

The Cardiff Cervical Cytology Study

Prevalence and epidemiology of cervical neoplasia

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SUMMARY The Cardiff Cervical Cytology Study showed a prevalence of carcinoma-in-situ that rose to a peak of 6·1/1000 in age group 35–44 and then decreased. Prevalence of microinvasive and occult invasive carcinoma rose to peaks of 1·8/1000 and 1·1/1000 respectively in age group 45–54 and then declined. Epidemiological analysis was based on comparison of three groups—dysplasia, carcinoma-in-situ and microinvasive carcinoma combined, and occult and clinical invasive carcinoma combined. For all groups prevalence increased with lower social class, was higher in widowed, divorced and separated women than in married women, and increased with decreasing age at first marriage and at first pregnancy and with increasing number of pregnancies. The magnitude of these associations was remarkably similar for all three histological groups. Screening for cervical neoplasia is based on the belief that the various histological categories are part of a continuum, a spectrum of disease, and the existence of a common epidemiological pattern for the three histological groups is consistent with such a hypothesis.

Screening programmes for cervical cancer are based on the assumption that cervical neoplastic disease is commonly the result of a progression from normal epithelium through dysplasia and carcinoma-in-situ to invasive cancer. Knox¹ in 1966 pointed out that this natural history cannot be verified pathologically because accurate diagnosis of each state requires complete removal of the lesion. He argued that inferences about the natural history could be drawn from population studies provided that they were designed to give accurate estimates of both the prevalence and the incidence of the various states. The major design feature of such a study was that each woman must be examined at least three times so that both prevalence and incidence could be estimated while allowing for the false negative error rate.

The Cardiff Cervical Cytology Study,^{2,3} started in 1965 and based on a defined total population, conformed to the major requirements outlined by

Knox, except that the population size was smaller than he recommended. Demographic data were obtained from the whole of the defined population, both screened and unscreened, so that the effect of selection bias on prevalence and incidence could be estimated.

In the present paper we describe the prevalence of the various histological states, compare these estimates with those reported by other workers, and discuss possible sources of error and bias. In addition the epidemiology of the various states is described and compared.

Materials and methods

The enumeration and definition of the population and the initial response rates have been described in detail elsewhere.^{2,3} Briefly, the study was based on a defined population, namely, all 'ever-married' women aged 25–69 resident within the Cardiff City

area. The total population numbered 70 869 women, of whom 45 915 (65%) had had at least one cervical smear test before February 1971 when entry to the study was terminated. The current analysis was based on 45 266 women of known age who had not had a hysterectomy or a previous invasive cancer of the cervix and who did not currently have any other gynaecological cancer.

The methods of taking and classifying smears and the general clinical management of patients have been described elsewhere.^{3,4} Smears were classified as normal, atypical, dyskaryotic (mild, moderate or severe), suspicious, or positive.

When no clinical lesion was present the usual initial surgical procedure was cone biopsy. In some cases with associated pelvic pathology, hysterectomy was carried out without preliminary biopsy. From June 1970 colposcopy was used increasingly and in these cases punch biopsy was often the initial surgical procedure.

All histology specimens were classified on a six-point scale as follows:

Normal or no relevant significant abnormality.

Dysplasia (mild/moderate).

Carcinoma-in-situ (including severe dysplasia).

Microinvasive carcinoma (including borderline invasion).

Occult invasive carcinoma (histological evidence only of invasion).

Clinically invasive carcinoma (macroscopic invasion).

The prevalence test was defined as the first smear test taken between 1965, when the study began, and February 1971, when entry to the study closed. For 96% of the women this was their first known cervical smear test. The cytological prevalence result was defined as the worst cytology at, or within three months of, the prevalence test.⁴

Operations yielding histological data occurred at widely varying times after the initial cytology. In many cases, particularly in those women with smears classified as mildly dyskaryotic, many further smears were taken before the decision was made to carry out a biopsy. It was essential to distinguish between prevalent (initially existing) neoplasia and incident neoplasia (arising subsequently). Therefore some time scale had to be defined within which pathology was related to the initial cytology, and hence considered to be prevalent, and outside which it was considered to be incident. Since the interval between cytology and operation was highly dependent on the cytological classification, time scales that varied with that classification were chosen, as follows:

Normal/atypical—9 months.

