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Metabolomics as a Tool for Biomarker Discovery in Gastric Cancer

David A. Drew^{1,2}, Samuel J. Klempner³, Andrew T. Chan^{1,2}

¹Clinical and Translational Epidemiology Unit, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts.

²Division of Gastroenterology, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts.

³Massachusetts General Hospital Cancer Center and Department of Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts.

Abstract

Globally, early detection and interception of gastric cancer remains limited by the lack of a broad screening paradigm for individuals with the exception of those at established hereditary risk (e.g., hereditary diffuse gastric cancer or *CDH1* germline mutation status). The path forward will likely rely on establishment of biomarkers using multiple -omic approaches to detect molecular profiles associated with gastric cancer risk that can in turn be leveraged to identify individuals who may benefit from more intensive evaluation, such as screening endoscopy. In this issue, Shu and colleagues describe the results of a case-control cohort study of Asian individuals that demonstrates baseline metabolite levels are predictive of future gastric cancer risk above and beyond lifestyle and demographic risk factors. We discuss the promise and limitations of these exemplar circulating biomarkers and emphasize the need for a multifactorial risk assessment to advance precision prevention and early detection of gastric cancer.

With gastric cancer rates rising and a lack of universal screening in most parts of the world, clinicians and researchers are focusing attention on novel methods of interception and early detection of GC. (1) In some parts of Asia, a higher prevalence of *H. pylori* infection and gastric cancer have paved the way for population-wide screening endoscopy programs. However, clinical evidence supporting efficacy for comparable screening programs outside of Asia is limited. Meanwhile surveillance endoscopy programs in non-Asian countries are largely restricted to populations with known, but rare, genetic risk factors (e.g., hereditary diffuse gastric cancer or *CDH1* germline mutations). Identification of novel risk factors at a population-scale will be critical to broaden screening and advance precision prevention approaches based on risk stratification biomarkers.

In this issue, Shu and colleagues identify several metabolites associated with gastric cancer risk that are, importantly, independent of *H. pylori* status and other established gastric cancer

risk factors. Using a nested case–control study within two large prospective population-based cohorts in Shanghai (Shanghai Women’s Health and Shanghai Men’s Health Studies; $n > 135,000$), the investigators identified 250 sex-balanced incident gastric cancer cases and incidence density sampling matched cancer-free controls with baseline (prediagnosis) plasma samples to test the hypothesis that perturbation in metabolism would be associated with risk of developing gastric cancer. Further, they postulated that altered metabolomic signatures could be leveraged to identify specific metabolites as biomarkers of risk. Baseline plasma samples were subjected to a global untargeted metabolome analysis using an unbiased LC/MS commercial platform. A total of 581 known metabolites were identified and included for downstream analysis. Following adjustment for multiple hypothesis testing, 18 metabolites were significantly associated with gastric cancer risk with eight showing an independent association from the other identified metabolites. This work provides proof-of-principle that leveraging circulating biomarkers and screening platforms—such as metabolites (metabolomics), proteins (proteomics), cell-free nucleic acids (DNA, RNA, mRNA), or exosomes—could be transformative in non-invasively identifying individuals at risk for gastric cancer that could inform earlier intervention with screening endoscopy to more effectively intercept and prevent gastric cancer.

The authors' work also offers important mechanistic insight into the etiopathogenesis of gastric cancer. Methylmalonate [the conjugate base of methylmalonic acid (MMA)] emerged as the metabolite with the most significant association with gastric cancer risk. This is not the first indication that MMA may be a potential biomarker for cancer. Recently, MMA was proposed as a therapeutic target in aging-associated tumor progression and aggressiveness (2). Gomes and colleagues demonstrated that MMA was increased in the sera of older (> 60 years) individuals compared with younger healthy donors (< 30 years) and that MMA alone is sufficient to promote epithelial–mesenchymal transition, chemotherapeutic resistance, and metastasis, ultimately, contributing to poorer survival. In preclinical models, these age-associated increases in MMA mediated upregulation of SOX4 via TGFβ pathway activation. Notably, Shu and colleagues identified a robust association of baseline MMA levels as a predictor of future gastric cancer risk in models that that appeared independent of age. However, the study did not incorporate molecular or pathologic characteristics of the incident tumors. Thus, a key outstanding question will be whether MMA and other metabolite levels are similarly predictive of early-stage versus late-stage cancers and whether this metabolite panel will be sensitive enough to discriminate at-risk patients with precancerous neoplasia over a longer time horizon.

