younger age groups the false negative rate is probably the same irrespective of age group. For women who had had confirmatory evidence of negative smears, which again predominated within three years of clinical cancer, either they had a short preinvasive history (as suggested in previous studies[8-14]) or the smear had failed to reflect underlying malignancy.

TABLE IV—*Review of 58 smears in 42 patients previously reported as negative at up to eight years before clinical cancer was found*

Smear review	Number of years								Total
	1	2	3	4	5	6	7	8	
Positive	5	1	5		1	1		1	14
CIN III	1	1	3	1	2	1		1	10
Suspect	3	4	1	1	1				10
Negative	2	5	2	2				2	13
Unsatisfactory	4	1	1	1	1	2		1	11

CIN III=Cervical intraepithelial neoplasia stage 3.

The confirmed negative smears (table IV) indicate that carcinoma of the cervix in younger women may have a much shorter preinvasive stage than the usually quoted 10 years,[10] which is based on the disease in older women. In fact, several studies have shown that some women have a negative smear reported within only a few years of developing invasive cancer of the cervix.[8-11] Twenty nine per cent of 366 women had had a negative smear in the five years before a diagnosis of invasive cancer,[8] compared with 16% of 95 women reported by Walker *et al.*[12] Again, this might reflect false negative reports or a short inductive history.

The high number of false negative smears may be explained by poor technique in taking smears or failure by the cytologist to recognise malignant cells. In our study there was a high incidence of "false negative" smears, with only 13 of the 58 smears reviewed being confirmed as negative. Two other small studies have shown a high incidence of false negative smears among women with invasive cancer, but all these smears had been taken within a year of the diagnosis of invasive cancer.[13,14] In contrast, our study had false negative smears throughout the eight year period (table IV). Husain *et al* suggested that as many as one in six abnormal smears may be missed if the doctor relies on a single smear; one third of these errors were due to laboratory error and two thirds were due to failure of collection.[15] They concluded that quality control should be from within the laboratory, but our study suggests that quality control may have to be more extensive and our findings may help to explain why the incidence of invasive cancer of the cervix has altered so little.[3] The Grampian and Tayside regions have had active cytology campaigns and tight laboratory control and they are two regions which show a significant reduction in the incidence of cancer of the cervix.[16]

In addition to arousing concern about the accuracy and effect of cytology, our study gives some insight into the clinical course of the disease (table IV). Pederson followed the spontaneous course of precancerous lesions of the cervix and found that a third of women with carcinoma in situ had developed invasive cancer within 10 years.[17] This work has never been repeated as it is regarded as unethical not to treat carcinoma in situ of the cervix; nevertheless, this attitude has meant that the clinical course of the disease is still uncertain. Elaborate mathematical models have been constructed,[18] but because so many assumptions have to be made one must question their validity. Indeed, Green questions the relation between carcinoma in situ and invasive cancer, though he appears to be almost alone in this view.[19] The data from table II suggest that

carcinoma of the cervix may have a preinvasive phase, which is variable in length: in some women it is less than a year and in others up to 10 years. If the unsatisfactory smears in our study are disregarded and all the other results are correct, an interval between smears of five years should have prevented four of our 47 cases; a three year interval should have prevented 10; and an annual smear might have prevented at least 25. The numbers are small but suggest that we need a much shorter smear interval than five years.

One of the most disturbing aspects of the study is related to those women aged under 45. These women are having more cervical smears than any other group[7] but constitute the one group that has shown an increase in mortality from cancer of the cervix.[3] and also has the highest number of false negative reports.

In conclusion, though the number of women with invasive cancer of the cervix could have been reduced by an annual smear, an even greater reduction could have been produced by improved quality control in the laboratory. An increased frequency of smears in the younger women should not be introduced at the expense of the older women, who still contribute most of the deaths.

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Style Matters

Improving reports of adverse drug reactions

Under the auspices of Ciba-Geigy a workshop on improving the informative value of published reports of adverse drug reactions was held in Morges, Switzerland, from 16 to 20 September 1984. The participants included those working in the pharmaceutical industry, departments of clinical pharmacology, and drug regulating agencies, editors of medical and scientific journals, and science correspondents of the general press. In a statement issued at the end of the meeting the workshop suggested that reports of adverse drug reactions should be classified into three main types, with the criteria below. These guidelines are intended for authors, editors, peer reviewers, and readers.

General "early" reports

Should be identified as unreviewed *suspicions*—as distinct from (reviewed) substantiated cases.

Case reports—reviewed

General information needed for peer review, acceptance, and publication:

Birth date or age; sex
Suspected drug and all drugs in current therapy
Start/stop/restart dates
Dose
Indication for drug treatment
Timing of events (suspected adverse drug reaction) relative to drugs and outcome
Other diseases/environmental factors, and timing
Prior experience with drug/adverse drug reactions to related drugs
Ancillary information in pharmaceutical industry and regulatory agency
Any coverage in previous publications
Other factors relevant to verify specific types of adverse drug reactions (for example, blood concentration in overdose, baseline laboratory data, race, and ethnic type)
Route of administration/formulation of drug

Multiple cases

Any report that provides series of cases should provide the following:

Age; sex
Number of patients treated
Number of patients with adverse reactions
Number of events

Correspondence about the workshop and these guidelines should be sent to: Professor Jan Venulet, Ciba-Geigy, CH 4002 Basle, Switzerland.