Dyskaryosis—24 months.

Suspicious/positive—indefinite.

The prevalent neoplasia was then defined as the worst abnormalities found within the above given time interval following the prevalence test.

The data are primarily presented as age-specific prevalence per 1000 women. In considering the epidemiology of cervical cancer, data are presented showing the association between age-specific prevalence and social class, marital status, age at first marriage and at first pregnancy, and total number of pregnancies. To assess the influence of the latter four factors independent of social class, age-specific prevalence was social class standardised using the direct method of standardisation.⁵ The total screened population was used as the standard population.

To facilitate comparison of the epidemiology of the different histological states an overall summary estimate of prevalence was calculated. This is described as the 'age and social class standardised prevalence ratio', or SPR, and was obtained by standardising prevalence to the age and social class distribution of the total screened population using the indirect method of standardisation.⁵ The SPR for any group is simply the ratio ($\times 100$) of the number observed in a particular histological state to the number expected, given the age and social class composition of the group.

To consider in detail the epidemiology of cervical neoplasia it was necessary to combine histological groups because of the small numbers of cases in some of them. Thus, in the detailed epidemiology, carcinoma-in-situ and microinvasive carcinoma have been combined, as have occult and clinically invasive carcinoma. The epidemiology of dysplasia is compared with that of the two main histological groupings but is not considered in greater detail because of the relatively small number of women so classified.

Results

The prevalence of the various cytological categories is shown by five-year age groups in Table 1. The prevalence of suspicious or positive smears increased with increasing age to a maximum of 11.2/1000 in age group 45–49 and then decreased slowly. The prevalence of dyskaryotic smears was highest (10.2/1000) in the youngest age group (25–29) and then decreased with increasing age. There was no very clear pattern to the prevalence of atypical smears except that it was markedly lower in the three oldest age groups. Conversely, the prevalence of normal smears was highest in those same three age groups.

The prevalence of the five histological categories is shown, by age, in Table 2. Carcinoma-in-situ, microinvasive carcinoma, and occult invasive

Table 1 Age-specific prevalence (per 1000) of the various cytological categories

Age groups (years)	CYTOLOGICAL CATEGORY				Total no. of women
	Normal	Atypical	Dyskaryotic	Suspicious/Positive	
25-	878.5	106.7	10.2	4.6	9 175
30-	898.4	90.1	6.7	4.7	6 823
35-	898.4	87.9	4.9	8.8	6 566
40-	890.2	95.0	6.7	8.1	6 313
45-	873.8	108.8	6.2	11.2	5 342
50-	893.4	92.8	4.9	9.0	4 107
55-	920.6	65.2	4.6	9.6	3 235
60-	924.4	65.0	2.6	8.1	2 340
65-	925.3	62.3	3.7	8.8	1 365
Total no. of women	40 450	4 181	293	342	45 266

Table 2 Age-specific prevalence (per 1000) of the various abnormal histological categories

Age groups (years)	Dysplasia	Carcinoma-in-situ	Microinvasive carcinoma	Occult invasive carcinoma	Clinical invasive carcinoma*	Total no. of women
25-34	1.1	4.7	0.6	0.0	0.3	15 998
35-44	0.5	6.1	1.5	0.6	1.1	12 879
45-54	1.0	5.7	1.8	1.1	2.3	9 449
55-64	0.5	4.5	0.5	0.9	5.0	5 575
65-69	0.7	3.7	0.0	0.7	6.6	1 365
Total no. of women	38	238	49	24	77	45 266

*Previously unknown clinical invasive carcinoma (see text).

