Commentary: Smoking and human papillomavirus infection: the pursuit of credibility for an epidemiologic association

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As the most important among the modifiable risk factors for many cancer types tobacco smoking is dutifully treated as a potent confounder when epidemiologists explore new candidate relations. The role for smoking changes from ‘confounder’ to ‘confounded’ variable in anogenital cancers. Among the latter, cervical cancer is a case in point. Smoking was first suspected as a risk factor for cervical cancer in the mid 60s but although most studies have replicated the finding1 the association was always seen with suspicion because of confounding by sexual activity.2 Number of sexual partners and age at first intercourse are unequivocal key determinants of risk, which has long suggested that an infectious sexually-transmitted agent plays an etiological role. Controlling for these two measures of sexual behaviour tended to dampen the associations with smoking in cervical cancer studies but in many of them it remained statistically detectable. Concerns about residual confounding by unmeasured sexual behaviours or insufficient control of confounding due to misclassification of sexual activity information led the International Agency for Research on Cancer (IARC) to defer judgment about a carcinogenic role for smoking in cervical cancer in its first monograph focusing on tobacco products in 1986.3

This intractable situation was nicely captured in 1994 in an insightful article in the Journal which demonstrated that, as long as the putative sexually-transmitted etiologic agent remains unmeasured and uncontrolled for in an epidemiological study, the association with smoking would continue to be hopelessly confounded, despite best efforts at adjusting for sexual activity variables.4 It did not help when the first molecular epidemiologic studies in the late 80s heeded this advice by placing the human papillomavirus (HPV) at centre stage for the first time. Paradoxically, HPV infection measured in these earlier studies was not associated with sexual activity, and was only feebly associated with cervical cancer.5 Epidemiologists learned that misclassification of HPV status could account for the incoherent results5 and were quick to adopt improved molecular techniques for detecting HPV, which led to the recognition of this virus as a necessary cause of cervical cancer6,7 and ushered in a new era in cervical cancer prevention via HPV vaccination and screening with HPV tests.

Once measurement error issues related to cervical HPV detection were largely resolved the smoking-cervical cancer association could be verified with reasonable confidence. The IARC revisited its previous conclusions and listed cervical cancer among those causally related to smoking in 2004.8 A pooled analysis of 23 modern molecular epidemiologic studies that included over 13 000 cases and 23 000 controls and carefully controlled for HPV status found an increased risk of squamous cell carcinomas with a dose–response relation with number of cigarettes.9

Although the controversy subsided, the role of epidemiology was not yet over; a mechanism for the carcinogenic action of tobacco smoking needed to be documented. The etiological pathway that begins with sexual activity as distal variable, then includes HPV infection as intermediate endpoint, and ends with cervical cancer is consistent with both ‘upstream’ and ‘downstream’ smoking effects relative to HPV infection. Documenting both still requires careful attention to confounding by sexual activity, which is strongly correlated with smoking habits. In this issue of the Journal, Vaccarella et al.10 advanced our understanding of the upstream relation by focusing on smoking as a determinant of HPV infection in the large IARC multi-centre study of HPV prevalence, which included over 10 000 women throughout the world. Their state-of-the-art methods for detecting HPV DNA in cervical specimens were conducted in world-class laboratories. The authors were acutely aware of the confounding problem and made clever use of the standardized questionnaire information to control for age, number of sexual
partners and for the responses by the women regarding their partners’ extramarital relations. Data on herpes simplex virus serology provided an extra handle to control for unmeasured sexual activity. In all, this strong study provides compelling evidence to the notion that current but not former smoking increases risk of HPV infection. The fact that the association is dose-dependent with number of cigarettes smoked suggests a causal mechanism, although this was seen primarily among those with only one partner. Could the authors have done more to assess the credibility of the association as a genuine causal relation? They were quick to admit that number of recent partners would have been a desirable covariate to be adjusted for, as this variable is a strong predictor of HPV infection. This information was not collected, thus some residual confounding was left to operate biasing the association away from the null. It would have been desirable also to have information on other sexual practice variables; not adjusting for them further contributed to the residual confounding. The question that remains is: how much? The fact that former smokers did not experience an increased risk assuages the concerns with residual confounding somewhat. Their findings have biological plausibility; evidence from laboratory studies show that current smokers have a reduced number of immune effector cells in the cervix and could thus be more susceptible to acquisition of new HPV infections or to delayed clearance of existing ones. Either way, the end result would be an increased HPV prevalence among current smokers. Is this association HPV-type dependent? Additional in-depth analyses from this study are no doubt planned and will further enhance our understanding of the natural history of cervical neoplasia.

The IARC HPV prevalence surveys have been among the most informative of the molecular epidemiologic studies to advance our understanding of cervical cancer etiology and of the means for preventing this disease. Their in-depth analysis of smoking, now in the public domain, provides useful insights on the role of smoking as a credible co-factor in cervical cancer causation. Much remains to be elucidated but the standard of proof is now much higher than it has ever been.

References