A colposcopic case control study of cervical squamous epithelial lesions

We are concerned that the findings of Dr Evans and his colleagues presented in their colposcopic study of genito-urinary medicine clinic attendees1 do not support their major conclusions that anogenital warts are not a risk factor for histological cervical HPV or CIN.

The first methodological difficulty with the study is the assumption that routine histopathological reporting can reliably diagnose the features of cervical HPV infection. Robertson et al2 confirmed previous observations of significant variability in histopathological reporting of cervical biopsies. They provided data concerning the reliability and reporting features of HPV infection alone and showed a Kappa statistic of 0·11, indicating very poor reproducibility. A more fundamental problem lies in the way the study results have been analysed.

The authors report that they conducted a case control study in order to discover whether anogenital warts were an indication for colposcopy, because of their possible role as a marker for cervical intra-epithelial neoplasia (CIN) or human papillomavirus infection (HPVI). Two criteria were used for proceeding to colposcopy in the study, namely, a history of, or current, anogenital warts, or an abnormal smear. The authors find that there was a strong association between abnormal smear and CIN. The association between anogenital warts and CIN was less strong. It is therefore argued that anogenital warts are relatively protective for CIN.

For a case control comparison to provide a valid estimate of the relative risk associated with an exposure, both cases and controls must be representative of all those with similar respective disease status in the population under consideration. In particular, inclusion in the study must be independent of the exposure under consideration to avoid selection bias. This latter condition is systematically violated in the author's study, since those women without warts must have abnormal cytology, which is known to be associated with CIN and HPV1.

A simple hypothetical example will illustrate the problem. Suppose we choose to study 100 women. Fifty of these are included because they have dyskaryotic smear and no warts, and the other 50 because they have warts and no dyskaryosis. Suppose the risk of CIN among women with dyskaryosis to be 0·4 (RR = 16) and that among women with warts to be 0·1 (RR = 4), that is assuming that the risk for women with neither is 0·025. By applying these risks to our hypothetical sample we obtain the numbers of subjects in each group who have CIN.

Dyskaryosis and CIN: 50 x 0·4 = 20
Warts and CIN: 50 x 0·1 = 5
Warts but no CIN: 50 x 0·9 = 45
We now perform a control–case comparison in the latter of the authors:
No CIN
CIN
Warts 45/75 5/25 (OR = 0·166)
Thus warts appear to be negatively correlated with CIN despite a true relative risk of 4.

It would appear that the negative association between anogenital warts and CIN reported in the authors' study suggests merely that women who have warts are less likely to have CIN than women with dyskaryosis. The conclusions of the study are therefore entirely unsupported. Furthermore the authors themselves note that 16% of those women found to have warts on examination were found to have CIN, and 18% of women with a past history of warts had CIN. A reanalysis of these valuable data based on a clearer understanding of epidemiological methods and principles should prove of considerable interest.

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Evans et al reply: Histological features of HPV1 have been shown to correlate well with HPV detection by DNA–DNA hybridisation.1 It would appear that the Scottish pathologists lacked experience in recognising these features.2 Our finding of a significant association between cervical HPV infection and CIN is further evidence that our data are meaningful and not random.

Unfortunately, Dr Renton and his colleagues have misunderstood our study and postulate an hypothetical example that is misleading. Put simply, the influence of warts, if any, on CIN in dyskaryotic patients is based on a comparison between patients with dyskaryosis alone and patients who