Table 3 Age-specific prevalence (per 1000) and social class

Social class	Carcinoma-in-situ plus microinvasive carcinoma			Occult plus clinically invasive carcinoma			Total no. of women*		
	I and II	III	IV and V	I and II	III	IV and V	I and II	III	IV and V
Age groups (years)									
25-34	4.3	4.9	7.6	0.3	0.4	0.0	3 745	8 571	2 778
35-44	4.6	7.7	11.1	1.7	0.9	3.2	3 465	6 784	2 159
45-54	4.7	7.8	10.2	1.6	3.1	5.7	2 536	4 772	1 763
55-69	4.3	3.0	7.9	4.3	4.2	7.9	1 633	3 346	1 512
Total no. of cases	51	141	75	18	38	29	11 379	23 473	8 212
Age-standardised prevalence ratio	70	95	145	70	75	147			

*For 2 202 women, social class was either unclassified or not known. Among these, 20 had carcinoma-in-situ or microinvasive carcinoma and 16 had occult or clinical invasive carcinoma.

carcinoma had a unimodal age distribution, with peaks of 6.1, 1.8, and 1.1 per 1000 respectively. For carcinoma-in-situ the peak prevalence occurred in age group 35-44 while for the other two groups it occurred in age group 45-54. The prevalence of clinically invasive cancer increased with age, reaching 6.6/1000 in age group 65-69. It should be noted that clinically invasive carcinoma strictly implies 'previously unknown clinically invasive carcinoma', since all cases known to have had clinical carcinoma before their prevalence test have been excluded from

the analysis. The prevalence of mild to moderate dysplasia was low, corresponding to the low biopsy rate for mild dyskaryosis,⁴ and exhibited no very clear pattern with age.

The detailed epidemiology for the two combined groups (carcinoma-in-situ/microinvasive carcinoma and occult/clinical invasive carcinoma) is shown in Tables 3 to 7. The relationship between social class and the prevalence of the two combined histological groups is shown in Table 3. Social Classes I and II have been combined, as have classes IV and V.

Prevalence of both histological groups in Social Classes IV and V was twice as high as in classes I and II.

Table 4 shows the association with *marital status*, which was subdivided as married or widowed/divorced/separated. Overall, prevalence was about 50% higher in the widowed/divorced/separated group. For the carcinoma-in-situ/microinvasive carcinoma group, the detailed age-specific prevalence shows that the marital status effect was present only among the younger women, for whom there was a twofold to fourfold difference. A similar, but less striking, age effect was also present in the occult/clinically invasive carcinoma group.

The association between *age at first marriage* and prevalence is given in Table 5. Prevalence was lowest in those whose age at marriage was 25 or over. Prevalence increased, marginally, in those married between the ages of 20 and 24 and was two to three times as high in those married before the age of 20. The pattern was similar for the two histological groups.

The association between *age at first pregnancy* and prevalence is shown in Table 6. The association was similar to that shown with age at first marriage, but more striking. Compared with those whose age at first pregnancy was 25 or more, prevalence was twice as high in those first pregnant between the age of 20 and 24 and three times as high in those first pregnant before the age of 20. Women with no pregnancies had the lowest prevalence. This pattern was almost identical for the two histological groups.

Prevalence increased steadily with increasing *number of pregnancies*, as shown in Table 7. Compared with those with no pregnancies, prevalence was almost 50% higher in those with one or two pregnancies, twice as high in those with three or four and three to four times as high in those with five or more pregnancies. Again the pattern was remarkably similar for the two histological groups.

