Effects of observer variation in population screening for cervical carcinoma

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SYNOPSIS A stratified random sample of 100 cervical smears was taken from routine population screening material and graded by three cytological laboratories. The sensitivity of the smear test for detecting cervical malignancies varied from 72 to 88%—a difference of 16%; for all severe epithelial abnormalities the sensitivity varied from 52 to 71% (a difference of 19%). The histological material pertaining to these smears was re-examined 'blindly' and then sent for diagnosis to a second pathologist. Using each set of histodiagnoses as reference, the sensitivity of the test for detecting cervical malignancies varied from 77 to 85%—a difference of 8%; the sensitivity for all epithelial abnormalities varied from 62 to 76% (a difference of 14%). The significance of these observer variations on the efficacy of screening for cervical carcinoma is discussed.

Results of screening by cervical cytology recall strategy, and the histopathology of gynaecological operation specimens in a district hospital serving a population of 250 000 over a period of five years have been analysed by Lederer and Lambourne (1973). In this communication variations by different observers in the grading of cervical smears and of histopathological findings in operation specimens of the same series are analysed in an attempt to determine how observer variation may affect estimates of the efficiency of cervical mass screening. The methods of investigation have also been detailed.

In order to assess observer variation, Evans (1970) sent the same batch of 100 smears to five cytology centres in Britain and compared their findings with his own. Having graded the smears into four classes, he found total disagreement with his diagnosis in 2%, grading differences of two classes in 6%, and of one class in 20% of the smears. Seybolt and Johnson (1971) submitted smears of 25 cases with doubtful cytological findings to eight 'leaders in the field of diagnostic cytology', and found marked diversity of interpretation, although, in the authors' opinion, only 18 of the 200 reports would have led to less than optimal management of the cases. Cocker, Fox, and Langley (1968) reported serious inconsistencies in histodiagnosis, not only between different pathologists, but also by the same pathologist after an interval of time.

The efficiency of a test in detecting epithelial abnormalities may be measured by means of its sensitivity, ie, the proportion of a particular abnormality discovered by the test. (Another measure commonly used is the 'false negative error rate', which is the complement of the sensitivity, ie, the proportion of conditions not discovered by the test.) The sensitivity of the cervical smear test is dependent on two separate factors: (1) the accuracy of the information recorded on the smear, and (2) the interpretation of both the smear and the confirmatory histological specimen.

Errors inherent in both of these factors were observed by Martin (1972) on examining the records of the 76 cases of invasive cervical carcinoma identified in San Diego, California, in 1967. In 33 of the 76 cases (43%) a cytological smear obtained within a year had been reported as negative. Review of the slides was not possible for 20 of the 33 cases, but of the 13 cases whose slides had not been discarded, a review sustained the original negative report in three cases (finding inadequate cellular material) but changed the cytological diagnosis from negative to positive or suspicious in the remaining 10. In one invasive carcinoma, the histological specimen had been incorrectly read.

The authors felt that differences in criteria for interpreting both cytological and histological specimens may be partly responsible for variations in estimates of the sensitivity of the smear test. Thus the following trial was carried out in order to assess

differences in grading of both cytological and histological specimens.

Divergences in Cytological Grading

METHOD

A stratified random sample of 100 smears was selected so that normal, atypical, and malignant smears were approximately equally represented. The batch thus included a grossly higher proportion of abnormal smears than would be obtained from a mass screening programme.

The smears were re-examined 'blindly' at the district hospital (referred to as D in the tables) and then sent to two well known cytology laboratories (referred to as A and B). All three centres used the same Papanicolau grading, classing the smears as I, II, III, or IV.

RESULTS

The findings of the three centres are summarized in table I which shows that A was more severe in

Grade	Cytologist		
	D	A	B
IV	23	37	23
III	18	16	17
II	28	39	29
I	30	7	25
Unsatisfactory	1	1	6
Total	100	100	100

Table I Grading of smears

grading than either B or D, classing more smears as grade IV and fewer as grade I, and apparent close agreement in grading between D and B. The gradings for each pair of observers are analysed in table II and their differences shown in figure 1. These show that A was more severe than B or D and that B and D were not as consistent as might be assumed from table I, their gradings differing by one class or more in 37% of cases.

A statistic which summarizes the differences

Fig 1 Pair-wise comparisons of cytological diagnoses.

between a pair of observers is the mean class difference (MCD)—the mean number of classes by which the grading of one observer differs from that of another; thus a MCD of +1 between X and Y indicates that on average a class graded as N + 1 by X is graded as N by Y. The MCD between B and D was low (0.03); those between both A and D and A and B were somewhat higher (0.49 and 0.44 respectively).

