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Letters to the Editor

RE: HELICOBACTER PYLORI *INFECTION AND COLORECTAL CANCER RISK: EVIDENCE FROM A LARGE POPULATION-BASED CASE-CONTROL STUDY IN GERMANY*

Zhang et al. (1) concluded that there is a serologic association between *Helicobacter pylori* (*H. pylori*) infection and the risk of colorectal cancer, especially for left-sided and early stage cancers, a finding that warrants confirmation and exploration of the underlying biologic mechanisms. However, as mentioned by the authors (1), the serologic measurement of infection status is less than perfect, which represents a specific limitation of their study.

Indeed, the serologic test does not discriminate between current and past infections and, apart from past infection that may even be more relevant for oncogenesis, such a distinction is essential because only current *H. pylori* infection induces humoral and cellular immune responses that induce or perpetuate chronic inflammatory processes in the gastrointestinal tract with potential oncogenic sequelae. Many cancers, including colorectal cancers, arise at the sites of chronic inflammation and infection (2, 3).

On the basis of histology, the practical gold standard for diagnosis of *H. pylori* infection, our own preliminary studies indicated *H. pylori* presence in malignant tissue in 34 of 41 (82.9%) patients with colorectal cancer (23 men; mean age, 73.6 years, standard deviation = 7.9 years) (4). It is important to note that in addition to using cresyl violet staining to detect *H. pylori*, we also documented its presence using an immunohistochemical method (using polyclonal rabbit anti-*H. pylori* antibody (dilution 1:50), DAKO, Athens, Greece) in malignant colonic tissues. Like Zhang et al. (1), we found a high incidence of left-sided cancers (29 of 41 patients (70.7%)). In addition, we found that the presence of *H. pylori* in malignant colonic tissue was associated with increased expression of the *Ki-67* oncogene in all tumor specimens and low expression in all adjacent tissue specimens (5). Moreover, p53 increased, and low expression was observed in 72.5% and 100% of tumor specimens and adjacent tissue specimens, respectively. Likewise, antiapoptotic Bcl-2 protein was observed in 60% and 9% of tumor specimens and adjacent tissue specimens, respectively, whereas proapoptotic Bax protein was observed in 9% and 100% of tumor specimens and adjacent tissue specimens, respectively (5). Therefore, *H. pylori* colonizing colonic tumor tissue seems to be associated with increased cell proliferation and impaired apoptotic process in malignant tissue compared with normal adjacent colonic mucosa, thereby contributing to colon cancer progression (5). In this regard, *H. pylori*-induced gastrin, which was also mentioned by the authors (1) as an oncogenic growth factor, shows antiapoptotic activity through upregulation of *Bcl-2* and contributes to gastric and colon carcinogenesis through stimulation of mutagenic and tumorigenic cyclooxygenase-2 expression (6).

Experimental data indicate that *H. pylori* infection leads to the development of chronic inflammation, hyperplasia, metaplasia, dysplasia, and recruitment and accumulation of bone marrow-derived cells (BMDCs), which may contribute to tumor formation in animal models with *H. pylori*-induced chronic gastric inflammatory process (2, 6). Because *H. pylori* also induces inflammatory changes in colonic mucosa, it would be reasonable to speculate that chronic *H. pylori* infection in humans also induces repopulation of the colon with BMDCs that might facilitate colon cancer development and progression (2, 6). In this regard, our own preliminary studies indicated increased expression of CD44 (a marker of human hematopoietic stem and progenitor cells) in malignant colonic tissue in 31 of our 41 patients (75.6%) with colorectal cancer (4). We also obtained comparable data for gastric cancer (2, 6). Therefore, these findings suggest the possible BMDCs involvement in *H. pylori*-associated colon and gastric cancer development and/or progression (2, 6).

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Editor's note: *In accordance with* Journal *policy, Zhang et al. were asked if they wished to respond to this letter, but they chose not to do so.*

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RE: "DERIVATION AND VALIDATION OF THE DENVER HUMAN IMMUNODEFICIENCY VIRUS (HIV) RISK SCORE FOR TARGETED HIV SCREENING"

Haukoos et al. developed a commendable risk score for prescreening for human immunodeficiency virus (HIV) testing in clinical settings (1). Their thoughtfully constructed model contains a number of important predictors of HIV infection. Although the authors concluded the contrary, the predictive utility of the model, as displayed in the receiver operating characteristics curve, seemed to us to strongly endorse the United States Centers for Disease Control and Prevention (CDC) guidelines for general HIV screening with highly sensitive tests (2).

The Denver sexually transmitted infection clinic data reflect a 0.5% prevalence of undiagnosed infection and an annual caseload of 10,000 patients (50 HIV-infected patients). Although values of sensitivity/specificity used to create Figure 2B in the article by Haukoos et al. were not reported, the joint maximum for both appears to be 80%/80% sensitivity/specificity on the curve for the derivation data. Applying the risk score at this cutpoint would result in referral of 2,030 patients for HIV-testing and detection of 40 HIV-positive patients, with 10 HIV-positive patients who received low risk scores not being tested. A value of the receiver operating characteristics curve that attains 95% sensitivity appears to occur at 20% specificity. Applying these properties, all but 2 HIV-infected patients would be detected, with the trade-off of conducting HIV testing on 8,008 patients. To identify all 50 infected patients, the figure suggests that one would need to screen nearly the entire population. The authors state as much, highlighting for the validation sample, "the top 3 risk groups represented 62.5%… of all patients diagnosed with HIV infection" (1, p 843), meaning that 37.5% of those infected would not be identified unless one also tested the lower-risk groups. The risk-score model appears to offer a very modest advantage over general HIV testing in the settings examined at the cost of obtaining extensive risk data to construct the score. This is aligned with a number of previous studies of targeted screening in clinical populations (3–5) and the CDC guidelines (2).

We have additional concerns about the populations and methods used. First, in selecting a model derivation population of individuals reporting to a sexually transmitted infection clinic for HIV testing and a validation population of individuals clinically and behaviorally indicated for HIV testing, the authors have partially conditioned their analytic data on risk factors included in the final model. This likely biases observed associations with HIV infection and may help to explain why some traditionally strong predictors of undiagnosed HIV infection (e.g., partner number, condom use) were not retained in the final model. Because populations at increased risk were used for the score development, it is also unclear how this model would perform for more general healthcare settings with patients who have a broader distribution of risks and for which the CDC guidelines were intended. Second, it is unclear how the authors ascertained whether HIV-positive individuals were previously undiagnosed. Substantial numbers of individuals who tested HIV-positive may have had a previous diagnosis, and this may be an important consideration because risk factors for failure to disclose a previous diagnosis may differ from risk factors for an undiagnosed HIV infection (6–8). Last, we question the validity of constructing a risk score based on the addition of model slope parameter estimates from a logistic regression model (Table 2). This method is typically reserved for linear regression, whereas in the context of a logistic regression model, these parameters contribute multiplicatively to risk (9).

Risk-score approaches to guide screening decisions are appealing, but in this case we feel that the data source limits the generalizability of the score to general populations. Even if it were generalizable, the results of the receiver operating characteristics curve indicate that a screening program, with higher costs required to identify patients for screening, would still require screening nearly everyone in a population to find those all of those living with HIV.

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