The detailed epidemiology of dysplasia has not been presented because of the small number of cases (Table 2). However, the *comparative* epidemiology for dysplasia and the other two histological groups is

Table 4 Age-specific prevalence† (per 1000) and marital status

Marital status	Carcinoma-in-situ plus microinvasive carcinoma		Occult plus clinically invasive carcinoma		Total no. of women*	
	Married	W/D/S	Married	W/D/S	Married	W/D/S
<i>Age groups (years)</i>						
25-34	4.9	20.6	0.3	0.0	15 456	497
35-44	7.2	16.2	1.5	2.8	12 257	603
45-54	7.8	6.2	3.0	7.0	8 528	913
55-69	4.1	5.2	5.9	5.8	5 161	1 769
Total no. of cases	249	38	77	24	41 402	3 782
Age and social class standardised prevalence ratio	95	154	94	129		

†Social class standardised.

*For 82 women, marital status was unknown. None of these 82 had any positive histology.

W/D/S = Widowed, divorced, or separated.

Table 5 Age-specific prevalence† (per 1000) and age at first marriage

Age at first marriage	Carcinoma-in-situ plus microinvasive carcinoma			Occult plus clinically invasive carcinoma			Total no. of women*		
	<20	20-24	25+	<20	20-24	25+	<20	20-24	25+
<i>Age groups (years)</i>									
25-34	9.8	3.9	3.1	0.2	0.2	0.4	4 202	9 554	2 030
35-44	11.8	7.6	5.1	5.1	1.3	0.8	2 205	7 263	3 298
45-54	12.9	8.7	4.5	8.8	2.3	3.1	1 281	4 867	3 255
55-69	5.6	4.4	4.3	12.1	6.6	3.8	726	2 882	3 288
Total no. of cases	88	144	50	34	41	25	8 414	24 566	11 871
Age and social class standardised prevalence ratio	159	93	68	228	84	70			

†Social class standardised.

*For 415 women, age at first marriage was unknown. Among these, five had carcinoma-in-situ or microinvasive carcinoma and one had clinical invasive carcinoma.

Table 6 Age-specific prevalence† (per 1000) and age at first pregnancy

Age at first pregnancy	Carcinoma-in-situ plus microinvasive carcinoma				Occult plus clinically invasive carcinoma				Total no. of women*			
	<20	20-24	25+	None	<20	20-24	25+	None	<20	20-24	25+	None
<i>Age groups (years)</i>												
25-34	13.9	5.3	1.8	3.2	0.8	0.1	0.2	0.0	2 386	7 974	3 688	1 782
35-44	17.3	9.4	4.5	1.1	8.2	2.2	0.5	1.1	965	5 580	5 333	934
45-54	12.7	11.3	4.8	4.7	7.4	4.6	2.6	1.3	612	3 331	4 640	817
55-69	6.5	5.8	4.4	2.4	5.1	10.5	4.4	2.5	345	2 100	3 634	807
Total no. of cases	59	146	68	13	14	53	30	4	4 308	18 985	17 295	4 340
Age and social class standardised prevalence ratio	205	119	64	50	195	141	66	42				

†Social class standardised.

*For 338 women, age at first pregnancy was unknown. Among these one woman had carcinoma-in-situ.

Table 7 Age-specific prevalence† (per 1000) and number of pregnancies

No. of pregnancies	Carcinoma-in-situ plus microinvasive carcinoma				Occult plus clinically invasive carcinoma				Total no. of women*			
	0	1-2	3-4	5+	0	1-2	3-4	5+	0	1-2	3-4	5+
<i>Age groups (years)</i>												
25-34	3.2	3.7	6.2	13.6	0.0	0.2	0.4	0.0	1 782	7 718	4 837	1 578
35-44	1.1	6.0	7.8	13.1	1.1	1.4	2.3	1.7	934	5 403	4 393	2 110
45-54	4.7	7.4	7.9	10.8	1.3	2.1	3.1	8.6	817	4 376	2 897	1 338
55-69	2.4	3.7	5.3	8.8	2.5	5.0	6.7	11.4	807	3 189	1 953	968
Total no. of cases	13	104	99	71	4	34	35	28	4 340	20 686	14 080	5 994
Age and social class standardised prevalence ratio	50	83	109	166	42	78	114	171				

†Social class standardised.

