Invasive cancer of the cervix in women with mild dyskaryosis followed up cytologically

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Mildly dyskaryotic smears are common, and women with such results are often followed up with further cervical smear tests. An important consideration in evaluating this practice would be the annual incidence of invasive cervical cancer. A reanalysis of five previous studies of the cytological follow up of women with mildly abnormal smear test results was undertaken to calculate this incidence. The annual incidence of invasive cancer in these women ranged from 0 to 420 per 100 000 women years. The large studies providing the most precise estimates had annual rates of 143 to 420 per 100 000 women years. This is 16 to 47 times greater than in women aged 15-34 years in England and Wales. The average rate was 208 per 100 000 women years. Women with mild dyskaryosis are at high risk of developing invasive cervical cancer despite cytological follow up. A full appraisal of the costs and benefits of colposcopy in this situation is urgently required.

Introduction

From a survey of several cytology laboratories in England and Wales it is estimated that mild dyskaryosis is reported in just over 2% of all the samples taken in the United Kingdom.¹ The management protocol for women with such abnormalities will have a substantial impact on the cost and effectiveness of the cervical screening programme. Some successful programmes in other countries have managed such women with repeated cervical smear tests,^{2,3} but cytology is not a precise science and cross sectional, retrospective,^{4,5} and prospective^{6,7} colposcopic studies have shown that mild dyskaryosis is associated with a high prevalence of cervical intraepithelial neoplasia stage III. These data have led some to recommend that all women with mild dyskaryosis should be referred for colposcopy after the first such result.⁸

Others, reporting the results of retrospective studies of the cytological surveillance of women with mild cytological abnormalities, have interpreted their data as justifying policies with more restrictive criteria for referral to colposcopy.⁹⁻¹² One study has drawn attention to the high incidence of invasive cancer in women with mild dyskaryosis.¹³

The main measure of the success of the cervical screening policy must be the incidence of invasive disease. Most studies of cytological surveillance have been too small to address this issue directly, but many have reported cases of invasive cervical cancer in women followed up cytologically because of a mildly abnormal smear test result.

The rate of development of invasive cancer after a mild cytological abnormality will depend to some extent on the length of follow up and is better expressed as an incidence than as a prevalence. We examined data from contemporary British studies to estimate the annual incidence of invasive cervical

Definitions of cervical malignancy

- *Cervical intraepithelial neoplasia* describes lesions with the characteristic histological features of malignancy that are confined to the epithelium of the cervix and show no evidence of invasion into the underlying stroma. Three grades of increasing severity are described. The increasing severity is thought to correlate with the risk of progression to invasive disease
- *Invasive carcinoma of the cervix* is a tumour of epithelial cells that invades at least some way into the underlying connective tissues of the cervix

cancer in such women and to compare it with the rate in the general population.

Methods

We searched by hand and on Medline for studies published in the past 10 years that reported the results of the cytological surveillance of women with mild cytological abnormalities. Studies were restricted to those conducted in the United Kingdom to avoid national differences in cytology policy and rates of invasive cancer. The authors were contacted to determine the number of women years of follow up in each study up to the time of the last contact. In one study in which the investigators were no longer able to provide a figure for the number of women years of follow up, an estimate was made from the published data by combining the intensive initial follow up period of two years on 1347 women with data on the numbers followed up in the subsequent 14 years.⁹ All cancers occurring in women who were lost to follow up were excluded. The annual incidence of invasive cervical cancer during the period of observation was calculated from these figures.

One other study of mild dyskaryosis was published during this period.¹⁴ The subjects were highly selected and some were referred to colposcopy at the outset. This contrasts with all the other studies, in which unselected, consecutive women with the appropriate cytological abnormality were followed up cytologically until clinical suspicion, a more severely abnormal smear test result, or a persistent mild abnormality dictated gynaecological referral. Data from this study have been included for completeness, but the number of women years of follow up is not known precisely and has been estimated with the help of the authors, Jones *et al.*¹⁴

The incidence of cervical cancer rises steeply up to 30 years of age, and the women in these studies with mild abnormalities were mainly aged 15-34. The incidence of invasion in this age group was calculated from data on cancer registrations in 1985 in England

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TABLE I—Annual incidences of invasive cancer in women with mild cytological abnormalities followed up cytologically

