Re: Helicobacter pylori and Interleukin 1 Genotyping: An Opportunity to Identify High-Risk Individuals for Gastric Carcinoma

In a recently published case–control study, Figueiredo et al. (1) reported that vacAs1-, vacAm1-, and cagA-positive strains of Helicobacter pylori were associated with increased gastric cancer (GC) risk, particularly among individuals with select interleukin 1 gene polymorphisms. The accompanying editorial (2) noted that the identification of key pathogenetic factors involved in H. pylori-associated gastric carcinogenesis may lead to more effective prevention and/or treatment strategies. However, several aspects of the study by Figueiredo et al. warrant further attention before these data can be appropriately interpreted. Most notably, the strain-type-specific GC risks observed in this study were much higher than those reported in previous investigations (3–5). For example, colonization rates for cagA-positive versus cagA-negative H. pylori strains among GC case patients were 15-fold higher than those in non-atrophic gastritis control subjects (odds ratio [OR] = 15.95% confidence interval = 7.4 to 29). In contrast, other studies (that have made the same comparison) have reported OR estimates ranging from 1.2 to 3 (3–5). Explanations for these discrepant findings in risk estimates were not comprehensively addressed in the Figueiredo et al. study. However, several study design features raise concerns that nonpathogenetic factors may have played a contributing role in these discrepant findings.

First, because no reference was made to covariate adjustment in the logistic regression analyses, simple confounding by age or sex (both of which differed markedly between GC case patients and control subjects) may have occurred. Second, because neither the case patients (i.e., hospitalized patients) nor the control subjects (i.e., shipyard workers) were likely to be representative of the general reference population, selection bias may have occurred. Third, based on the large percentage of GC case patients (41%) who had inadequate material for H. pylori genotyping, additional selection bias might have been introduced.

Fourth, the detection of H. pylori strain types by tissue genotyping may have been a more sensitive technique than standard serum antibody measurements used in other studies. This last possibility represents a potential strength of the study by Figueiredo et al. (1); however, this increased sensitivity does not appear to be the primary determinant of atypical risk estimates. For example, if the sensitivity for cagA tissue genotyping and cagA serum antibody measurements are assumed to be 100% and 70%, respectively (6), then adopting the former assay method to reanalyze data from a previous study by our group (3) would only have been expected to increase the risk estimate for GC among cagA-positive subjects versus cagA-negative subjects from 1.2 to 1.6. Clearly, this revised risk estimate is still much lower than the GC risk estimate associated with cagA-positive H. pylori colonization in the study by Figueiredo et al. (1).

One additional factor to consider is that cagA-positive strains of H. pylori may be more sensitive to gastric acid than cagA-negative strains (7). Thus, differential acid susceptibility could further contribute to a higher cagA-positive H. pylori colonization rate among GC patients than in non-atrophic gastritis control subjects without necessarily implying a causal association.

In summary, although we found the data presented by Figueiredo et al. (1) to be interesting, the conclusions reached by the investigators may have been based on somewhat generous risk estimates from a highly select subject population. Further investigation of bacterial and host genotyping in H. pylori-associated GC in well-designed, population-based prospective studies may afford additional clarity.

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RESPONSE

As indicated in the above correspondence, the Helicobacter pylori strain-type-specific gastric cancer (GC) risks observed in our study (1) were, indeed, higher than those in the studies mentioned by Kamangar et al. However, there is at least one study (2) that shows an increased risk for GC in subjects infected with cagA-positive versus cagA-negative H. pylori strains, with an odds ratio (OR) of 9.5 (95% confidence interval [CI] = 3.6 to 26.8). This risk for GC was even further increased (OR = 25.9, 95% CI = 5.8 to 75.3) when the analysis was restricted to distal GC. Kamangar et al. also raised the concern that these discrepant OR estimates may be related to the features of our study design. First, sex and age adjustments in the logistic regression analysis were not reported in our study because the comparison of strain-type frequencies with sex and age of the case patients...
and control subjects did not reveal any statistically significant association. Sex and age are well-established risk factors for GC and, as expected, adjustments for these covariates resulted in an increase (not a decrease) in the OR estimates. For example, the sex- and age-adjusted OR for GC associated with cagA-positive strains was 36.6 (95% CI = 9.6 to 139.7).

Second, the phenotypic frequencies of the ABO and Rhesus blood group genetic systems in our case patients and control subjects were similar to those observed in the general population (i.e., A = 44%, B = 8%, AB = 4%, O = 44%, Rh-positive = 85%, and Rh-negative = 15%). Moreover, both case patients and control subjects were recruited from the same geographic area. Therefore, there is no reason to believe that our study groups are not representative of the general population, at least in terms of genetic and geographic background.

Third, we agree with Kamangar et al. that some selection bias could have been introduced by the fact that some of our GC case patients did not have adequate material for H. pylori genotyping. However, to the best of our knowledge, our study has the largest number of GC cases genotyped for H. pylori-virulence-associated cagA and vacA genes in gastric tissue.

Fourth, we agree with Kamangar et al. that the difference in sensitivity between serology and tissue genotyping cannot fully account for the discrepant risk estimates for GC reported among different studies.

Finally, the consideration that differential strain susceptibility to gastric acid could contribute to a higher cagA-positive strain colonization rate among GC patients is difficult to interpret, partly because it questions the role of cagA as a virulence factor and partly because there are numerous studies demonstrating the importance of cagA in strain virulence (3–5). Moreover, if H. pylori cagA-positive strains are more sensitive to gastric acid than cagA-negative strains, then how does one explain the predominance of cagA-positive strains in high-acid situations such as in duodenal ulcers?

In conclusion, the reasoning underlying the discrepancy in OR estimates between our study and those of others is not easily addressed. Factors such as the worldwide heterogeneous prevalence of type-specific H. pylori strains (6) and the genetic background of the host population are likely to contribute to discrepancies in GC risk associated with specific H. pylori strain types. As noted in the accompanying editorial (7), it is too early to generalize from this work. Nevertheless, we believe that the outcomes of this type of study (i.e., identification of risk factors and a better definition of risk) are important because they might be able to provide the means to identify individuals who are at greatest risk of developing GC. As a consequence, it may become possible to target such individuals with selective interventions designed to prevent and/or reduce the incidence of GC in the general population.

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