LETTERS TO THE EDITOR

RE: “GENITAL HUMAN PAPILLOMAVIRUS INFECTION: INCIDENCE AND RISK FACTORS IN A COHORT OF FEMALE UNIVERSITY STUDENTS”

In the recent, excellent Journal article entitled, “Genital Human Papillomavirus Infection: Incidence and Risk Factors in a Cohort of Female University Students,” the authors (1) identified and puzzled over two risk factors for human papillomavirus (HPV) infection—smoking and oral contraceptive use. The increased risks observed with exposure to either of these factors were similar and significant, about 40–50 percent over baseline. For each, the authors concluded that perhaps the risk factor was linked to some behaviors for which they had inadequately controlled.

I would like to offer an alternative hypothesis—that smoking and oral contraceptive use adversely affect levels of either folate or vitamin B12 and that the resulting “mal” nutrition adversely affects HPV infection status (e.g., immune response/clearance). A number of pieces of evidence make this idea viable. Both contraceptive use (2–4) and smoking (5–7) may adversely affect levels of folate and/or vitamin B12. Furthermore, a deficiency of either vitamin can result in elevated homocysteine levels. Both low folate (8) and elevated homocysteine (9) have been hypothesized to be risk factors for cervical intraepithelial neoplasia or cervical cancer.

Although some attention (i.e., case-control studies of cancer patients) has been paid to the hypothesis that elevated homocysteine levels or decreased folate levels (and consequently decreased levels of the universal methyl donor, S-adenosylmethionine) may be risk factors for cervical cancer, perhaps the associations are early rather than late. Could decreased folate or vitamin B12 levels (as might occur secondary to oral contraceptive use or smoking) be risk factors for HPV persistence? A few studies suggest this as a possibility. A study of university women using oral contraceptives found those whose folate levels were low to be at risk for a positive viraPap (HPV DNA dot-blot assay) result (10). A more recent study suggested that low vitamin B12 levels may be associated with persistent HPV infection (11). Recall that the young women in the study at issue (1)—the cohort study of university women—were tested, on average, every 4 months. Infections of 1–2 months’ duration could more easily have been missed.

This question could be addressed rather easily if the authors (1) have banked serum; testing serum vitamin B12 and folate levels is fairly inexpensive.

REFERENCES

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TWO AUTHORS REPLY

We appreciate Dr. Hendricks’ comments (1) on our paper (2). The potential mechanisms by which smoking and oral contraceptive use may modify either the risk of human papillomavirus (HPV) acquisition or progression to cervical neoplasia are not well understood, and additional research in this area is warranted.

The hypothesis offered by Dr. Hendricks (1)—that smoking or oral contraceptive use may affect HPV infection status by depleting levels of either folate or vitamin B12—is an interesting one, and epidemiologic studies that have explored this issue have produced mixed results. Dr. Hendricks cites studies that support the hypotheses that smoking and oral contraceptive use adversely affect folate and/or vitamin B12 and that depleted levels of these nutrients
increase the risk of persistent HPV infection or cervical neoplasia. Other studies, however, have reported conflicting results. A study conducted among adolescent females in Canada reported no association between either smoking or oral contraceptive use and lower serum or red blood cell folate levels after controlling for folate intake, nor was smoking associated with lower serum B12 levels (3). Other studies have also reported no association between oral contraceptive use and levels of folate (4, 5). Furthermore, the majority of case-control studies of folate/vitamin B12 and cervical neoplasia have failed to find any association (6), and results from clinical intervention trials of folic acid do not suggest that folic acid supplementation alters the natural history of HPV infection (7, 8). Dr. Hendricks suggests that perhaps the associations between these nutrients and cervical cancer are early rather than late, citing a study that found an association between low vitamin B12 levels and persistent HPV infection (9). This study reported no association between folate and HPV persistence, however, and the same researchers also failed to find an association between either folate or vitamin B12 and HPV persistence among a smaller cohort of Hispanic women (6). Furthermore, if smoking- or oral-contraceptive-related folate/vitamin B12 depletion does adversely affect HPV infection status, we might expect to see a more consistent relation between smoking/oral contraceptive use and HPV infection in the literature; in contrast, the majority of studies have reported null associations (reviewed in our paper (2)).

While we do have banked serum from women enrolled in this study, there is some evidence to suggest that serum B12 radioimmunoassays may give falsely low results in oral contraceptive users (10) and that folate can be more accurately measured in red blood cells than in serum.

REFERENCES

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In their recent Journal article, Charles et al. (1) examined the association between prostate cancer mortality and occupational exposure to magnetic fields and polychlorinated biphenyls. The authors took advantage of the availability of a high-quality data set from a well-described occupational cohort. Numerous studies describing results from analyses of the same data set (e.g., Savitz and Loomis (2), Savitz et al. (3)) have contributed significantly to the understanding of associations between occupational exposure to magnetic fields and mortality from various causes.

The authors of this study (1) carefully weighed its strengths and limitations. They failed, however, to discuss one of the most serious limitations of their analyses. The study examined prostate cancer mortality rather than incidence. Mortality from any type of cancer is affected by not only the incidence of the cancer (which ideally should be used for etiologic research) but also the survival of cases after diagnosis. The survival of cancer cases could depend on various factors, such as the stage of cancer at diagnosis, the type of treatment, and the presence of any comorbidity.

For prostate cancer, the distinction between incidence and mortality is especially important. As a result of relatively good survival, there is a large discrepancy between prostate cancer incidence and mortality rates. On the basis of data from the Surveillance, Epidemiology, and End Results (SEER) program (4), during 1973–1988 (a period included in the Charles et al. study (1)), the annual age-adjusted prostate cancer mortality rates were, on average, only 29 percent of the corresponding annual age-adjusted prostate cancer incidence rates among White men (range, 24–55 percent) and 38 percent among Black men (range, 35–41 percent).

To illustrate the unreliability of mortality data as a substitute for incidence data, we can look at racial differences in incidence and mortality rates for prostate cancer in the United States. Based on SEER data (4), during 1973–1988, the annual age-adjusted incidence rates were, on average, 1.51-fold higher among Black men than among White men.