While the MCD measures the overall differences in grading between two observers, it gives no indication to their consistency; thus a MCD of +1 may be obtained from either a consistent set of differences (1,1,1,1) or a random set (0,3,-2,3,1). The standard deviation (SD) of the class difference variable is a measure of consistency, a low SD indicating good and a high SD poor consistency.

The consistency between each pair of cytologists was only moderate, the SD of the grading differences ranging from 0.81 to 0.94. This is important for the differences between B and D, since it shows that their low MCD was the result of balance between their differences rather than perfect agreement.

Divergences in Histological Grading

METHOD

In order to assess the effect of differences in grading

A						B						D					
Grade	IV	III	II	I	Total	Grade	IV	III	II	I	Total	Grade	IV	III	II	I	Total
IV	19	4	—	—	23	IV	17	7	11	—	35	IV	16	5	1	1	23
III	8	6	4	—	18	III	4	7	5	—	16	III	4	6	5	2	17
II	6	4	15	3	28	II	2	3	11	20	36	II	2	6	17	4	29
I	4	2	20	4	30	I	—	—	2	5	7	I	—	1	4	20	25
Total	37	16	39	7	99	Total	23	17	29	25	94	Total	22	18	27	27	94

Table II Pair-wise comparison of cytological diagnoses¹

¹Numbers within the diagonal lines represent complete agreement between the two diagnoses

Histology	Total Smears		Cytodiagnosis						Cytologist	
			III	or	IV	I	or	II		
			No.	%		No.	%			
Invasive carcinoma	10	25	5	50		5	50		D	
<i>In-situ</i> carcinoma	15		13	87	18	2	13	7		28
Severe dysplasia	27		9	33		18	67			
All severe epithelial abnormalities	52		27	52		25	48			
Normal or mild dysplasia	20		7	35		13	65			
Invasive carcinoma	10	25	8	80		2	20		A	
<i>In-situ</i> carcinoma	15		13	87	21	2	13	4		16
Severe dysplasia	27		16	59		11	41			
All severe epithelial abnormalities	52		37	71		15	29			
Normal or mild dysplasia	20		7	35		13	65			
Invasive carcinoma	10	25	8	80		2	20		B	
<i>In-situ</i> carcinoma	15		14	93	22	1	7	3		12
Severe dysplasia	27		10	37		17	63			
All severe epithelial abnormalities	52		32	62		20	38			
Normal or mild dysplasia	20		5	25		15	75			

Table V Variations in cytological diagnoses

Conditions Detected	Cytologist			Mean Sensitivity (%)	Maximum Variation
	D	A	B		
Invasive and <i>in-situ</i> carcinoma	72	84	88	81	16
<i>In-situ</i> carcinoma	87	87	93	89	6
All severe epithelial abnormalities	52	71	62	62	19

Table VI Variations in sensitivity caused by differences in cytological grading

and *in-situ* carcinomas detected by cytology varied from 18/25 (72%) by D to 22/25 (88%) by B, a difference of 16%.

As the primary aim of the smear test is to discover precursors of invasive carcinoma, the sensitivity is often defined as the proportion of *in-situ* carcinomas detected (Spriggs, 1972). Of the 15 cases classified histologically as carcinoma *in-situ*, 13 or 14 were graded as III or IV by the three cytologists, giving sensitivities of 87 or 93% respectively—a variation of only 6%.

On combining severe dysplasia, carcinoma *in-situ*, and invasive carcinoma, and defining sensitivity as the proportion of these conditions detected, the sensitivity fell quite substantially, as between 11 and 18 of the 27 cases of severe dysplasia were graded cytologically as I or II. The sensitivity of the test in detecting abnormalities more severe than mild dysplasia thus varied from 52 to 71%—a variation of 19%.

The analysis also shows that in 14 to 21% of the smears graded as III or IV, histological examination revealed no more significant lesion than mild dysplasia.

DIFFERENCES IN HISTOLOGICAL GRADING

To assess the variations in sensitivity caused by differences in histological grading, the cytodiagnoses were compared in turn with the original gradings (O), the review gradings (D), and those of the second pathologist (A). In order to use the maximum information available, all three sets of cytodiagnoses were used, giving three cytological gradings for each of the 42 operation specimens examined. The results are shown in tables VII and VIII.

Of the 69 cytodiagnoses of the cases for which O returned a histological report of a cervical malignancy, 53 had been graded as III or IV, giving a sensitivity of 53/69 (77%). The sensitivity using D's histodiagnosis was 46/54 (85%) and that of A was 28/36 (78%). The proportion of cases warranting further treatment missed by the test thus varied from 15 to 23%.

