Correspondence

Multifactorial audit of invasive cervical cancer

We read with interest the article by Dr Slater,1 in which he makes recommendations for the Cervical Screening Programme based on 20 deaths from cervical cancer occurring in the Rotherham district.

We have several comments. The cases were selected from cytology records and this method is bound to underestimate the number of patients who develop cervical carcinoma and who have never had a smear (six patients in this study). These patients are very hard to locate, and the Avon Cervical Screening Cancer Registry records and mortality data from the Office of Population Censuses and Surveys (OPCS), as well as histology records. In our experience none of these sources success- fully identifies all cases.

Another factor discussed is the issuing of an inappropriate laboratory report. The table quotes this as occurring in 16 of 20 cases (80%) which appears to be mathematically incorrect. It is worth noting that of these (presumably six) cases only four involved missed dyskaryosis and this was of the “easily missed” variety. As stated, there is as yet no definition of an acceptable false negative rate in the Cervical Screening Programme and we look forward to forthcoming guidelines on this important matter.

Dr Slater also comments on the lack of failsafe procedures for inadequate smears. While it is true that the national guidelines refer to “screening work with abnormal smears”, there is no reason why laboratories or FHSA should not also include follow up of inadequate smears in their failsafe systems. Indeed, the Avon Cervical Screening Programme has incorporated such a mechanism.

A further point of interest is Dr Slater’s suggestion that opportunistic smears should be performed during hospital visits. We contend that this is impractical and potentially dangerous. Most hospital wards and non-gynaecological outpatient departments do not have the equipment or trained personnel to perform cervical smears and the resulting specimens are likely to be of poor quality, which may well lead to a false sense of security, or inadequacy, leading to increased workload and patient anxiety because the smears need repeating.

Finally, we would like to point out how small the numbers in this audit are. Expressing the results in terms of percentages seems rather meaningless and no values for statistical significance are included. While this audit makes interesting anecdotal reading, we feel that the results derived are of limited value in assessing the effectiveness and quality of the National Screening Programme.

K DENTON
M BRETT
Department of Cellular Pathology, Cytopathology Department, Southmead Hospital, Bristol BS10 5NB

Dr Slater comments:
I thank Drs Denton and Brett for their interest in my recent article.

I wholeheartedly agree that there are numerous sources from which to obtain such patient information. My study merely highlighted that derived from the Rotherham Hospital records. In fact, as they suggested, the results were derived from both the cytology and histopathology records. The identification of all cases of cervical cancer, along the lines recommended by the authors, will be an important aspect of the work of the proposed “Regional” Quality Assurance Teams (QATs).1

I apologise for any confusion conveyed with the mathematics in my report. The figure in brackets represents the percentage number of times the factor occurred in the patients. The reason for the apparent discrepancy is that some factors occurred more than once in one specific patient. Retrospectively, this should have been emphasised by a gap between the two columns.

I am pleased to hear that the Avon Cervical Screening Programme has incorporated inadequate smears into their failsafe procedures. Unfortunately, the same cannot be said for most of the remainder of the UK. Sadly, funding for these procedures will not be made available until this aspect is specifically incorporated into national guidelines.

I fully acknowledge that it is usually inappropriate for cervical smears to be undertaken during “non-gynaecological” hospital attendances. As highlighted in my discussion, my proposal was to incorporate cervical smear history into the routine past medical history. Appropriate advice and reference could then be given.

I am appreciative that the numbers in my audit were small. The reason for the article was merely to generate national discussion, as evidenced by the current correspondence. I was always trying to highlight factors that could be used regionally on a unified basis in the new QATs. It would appear highly desirable that all QATs approach this important area of audit in a similar way so that there can be national amalgamation and comparison of data.


I was puzzled by Dr Slater’s assertion that failsafe systems for follow up abnormal smears should be “almost up of adequate smears”. He is suggesting that the National Guidelines on failsafe should be changed, but the only evidence given is a single case of cancer occurring when an inadequate smear had not been repeated for two years.

It is worth remembering that the main responsibility for follow up is with the smear taker. Failsafe mechanisms for abnormal smears is worthwhile because dyskaryosis has a strong association with cervical intraepithelial neoplasia and cancer. Failsafe mechanisms are especially important in cases where women have been suspended from FHSA recall. To justify failsafe of inadequate smears requires evidence that there was an association between inadequacy and disease of a similar order to that between dyskaryosis and disease.

When I have looked at cervical cancers presenting at Watford General, I have found several occurring in women who last smear was taken more than five years before and was normal. Dr Slater’s argument, we would also have to institute failsafe procedures for all normal smears!

