Correspondence

p53 in human papillomavirus associated anogenital cancers

It was interesting to read the paper by Ogunbiyi *et al*¹ regarding the investigation of p53 protein expression in anal squamous neoplasia in association with human papillomavirus (HPV) 16. A similar study was recently undertaken² addressing the relation between p53 protein expression and HPV infection in cervical neoplasia. Comparison of these two studies reveals several interesting observations with regard to the role of p53 in HPV positive cancers.

Both studies revealed a strong association between the detection of HPV sequences and p53 antigen expression in invasive cancers. p53 immunocytochemistry was positive in 69.5% of HPV 16 positive invasive anal cancers¹ and in 86% of HPV 16/18 positive invasive cervical cancers.²

Both studies showed uniform positive reactions with the panels of antibodies for p53 antigen detection: DO-1, CK-1, DO-7 and PAb 240, DO-7.² However, while p53 protein expression involved almost all tumour cells in the anal cancer group, only focal isolated cells or groups of cells expressed p53 protein in the cervical cancer study. Nevertheless, the immunocytochemical expression of p53 in both HPV positive anal and cervical cancers is inconsistent with the hypothesis that wild-type p53 cell regulating functions are annulled in HPV positive cancers as a consequence of complexing with HPV E6.^{3,4} As p53 regulates entry into the S phase of the cell cycle, disruption of its function by complexing with E6 and subsequent degradation via the ubiquitin system⁵ has been the proposed form of inactivation of p53 in HPV positive cancers.⁴ Hence, the dual detection and co-localisation of p53 antigen and integrated HPV 16 DNA, albeit in isolated cells, in cervical cancers questions this hypothesis.² Alternatively, the reliability of p53 immunocytochemistry may be in doubt.⁶

These findings emphasise the need for further studies elucidating the role of p53 in HPV positive cancers. These studies should combine p53 protein localisation by immunocytochemistry and semiquantitative western blot analysis with p53 gene sequencing in HPV positive and negative anogenital cancers.

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Paget's disease of the breast

O'Sullivan *et al*¹ recently reported a case of Paget's disease of the nipple without associated carcinoma. We have previously studied 11 cases of this disease in women.² To avoid the usual flattening of mammary specimens, they were placed in a net during formalin fixation. Sections were cut parallel to the thoracic wall and not perpendicular to it. Using this method, 17 to 42 ducts were found under the nipple compared with the usual eight to 12.

We found a consistent association between Paget's disease and intraductal eosinophilic cell carcinoma. Three patients had an invasive underlying tumour: in one case it was not anatomically related to the ductal carcinoma, which occupied nine of the 17 ducts found in the nipple; in the other two patients the invasive and ductal tumours were in contact, but many of the ducts, some of which were opposite the tumour, also contained carcinoma. However, according to the traditional view of Paget's disease, as the ducts divide dichotomously, only one or a very small number of ducts should have contained carcinoma.

There was no invasive tumour in the other eight cases. The nipple or areola contained from eight to 35 ducts with in situ carcinoma or comedocarcinoma, sometimes extending deep into the breast.

Paget's cells are cytologically different from the duct carcinoma cells. Moreover, using a mathematical model, we calculated that it would take 115 days for a Paget's cell to move 1 cm in the epidermis which exceeds the life of a cancer cell. Over this period the epidermis would be renewed seven times and Paget's cells would be exfoliated. This suggests that Paget's cells arise in the basal layer of the epidermis. The synchronous ductal carcinoma probably occurs at the epidermal junction of the ducts.

Specimens of mammary (and extra-mammary) Paget's disease should be studied with sections cut parallel to the skin, providing a better view of the ductal lesions.

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- 1 O'Sullivan ST, McGreal GT, Lyons A, Burke L, Geoghegan JC, Brady MD. Paget's disease of the breast in a man without underlying breast carcinoma. *J Clin Pathol* 1994;47:851-2.
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Detection of integrated human papillomavirus 16 DNA in squamous cell carcinoma of the cervix

It was both gratifying and interesting to read the paper by Kristiansen.¹ Gratifying, because an independent laboratory has now conclusively confirmed the previous finding² of the punctate/dot non-isotopic in situ hybridisation signal (NISH type 2) representing integrated human papillomavirus (HPV) 16 DNA in squamous cell carcinoma of the cervix. Interesting, because Kristiansen and colleagues showed a 100% concordance between NISH signal patterns (representing episomal and integrated virus) and the gold standard for determining the physical state of HPV DNA, two-dimensional gel electrophoresis; Southern blot analysis with *Pst*I digestion demonstrated integrated HPV 16 DNA in only 54% of squamous cell carcinomas of the cervix.

This raises interesting questions about the sensitivity of Southern blot analysis in determining the physical state of HPV DNA, as junction fragments essential for determining integrated virus may be masked by episomal virus. As several previous studies (using Southern blot analysis) have not demonstrated integrated virus in all HPV positive cervical cancers, a role for viral integration in cervical carcinogenesis has somewhat waned. The findings of Kristiansen and coworkers certainly strengthen the role of HPV DNA integration in cervical neoplasia and suggests that this physical state may still be crucial. It also clearly questions the methodology that should be used to determine the integrated physical state of HPV DNA in cervical cancer.

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Book review

Diseases of the Liver and Biliary Tract: Standardization of Nomenclature, Diagnostic Criteria, and Prognosis. Eds CM Leavy, S Sherlock, N Tytgstrum, R Zetterman. (Pp 219; \$50.50.) Raven Press. 1994. ISBN 0-7817-0211-9.

If you were asked to guess to whom the credit for this book is largely due, you probably would not spring to say that it was the late Sammy Davis Jr. Yet the manuscript is the culmination of a process initially begun by an ad hoc International Hepatology Informatics Group who met under the auspices of the National/International Liver