*For 166 women, number of pregnancies was unknown. None of these had abnormal histology.

shown in the Figure. The overall age and social class standardised prevalence ratios provide the means of comparison.

As with the two main histological groups, prevalence of mild to moderate dysplasia increased with lower social class, was higher among widowed, divorced, and separated women, and increased with decreasing age at first marriage and at first pregnancy, and with increasing total number of pregnancies. Not only were the directions of the associations the same for all three histological groups but also the magnitudes of the associations were remarkably similar.

Discussion

Many authors have reported on the epidemiology of cancer of the cervix (for reviews see Wynder,⁶ Rotkin,⁷ and the Walton Report⁸). The majority of the studies are case-control studies based on patients with clinically invasive cancer. A few of the case-control studies (for example, Aitken-Swan and Baird⁹) include a carcinoma-in-situ group and some studies (for example, Christopherson and Parker¹⁰)

are based on population screening programmes. Almost without exception, these studies find that cervical cancer is more common in lower social class groups, in widowed/divorced/separated women, and in women with early age at first marriage and first pregnancy and large numbers of pregnancies. Our study, in which prevalences are based on a defined population, agrees with these findings. Prevalence of cervical neoplasia is nearly twice as high in Social Classes IV and V as in classes I, II, and III and it is 50% higher in widowed, divorced, and separated women than in married women. Prevalence increases with decreasing age at first marriage—it is slightly increased in those first marrying between the ages of 20 and 24 compared with those first marrying at 25 or later, while in those marrying before the age of 20 it is increased two to three times. The association with age at first pregnancy is similar. Prevalence increases steadily with increasing number of pregnancies. In women with five or more pregnancies it is three to four times as high as in women with no pregnancies, and is twice as high as in those with one or two pregnancies.