Dr Slater comments:
I am appreciative to Dr Rubin for his interest in my article. Although not specifically itemised, my previous audit of deaths from cervical cancer also identified occasional cases where inadequate smears had not been repeated.1 Furthermore, I hope that my article will encourage larger regional audits that will more accurately ascertain the size of the problem. To date, however, inadequate smears have been undoubtedly the “poor relative” of cytopathology reports. For example, there is still no national recommendation with regard to the time within which an inadequate smear should be repeated. Similarly, the potential clinical importance of inadequate smears misrepresented as negative remains poorly emphasised. Indeed, there are no requirements, in my opinion, unreasonably, to exclude inadequate smears from the national proficiency testing scheme. I agree wholeheartedly that failsafe mechanisms were investigated for the follow up of abnormal smears and that the primary responsibility for follow up still remains with the smear taker. In these days of laboratory computerisation, however, it would not appear totally unreasonable that there are secondary checks. Furthermore, inadequate smears have indeed been repeated within, say, three months.

I appreciate the comments of Drs Denton and Brett. It is good to receive such interesting and constructive feedback.

Detection of autoantibodies to neutrophil cytoplasmic antigens

ACP Broadsheet No. 143 has recently been distributed to Australian pathologists.1 It states that indirect immunofluorescence (IIF) is the technique of choice in testing serum samples for antineutrophil cytoplasmic antibodies (ANCA) but that ELISAs should be confirmed using formalin fixed neutrophils and that antibody levels determined by titration of fluorescence. Most laboratories would use IIF to screen for ANCA, but would confirm positive serum samples, determine antigen specificity and antibody titre using enzyme linked immunosorbent assays (ELISAs) for proteinase 3 and myeloperoxidase antibodies, rather than the techniques described in the Broadsheet.

Antigen specific ELISAs have a number of advantages over the other techniques. These ELISAs will confirm the presence of ANCA that have been detected by IIF; non-specific binding can occur with IIF, but is unlikely to occur with both methods. In addition, ELISAs will confirm the presence of ANCA in serum samples with a coincidental antinuclear antibody (ANA). ANA may obscure perinuclear fluorescence, and ANA occur in up to 40% of some series of patients with Wegener’s granulomatosis or microscopic polyarteritis.2

The most important advantage, however, is that the ELISAs will determine antigen
specificity in an ANCA positive specimen, and hence whether a diagnosis of Wegener’s granulomatosis or microscopic polyarteritis is more likely. Serum samples associated with cytoplasmic fluorescence (cANCA) and antineutrophil cytoplasmic antibodies in these organs do not correlate with disease activity, and it is not associated with ANCA. However, probably half of all patients with microscopic polyarteritis have features of classic polyarteritis too. It is these patients who have pANCA with antimeylperoxidase specificity.


Dr Lock comments: I read with interest the comments of Dr Savage regarding the ACP Broadsheet on the detection of ANCA. Several points were raised and I should like to address them in the order they were presented. Savage contends that “most laboratories . . . confirm positive serum samples . . . using ELISAs”. While this may be true in mainland Europe and, presumably, in Australia, in the UK only one third of the laboratories registered with UK NEQAS use ELISAs. A slightly higher proportion, just over 40%, use formalin fixation. That said, however, it is our practice to further subtype all fluorescence positive results by ELISA for proteinase 3 and myeloperoxidase antibodies.

I would agree that proteinase 3 antibodies have a high specificity for a diagnosis of Wegener’s and myeloperoxidase antibodies a high specificity for microscopic polyarteritis. However, I feel that the statement that these specificities “occur in almost no other disease” is very broad. False positive results do occur. For example, myeloperoxidase antibodies may be found in various atypical granulomatous diseases and Henoch Schönleup purpura1 and in rheumatoid arthritis.2 Furthermore, proteinase 3 and myeloperoxidase antibodies are the major reactivities in necrotising vasculitis, but are not the only reactivities. Anti-elastase and anti-h-lamp-2 have been described.

To dismiss atypical patterns as being of no clinical significance is perhaps ungenerous. I agree that they have poor specificity, but are supportive data in the right clinical background—for example, in ulcerative colitis. Furthermore, we have found that the titre of IgA class ANCA does correlate with disease activity in childhood Henoch Schönleup purpura.

Whether ELISAs are better indicators of disease activity remains to be confirmed. Certainly fluorescence tides have not been a universal finding in Wegener’s and perinuclear ANCA suggests problems with the interpretation of ELISA.1 It is also possible that the number of cases demonstrating a type 3 NISH signal is very low. Nevertheless, it is less than that reported previously, where half of the archival lesions defined morphologically as C III were shown to be 5-bromo-4-chloro-3-indolylphosphate as a substrate in the substrate system tends to diffuse within the nucleus and not impart a crisp clear punctate signal (type 2) as is demonstrated with peroxidase/ammonium carbazole. (Cooper, Herrington and McGee, personal observations). This is crucial if ANCA is to be used as a method to detect the physical state of HPV; as caution is required regarding both technique and interpretation.

K COOPER
Department of Anatomical Pathology, School of Pathology, South African Institute for Medical Research & University of Witwatersrand, P.O. Box 1038, Johannesburg 1995, South Africa