These figures are more consistent than those of the cytodiagnoses, but still produce a difference of 8% in the estimates of the test's sensitivity.

If, as before, we were to consider only the detection of *in-situ* carcinoma, the sensitivity varied by 18 from 72% by both O and A to 90% by D.

Histologist	Diagnosis	Total Cases	Total Smears	Combined Cytodiagnosis					
				III		or IV		I	
				No.	%	No.	%	No.	%
O	Invasive carcinoma	10	30	25	83	5	17		
	<i>In-situ</i> carcinoma	13	39	28	72	11	28		
	Severe dysplasia	16	48	19	40	29	60		
	All severe epithelial abnormalities	39	117	72	62	45	38		
	Normal or mild dysplasia	3	9	4	44	5	56		
	Invasive carcinoma	8	24	19	79	5	21		
D	<i>In-situ</i> carcinoma	10	30	27	90	3	10		
	Severe dysplasia	21	63	29	46	34	54		
	All severe epithelial abnormalities	39	117	75	64	42	36		
	Normal or mild dysplasia	3	9	1	11	8	89		
	Invasive carcinoma	6	18	15	83	3	17		
	<i>In-situ</i> carcinoma	6	18	13	72	5	28		
A	Severe dysplasia	16	48	36	75	12	25		
	All severe epithelial abnormalities	28	84	64	76	20	24		
	Normal or mild dysplasia	14	42	12	29	30	71		

Table VII Variations in histological diagnoses

Conditions Detected	Histologist			Mean Sensitivity (%)	Maximum Variation
	O	D	A		
Invasive and <i>in-situ</i> carcinoma	77	85	78	80	8
<i>In-situ</i> carcinoma	72	90	72	78	18
All severe epithelial abnormalities	62	64	76	66	14

Table VIII Variations in sensitivity caused by differences in histological grading

Considering all severe epithelial abnormalities, the sensitivity fell to 62% (O), 64% (D), or 76% (A)—a variation of 14%.

Thus, variations in histopathological grading both between different pathologists and the same pathologist after a lapse of time produced variations in the estimates of the test's sensitivity of 8% for detecting both invasive and *in-situ* carcinoma, 18% for *in-situ* carcinoma alone, and 14% for epithelial abnormalities more severe than mild dysplasia.

Discussion

Although population screening for cervical cancer has been common practice in Great Britain for over 10 years and for much longer in parts of North America, doubts on the value of screening programmes have been expressed mainly by epidemiologists on the basis of analysis of mortality and morbidity statistics.

Thus Ashluwalia and Doll (1968) pointed out that a comparable fall in incidence and mortality had occurred in parts of Canada not affected by the British Columbia screening programme (Boyes,

1969; Boyes, Worth, and Fidler, 1970). The conclusion of McGregor, Fraser, and Mann (1971) that a fall in incidence of invasive carcinoma in Aberdeen was attributable to the local screening programme has been criticized by Wilson, Chamberlain, and Cochrane (1971) and similar criticism seems valid for the report by Dickinson, Mussey, Soule, and Kurland (1972) from Rochester. Pedersen, Hoeg, and Kolstad (1971) in a detailed analysis of the experimental programme carried out by the Norwegian Cancer Society in the county of Østfold show that although the programme achieved a more favourable stage distribution of invasive carcinomas, there was no reduction in incidence of invasive carcinoma although hundreds of cases of dysplasia and carcinoma *in-situ* had been eliminated. A similar fall in stages II and III cases had occurred in the rest of Norway. They attribute the shortcomings of the programme to (a) failure to reach the high risk social class of the population; (b) the rapid development of some cervical cancers, which remain undetected unless the screening is carried out at impracticably short intervals; (c) observer and sampling errors inherent in the test which allow

lesions to pass undetected. Koss (1972) refers to the problem of differences in terminology and observer variation in the detection of cervical carcinoma by cytology.

We have in this analysis substituted the vague term 'false error rate' by the concept of sensitivity of the test, which allows analysis of diagnoses of various degrees of epithelial abnormality. This seemed important as different preventative and therapeutic procedures have been based on frequently loosely defined morphological criteria. Although in their investigations both cytologists and histologists used the same clearly defined criteria and although the senior technicians in Laboratory D responsible for screening had originally been trained in laboratory A, significant observer variations were noted.

Results of our investigations, with reservations due to the small sample and its selection, indicate that observer variation is partly responsible for the discrepancies of opinions on (1) the significance of epithelial changes of the cervix; (2) the concept of the development of invasive carcinoma through phases of severe dysplasia to carcinoma *in situ*; and, consequently, on (3) the efficacy of mass screening in reducing morbidity of and mortality from carcinoma of the cervix.

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