Reference	Year	Grade of dyskaryosis included	No of women in study	No of women years of follow up	Average No of years of follow up	No of women with invasive lesions (microinvasive lesions)	Rate per 100 000 women years (95% confidence interval)
Robertson <i>et al</i> ^a	1988	Mild	1781	4905	2.75	? (?)	143 (57 to 294)
Fletcher <i>et al</i> ³	1991	Borderline,* mild, and moderate	666	1190	1.79	5 (0)	420 (134 to 983)
Kirby <i>et al</i> ⁶	1992	Mild and moderate	500	3473	6.95	5 (3)	144 (46 to 337)
Cooper <i>et al</i> ²	1992	Mild	305	700	2.30	1 (1)	143 (4 to 796)
Hirschowitz <i>et al</i> ¹¹	1992	Borderline*	437	2676	6.12	10 (7)	374 (186 to 714)
Jones <i>et al</i> ¹⁴	1992	Mild	214	502	2.35	0	0 (0 to 737)

*Borderline nuclear abnormalities.

†Study not strictly comparable with others.

and Wales,¹⁵ and this figure was compared with the incidences in the studies.

Results

Table I summarises the results. The absence of invasion in the study by Jones *et al* reflects the small number of women years of follow up and the highly selective nature of the inclusion criteria.¹⁴ Data from the large studies, which provide the most precise estimates, suggest that the annual incidence of invasion might be between 143 and 420 per 100 000 women years. The average rate for all six studies was 208 per 100 000 women years. These figures are 16-47 times greater than the incidence of 9 per 100 000 women aged 15-34 in England and Wales in 1985. Fletcher *et al* found a 62-fold increase in invasive cancer: they recorded five cases of invasive cancer in women aged 15-34, the expected number of cases based on age specific national rates being 0.08.¹³

Three of the studies were restricted to women with mild dyskaryosis.^{9,12,15} One study included only women with borderline results,¹¹ one study included both mild and moderate dyskaryosis but did not indicate the proportion of subjects with mild disease,¹⁰ and the last study included borderline results (30%), mild dyskaryosis (64%), and moderate dyskaryosis (6%). There seems to be no correlation between the scope of the inclusion criteria and the incidence of invasive disease.

Table II shows the proportion of women who were referred for biopsy during the different studies. Unfortunately, cumulative rates are not available for all the studies, but it is quite clear that there were differences in management between the studies, with the proportion referred for colposcopy and biopsy ranging from 14% at 4½ years to 64% at 4 years. The two studies with the highest rates of invasion had the lowest rates of biopsy.^{11,13} These differences in the incidence of invasive disease may be due to different management policies or to differences in the risk profiles of the populations studied.

In cytological follow up studies it is not possible to be certain whether invasive cancer was coexistent at the time of the dyskaryotic smear test result or arose during follow up. If most cases of invasive cancer were coexistent at the time of the initial result, a high proportion of invasive cancers would occur in the early period of follow up. These data do not allow a detailed

examination of the time interval between the initial abnormal result and the diagnosis of invasion. In those reports which specifically mention this issue, however, four cases were probably invasive at the time of the initial smear test since invasive cancer was diagnosed within two months, whereas in 11 other cases, invasive disease occurred over several years.^{9,13} Moreover, if most cases of invasive cancer were coexistent at the time of the initial dyskaryotic result the studies with shorter periods of follow up might be expected to have higher annual rates than those with longer average follow up. This pattern is not observed (table I), and these data suggest that the risk of invasive cancer persists throughout follow up, even up to five to 10 years after a mildly dyskaryotic result.

Discussion

These data show that women with mildly abnormal smear test results who are followed up with cytology have a much higher incidence of invasive cancer than the general population. Some of these cases were invasive from the outset, but the remainder probably progressed from preinvasive lesions. They are clearly a high risk group that requires very careful management, and these data argue the need for a large, well designed study to compare early referral to colposcopy with cytological follow up.

In an attempt to perform a decision analysis of this problem, Johnson *et al* recently calculated the risk of cancer by combining single estimates of the prevalence of invasive disease after treatment of cervical intra-epithelial neoplasia; the prevalence of positive, follow up smear test results, the prevalence of abnormal smear test results after a period of normality; and the failure rate of cytology.¹⁶ This complex calculation is an indirect way of deriving the same data that we have presented in this article. Furthermore, Johnson *et al* used prevalence data rather than incidences. When our five year cumulative incidences and the five year cumulative rate of invasive cancer after treatment of 500 per 100 000 from the study of Pearson *et al*⁷ (cited by Johnson *et al*) are used in Johnson *et al*'s calculations, immediate referral to colposcopy would result in a 54-84% reduction in the risk of invasion.