Indeed, the most successful early detection strategies in cancer are founded in a deep understanding of the molecular events that underlie tumorigenesis and recognition of precursor lesions. Defined epidemiologic and environmental factors can further inform risk stratification and identify populations for which early detection strategies could be intensified. Although some gastric cancer proceeds via a clearly defined sequence of metaplasia-dysplasia-carcinoma, there remains significant heterogeneity and a knowledge gap in the stepwise evolution of gastric cancer subtypes, particularly diffuse-type lesions. Additional studies that consider the sensitivity of this or other biomarker-based prediction models in context of gastric cancer subtypes (intestinal vs. diffuse-type) will hopefully come to bear. And although altered cellular metabolism is a hallmark of cancer, in the absence of

a clearly defined roadmap of the metabolic underpinnings of gastric cancer, we are limited in our ability to link the metabolites identified in this report to specific mechanisms of gastric tumorigenesis. Similarly, approaches that rely solely on metabolites may be limited by variability introduced by external influences ranging from sample collection (time of day, time relative to last meal, etc.) to processing methods to the stability of analytes over time.

Overall, these results further support that mechanistically-informed biomarkers linked to specific risk profiles or response to preventative agents may advance the promise of precision cancer prevention (3–5). Moreover, the addition of ‘omics data to prediction models based on traditional demographic and epidemiologic risk factors may prove most fruitful in moving the needle for tailored gastric cancer prevention in the absence of universal screening guidelines. Non-invasive biomarkers informing risk assessments are certain to be a more cost-efficient means than broad-based endoscopic screening paradigms, even if these more invasive approaches are informed by traditional risk factors. Indeed, Shu and colleagues demonstrated that the prediction accuracy of the models based on traditional risk factors including BMI, smoking status, *H. pylori* infection status, gastritis, and family history of gastric cancer, were significantly improved when incorporating the identified metabolite panel. However, the AUC for these models demonstrated that there remains room for further improvement. Moreover, because the study population was entirely Asian, it is uncertain how generalizable this specific metabolite panel may be for other populations, particularly those without established gastric cancer screening programs. Further improvement in predictive accuracy and broader generalizability will result from testing new metabolite panels on additional patient samples derived from larger and more diverse populations.

Finally, there are other potential sources beyond peripheral blood that can be used to identify noninvasive biomarkers for early detection in gastric cancer (Fig. 1). Detection of nucleic acid fragments, both RNA and DNA in stool, saliva, and urine have all been explored in previous studies (6), and are attractive for early detection owing to high specificity (7–9). Identification of novel biomarkers among patients with precancerous lesions has been identified as an area of high unmet need by the 2020 Gastric Cancer Summit (10). Achieving this goal will require development of robust, highly annotated biobanks of patients at risk for or with gastric cancer, especially early-stage gastric cancer and precancerous neoplasia. This will offer an efficient vehicle for discovery and rigorous validation of ‘omic biomarkers such as those identified by Shu and colleagues that may eventually transform our approach to gastric cancer prevention.

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Figure 1.

'Omics-based approaches for noninvasive biomarkers of gastric cancer risk. Early detection of individuals at risk for gastric cancer will likely require the development of multifactorial risk assessments that consider biomarkers identified via different -omics technologies. In the absence of broader implementation of screening endoscopy, these noninvasive precision prevention approaches may offer a platform that sensitively defines which individuals are likely to require more intensive surveillance for gastric cancer beyond existing lifestyle and demographic risk factors.