Editorial

The Human Microbiome Project: Getting to the Guts of the Matter in Cancer Epidemiology

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With the completion of the Human Genome Project, we have a new array of tools to carry out genetic epidemiologic studies. Thanks to the Human Microbiome Project (1), launched recently by the NIH Roadmap for Medical Research, we will be in a position to expand our understanding of the human genetic landscape to include the microbes that reside in and on the human body and contribute to human health and disease. Microorganisms make up only 1% to 2% of the mass of the body of a healthy human, but microbial cells are estimated to outnumber human cells by 10 to 1 and the number of microbial genes (i.e., the microbiome) is suggested to outnumber human genes by 100 to 1. Whereas it is recognized that microbes play major roles in maintaining health and causing illness, relatively little is known about the role that microbial communities play in human health and disease and how they influence human development, physiology, immunity, and nutrition.

The majority of microbes that colonize humans live in the distal gut. Traditional medical microbiology has typically focused on the study of individual species as isolated, culturable units, and for good reason, particularly on pathogens. However, the gut is a complex ecosystem of microbial communities. Advances in DNA sequencing technologies and other molecular techniques have allowed for more comprehensive examination of microbial communities and have revealed that more than 80% of gut bacterial species are refractory to culturing methods. The 16S rRNA gene, present in all microbes, is a useful tool for characterizing gut microbial community structure, in that it has enough sequence conservation for accurate alignment but enough variation for phylogenetic analyses. There are an estimated 500 to 1,000 species and over 7,000 strains in the human gut (2). Fecal bacterial profiles are representative of interindividual differences in gut microbial communities, with the differences between individuals being greater than the differences between different sampling sites within an individual (3). Further, microbial community structure has been shown to be stable over a period of at least a year (4).

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A growing body of evidence suggests an important role of the gut microbiota in relation to the risk of cancer. Chronic gastric inflammation caused by *Helicobacter pylori* infection and chronic intestinal inflammation associated with a dysregulated immune response to commensal bacteria in inflammatory bowel disease are established risk factors for gastric and colon cancers, respectively (5). Although, to date, much of the focus on the gut microbes has been on their relationship to gastrointestinal malignancies, their capacity to influence inflammation and other downstream pathways systemically (6) suggests the potential for a farther reaching effect of the gut microbial community on the risk of cancer in other tissues, too. Examples of functional contributions of the gut microbiota that may influence cancer susceptibility in the broader sense include the harvest of otherwise inaccessible nutrients and/or sources of energy from the diet, metabolism of xenobiotics (i.e., dietary constituents, drugs, etc.), renewal of gut epithelial cells, and development and activity of the immune system (7).

The mission of the Human Microbiome Project is to generate resources to enable a comprehensive characterization of the human microbiota and analysis of its role in human health and disease. Broadly, the project has set the following goals: determining whether individuals share a core human microbiome; understanding whether changes in the human microbiome can be correlated with changes in human health; developing the new technological and bioinformatic tools needed to support these goals; and addressing the ethical, legal, and social implications raised by human microbiome research (1). To this end, sequencing is a primary focus of the Human Microbiome Project. Initially, researchers will sequence 600 microbial genomes, completing a collection that will include ~1,000 microbial genomes and which can contribute toward a reference microbiome data set. This will be expanded to a metagenomic approach using whole genome shotgun sequencing in order to provide insights into functional pathways present in the human microbiome. On the heels of this initial work will come the need for observational epidemiologic studies to characterize the variability in ''normal conditions,'' and ultimately disease predisposition and pathogenesis (7).

In molecular epidemiologic studies of cancer risk, we can interrogate the human genome retrospectively using case-control designs. Unfortunately, the same probably cannot be said for characterizing the relationship between the gut bacterial genome and cancer risk. The

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interindividual variability in the gut microbiome is influenced by host physiology, pathobiology, environment, and lifestyle. Consequently, as for exposure biomarkers, case-control designs are not appropriate, because the disease itself, the symptoms of the disease, and its therapy all have the potential to alter gut microbial composition. Further, changes in the microbiome may precede the development of, or even contribute to, the emergence of factors related to cancer susceptibility. For example, higher numbers of *Firmicutes* and fewer *Bacteroidetes* in the gut have been associated with increased energy storage and obesity in humans (4) and a small, prospective study in children suggests that aberrant compositional development of the gut microbiota may precede becoming overweight (8).

A prospective approach, using population-based cohort studies, is going to be necessary to characterize the impact of the gut bacterial community on cancer risk. Unfortunately, to date, few cohort studies include the collection of fecal samples. To quote Taro Gomi, author of several beloved children's books, ''Everyone poops.'' (9). In that regard, there is plenty of sample available, and as long as we establish sampling approaches that make it easy for participants to collect fecal aliquots and that preserve the microbial DNA and RNA in the fecal sample, we have the capacity to develop an invaluable resource. Application of the new molecular techniques for characterizing the gut microbiome has meant that the previous logistical nightmares of immediate delivery of fecal samples to the laboratory for culturing are no longer an issue, and the storage of samples for nested case-control studies is an option.

In summary, achieving the mission of the Human Microbiome Project is going to require the collaborative effort of investigators from a wide range of disciplines, including epidemiology. Establishing repositories of fecal samples from well-characterized, population-based cohorts will provide the necessary resource to contribute to the ultimate goals of the Human Microbiome Project and the opportunity to understand the role of the gut microbiome in cancer susceptibility and the etiology of specific cancers. Elucidating the complex interplay of the gut microbiome, host genetics, and environmental exposures may help to guide future cancer prevention strategies.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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