Objections to colposcopy are cost, lack of resources, and the psychological impact on women. One comparison of the cost of colposcopy with that of multiple repeated smear tests has suggested that immediate colposcopy would be cheaper.¹⁶ We are unaware of any published study comparing anxiety in women being followed up cytologically with that in women attending for immediate colposcopy, but, in our experience, many women with mild dyskaryosis ask for colposcopy even when cytological surveillance has been recommended to them. There is no doubt that colposcopy does induce a great deal of anxiety, but such anxiety can be reduced substantially by explanatory leaflets sent out with the appointment.¹⁸ This is obviously an important area that requires urgent investigation.

Until such time as the primary screening test is more accurate or an efficient, alternative secondary test

TABLE II—Biopsy rates in women with mild cytological abnormalities followed up cytologically. Studies are arranged in descending order of biopsy rate

	Year	Crude biopsy rate (%)	Cumulative biopsy rate	No of invasive lesions per 100 000 women years
Cooper <i>et al</i> ²	1992	178/305 (58)	64% at 4 years	143
Robertson <i>et al</i> ^a	1988	722/1347 (54)	Not stated	143
Jones <i>et al</i> ¹⁴	1992	87/214 (41)	Not stated	0
Kirby <i>et al</i> ⁶	1992	Not stated	19-26% at 4 years 40-42% at 10 years	144
Hirschowitz <i>et al</i> ¹¹	1992	98/437 (22)	15% at 4 years 30% at 8 years	374
Fletcher <i>et al</i> ³	1991	45/666 (7)	14% at 4½ years	420

becomes available^{19 20} it seems sensible for this high risk group of women to be referred for colposcopy after the first report of mild dyskaryosis.

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Managing patients who refuse blood transfusions: an ethical dilemma

Patients who refuse blood transfusions after severe blood loss have a poor prognosis but survival is possible. Below Simon Finfer and colleagues describe how they managed two patients who presented after a car crash. We asked an ethical expert, a former pathologist who is a Jehovah's Witness, and a lawyer to comment on the issues that these cases raised.

Major trauma in two patients refusing blood transfusion

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Patients with severe injuries who refuse blood transfusion present complex medical, legal, and moral problems. In many cases treatment may seem futile but occasionally patients will survive despite severe haemodilution. We report the cases of two men who were badly injured when their car was impaled on a motorway crash barrier.

Case reports

The front seat passenger was a 29 year old man. He had an open fracture of the left femur, laceration of the left femoral artery, and a closed fracture of the right femur. He was conscious, and despite repeatedly being told that he would probably die he refused transfusion. He was resuscitated without blood products and transferred to hospital. His haemoglobin concentration on arrival was 73 g/l. His left leg was amputated above the knee and he had external fixation of the right femur.

After surgery he was admitted to the intensive care unit and treated with mechanical ventilation, intravenous iron-dextran, vitamin B12, folic acid, and erythropoietin. The following day his haemoglobin concentration was 16 g/l and he required an intravenous infusion of noradrenaline to support his arterial blood pressure. His acute physiological and chronic health evaluation 2 score was 13 (predicted mortality 6%), but it seemed unlikely that he would survive. He was again offered a blood transfusion, but refused. Two days later his haemoglobin concentration had increased to 32 g/l and mechanical ventilation and the noradrenaline infusion were successfully discontinued. He was then transferred to the ward.

He had internal fixation of his right femur with the aid of a cell saver two weeks later. He recovered well and was discharged home. His injury severity score

and revised trauma score were 17 and 7.84 respectively, predicted survival by the trauma related injury severity score was 99%.

The driver, a previously healthy 30 year old man, suffered partial amputation of the left leg with an open fracture through the knee joint. His right leg was crushed with extensive degloving and the compartment syndrome. He was trapped in the car for two hours, during which time he was conscious and refused blood transfusion. On arrival in accident and emergency his haemoglobin concentration was 28 g/l and arterial pH 7.18. Despite repeated explanations of the risk to his life he continued to refuse blood transfusion. His left leg was amputated above the knee, and he had right leg fasciotomies. At the end of the procedure he had a cardiac arrest from which he could not be resuscitated. At the time of cardiac arrest his haemoglobin concentration was 9 g/l. His predicted survival by the trauma related injury severity score was also 99%.

Comment

Doctors are legally obliged to treat all patients to whom they have a contractual duty, and this includes patients who impose conditions on treatment. A doctor can refuse to treat such a patient only when no harm results to the patient or a colleague takes over care.² We agreed not to give blood, although we thought that both patients would die without it. The survival of our first patient shows that aggressive resuscitation and, if necessary, intensive care must be offered to trauma victims who refuse blood transfusion as it is possible to survive extreme haemodilution. However, both patients had a predicted survival of 99%, and the early death of our second patient must be attributed to his refusal to accept blood transfusion.

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