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RE: "CONDYLOMA AND INTRAEPITHELIAL NEOPLASIA OF THE UTERINE CERVIX: A CASE-CONTROL STUDY"

We question the finding of Brisson et al. (1) of different odds ratios for age at first sexual intercourse for condyloma and cervical intraepithelial neoplasia (CIN) and their inference that this is explained by different human papillomavirus (HPV) DNA etiologies.

The control group and the two case groups are not three distinct groups but represent three overlapping stages in the disease continuum of cervical neoplasia. Since 50 of 137 controls had cytologically and histologically normal cervices, the control group included a substantial number of women with mild abnormalities such as chronic inflammation and dyskeratosis. These may be induced by early human papillomavirus infection, so the control group would contain many more cases of early condyloma than of early cervical intraepithelial neoplasia. This could bias the resulting odds ratios for risk factors toward the null more for the cases of condyloma than for the cases of cervical intraepithelial neoplasia and could explain the lower odds ratio for age at first intercourse for the condyloma case group.

The authors do not report the cervical intraepithelial neoplasia level of the cases. If, as is generally the case, the majority of cases of cervical intraepithelial neoplasia were CIN 1 or CIN 2, the percentage of human papillomavirus-positive cases which are only type 6 or type 11 is not "rare" but may range from 43 per cent (2) to 58 per cent (3) among CIN 1 cases and 12 per cent (2) to 18 per cent (3) among CIN 2 cases.

The prevalence of HPV DNA type 16 or type 18 in normal cervices has also been reported to be as high as 38 per cent (4) to 48 per cent (5). Therefore, the authors' equation of HPV DNA type 16 or type 18 with cervical intraepithelial neoplasia and not condyloma may not be sufficiently accurate to support the explanation for a difference in the odds ratios of age at first intercourse for cervical intraepithelial neoplasia and condyloma – that a risk factor may be more of a promoter for one type of HPV DNA than for another.

Age at first intercourse is a crude indicator of potential for a sexually transmitted disease exposure, and a small difference in the odds ratios for age at first intercourse and case status does not justify the inference that condyloma and cervical intraepithelial neoplasia are different entities. Instead, it is reasonable to expect to find differences in odds ratios for risk factors for different stages in the same disease continuum.

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THE FIRST AUTHOR REPLIES

We thank Drs. Grubb and Coker (1) for their thoughtful comments. In our study (2), we observed that age at first sexual intercourse was related to cervical intraepithelial neoplasia but not to condyloma. Grubb and Coker (1) suggest that this difference in relations could have resulted from inadequacies of our control group. We used the same control group when assessing the associations of age at first intercourse with cervical intraepithelial neoplasia and condyloma. It is reasonable to be concerned by the possibility that, because of our controls, observed associations may be underestimates of true relations. However, the underestimation would have occurred similarly for cervical intraepithelial neoplasia and for condyloma. Thus, deficiencies of our control group cannot explain the difference in associations we observed. Grubb and Coker (1) allude to the difficulties in distinguishing low grades of cervical intraepithelial neoplasia from condyloma. We agree that this is an important difficulty in studies of intraepithelial lesions of the cervix. Because of this possible misclassification, however, the difference in the associations of cervical intraepithelial neoplasia and condyloma with age at first birth may be even greater than the one we observed. In our view, the main possible explanation for the difference we observed is random variation. Thus, the associations of age at first intercourse with cervical intraepithelial neoplasia and condyloma must be compared in other studies.

Grubb and Coker (1) also question our hypothesis that the epidemiology of cervical lesions may vary according to the type of human papillomavirus to which they are linked. Several types of human papillomavirus have been found in cervical cancer and in intraepithelial lesions of the cervix. The DNA of each type of human papillomavirus is substantially different from that of other types on the basis of DNA homology. Such differences in DNA could lead to differences in the biology of the lesions these viruses induce. For instance, it has been suggested that cervical lesions linked to human papillomavirus type 18 may have a tendency to progress more rapidly than those linked to human papillomavirus type 16 (3). Moreover, different types of human papillomavirus were reported to be associated with some differences in histologic features of the cervical cancers in which their DNA was found (4). Human papillomavirus type 18 may be linked more closely to adenocarcinoma than to adenosquamous and squamous carcinoma of the cervix. Given these observations, it would seem reasonable to suggest that the epidemiology of lesions may vary according to type of human papillomavirus. Nevertheless, at this point, we consider this idea simply to be an interesting hypothesis which needs to be verified.

Grubb and Coker (1) state that age at first intercourse is a crude indicator of exposure to sexually transmitted agents. Although we agree, we believe that, in addition, age at first intercourse may also be an indicator of the susceptibility of cervical epithelium to these agents. In our data, the strength of the association of number of sexual partners (which is an indicator of exposure to sexually transmitted agents) with cervical intraepithelial neoplasia was similar to that with condyloma, whereas age at first intercourse seemed to have different relations to these entities.

Finally, Grubb and Coker (1) assert that it is reasonable to find differences in the effect of a given risk factor for different stages in the same disease continuum. We feel that it is also reasonable to find differences in effects for different disease entities.

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