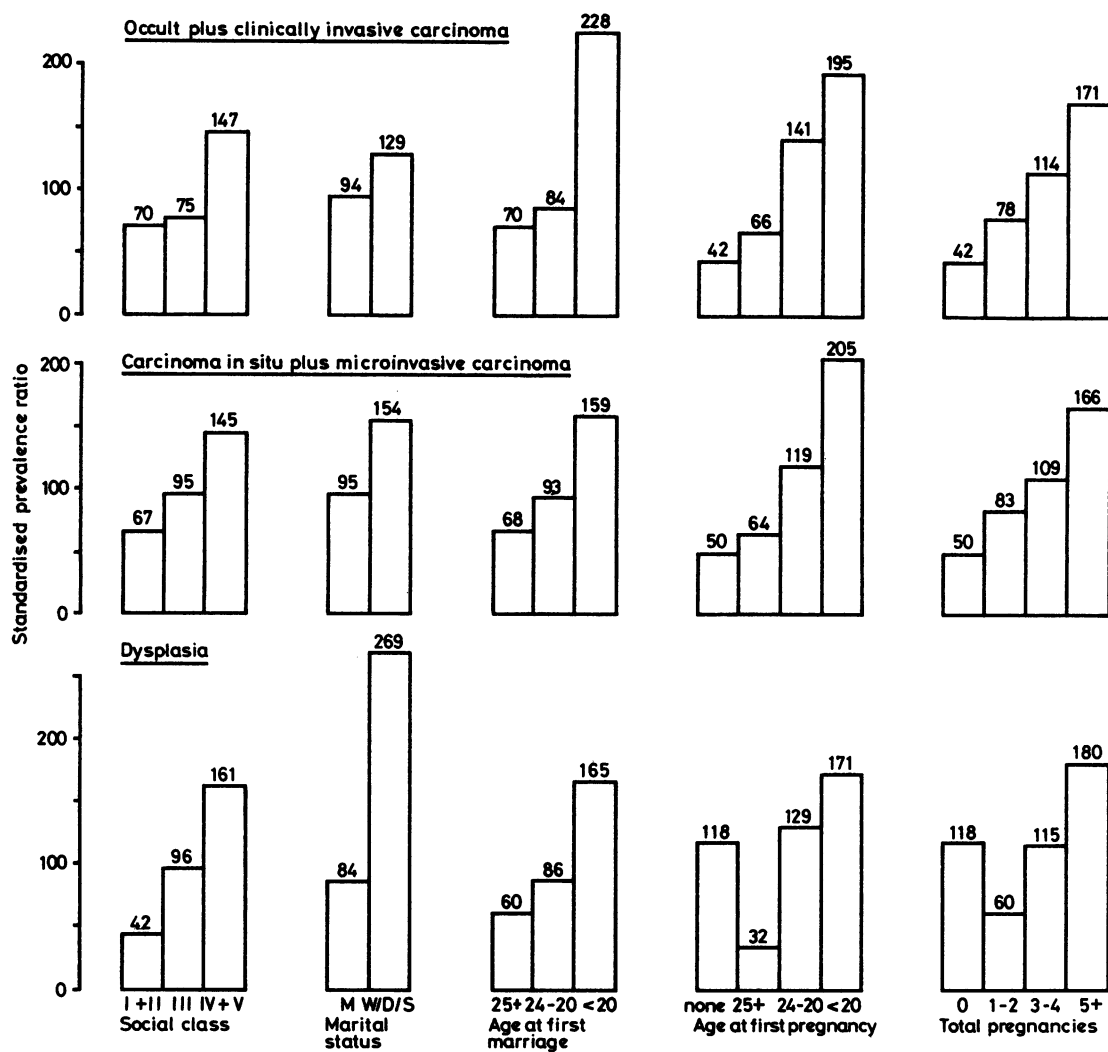


Figure The comparative epidemiology of the various histological categories.

An important and interesting aspect of our data is that the epidemiology of the three histological groups—mild to moderate dysplasia, carcinoma-in-situ/microinvasive carcinoma, and occult/clinically invasive carcinoma—can be compared within a single large population study. The current belief, which provides the rationale for screening, is that these various states are part of a continuum, a spectrum of disease. If this is so, then the various states should have a common epidemiology. Despite the relatively small numbers in some of the subgroups, our data show that the epidemiology of the three histological groups is remarkably similar.

In addition to providing this insight into the epidemiology of cervical neoplasia, these estimates of the prevalence of the various histological states can be used, in conjunction with estimates of incidence and false negative error, to draw inferences about the natural history of the disease. It is essential, therefore, to consider the accuracy of the estimates. The two main potential sources of error are selection bias and classification errors.

To minimise selection bias we attempted to screen a total population. The overall response rate was 65%. Basic demographic data were obtained from those women who accepted the offer of a cytology

test and also from those who refused. We have shown elsewhere³ that response decreased with increasing age and was lower in Social Classes IV and V than in classes I and II. Since prevalence is higher in Social Classes IV and V overall average age-specific prevalence is underestimated. The size of this bias can be estimated by standardising the age-specific prevalence to the social class distribution of the total defined population, screened and unscreened. For the two main combined histological groups the underestimate in prevalence due to the differential social class response rate is typically 0.05–0.2/1000, the bias tending to increase with age.

The other main selective bias arises because women with symptoms tend to select themselves into the screened population. Carcinoma-in-situ, microinvasive and occult invasive cancer were found slightly more frequently among women with symptoms than among those without, while clinically invasive carcinoma was almost always associated with symptoms. This bias therefore results in an overestimation of prevalence. The magnitude of the bias is difficult to quantify because information regarding symptoms was not recorded for the non-responders. The maximum possible bias can be estimated by assuming that all non-responders were symptomless. For the preclinical cancers the maximum bias is 0.1–0.5/1000, again tending to increase with age. The actual bias will be less than this, and since it acts in the opposite direction to that resulting from the differential social class response rate, it is likely that, for the preclinical cancers, the two main selective biases approximately cancel each other out.

The picture is different for clinically invasive cancer, particularly among the older age groups. Here, because of the low response rate, the maximum possible bias is an order of magnitude higher than that resulting from the differential social class response. It seems quite possible that for clinical cancer the true bias will approach this maximum and hence our prevalence of previously undiagnosed clinical cancer is almost certainly grossly overestimated for the older age groups.

Classification errors of two types can occur—incorrect classification of incident cases as prevalent, and incorrect histological classification. We attempted to differentiate between prevalent and incident pathology by defining time intervals after the prevalence smear test in which the histology must fall to be classed as prevalent, these intervals varying with the cytological classification. Few problems arose if the cytology was normal/atypical or suspicious/positive, because in the first case there was rarely any subsequent histology available and in the latter histological examination almost always

followed immediately on the abnormal cytology. Problems arose when the prevalence cytology was dyskaryotic. Such women were routinely rescreened at three- or six-month intervals and, in a few cases, usually those with persistent mild to moderate dyskaryosis, biopsy could occur up to six years after the prevalence test. It was clearly impossible to determine whether the resultant histology in such cases was prevalent or incident. This difficulty is rarely mentioned in the literature although it is alluded to by Fidler, Boyes and Worth¹¹ with regard to the British Columbia study. We decided to impose an upper limit of two years for classifying prevalence.

The histological classification system is probably best assessed by comparing our estimates of the prevalence of the various states with those reported by other workers. This is difficult because many studies do not report true prevalence, but instead quote detection rates which are variable mixtures of prevalence and incidence. The best comparative data are those from British Columbia.¹¹ Our age-specific prevalence of carcinoma-in-situ is slightly lower than theirs. They did not report prevalence separately for microinvasive and occult invasive carcinoma. From their detection rate data, it seems likely that the prevalence of occult invasive carcinoma is similar in the two areas but that our prevalence of microinvasive carcinoma is higher than theirs, such that the sum of the prevalence of carcinoma-in-situ and microinvasive carcinoma is very similar in the two areas. This effect may well have arisen because of minor classification differences.

Our average prevalence of histologically proven dysplasia was just over 0.8/1000. Comparable estimates are difficult to find because of varying criteria, definitions, and population bases. In particular, clear distinctions are not always made between cytological and histological terminology. Stern¹² reported an average prevalence of dysplasia of 5.4/1000, the prevalence showing a steady decline from 10.9/1000 at age 20–29 to 3.0/1000 over the age of 70. It is not clear how many of Stern's dysplasia cases were biopsy-verified. Her figures are remarkably similar to our age-specific prevalence of the cytological category dyskaryosis. Other studies (for example, Hulka and Kupper¹³) suggest a prevalence of histologically confirmed dysplasia relative to carcinoma-in-situ much higher than we have found. These differences may, in part, arise from variations in the management of the minor cytological abnormalities. In our study, only 28% of women classified as having mild dyskaryosis had a biopsy within two years of their prevalence test.⁴ The corresponding figures for those classified initially as having moderate and severe dyskaryosis were 46% and 63%. However, if this conservative management

is a major reason for our low prevalence of dysplasia, then it must be concluded that dysplasia is frequently a transient condition, as the majority of our patients with dyskaryosis not subjected to biopsy subsequently had only normal or atypical smears.⁴ It seems more likely that these differences arise from differences in the classification of dysplasia.

In summary, there is every reason to believe that our estimates of the prevalence of carcinoma-in-situ, microinvasive and occult invasive carcinoma are accurate, and that when considered in conjunction with future estimates of incidence and false negative error they should yield new insights into the natural history of cervical neoplastic disease. The relevance and importance of dysplasia is likely to remain obscure until there exists a standard, reproducible classification system in which, in particular, the term dysplasia is not used to describe both cytological and histological abnormalities.

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