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Probiotics and Cancer Prevention as a Part of the Healthy Microbiome

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Probiotics–beneficial microorganisms–must be understood within the context of the microbiome and their interaction with the human host. The microbiome was first mentioned around 400 BC by Hippocrates, the father of medicine. Although he did not define the microbiome explicitly, he is quoted as saying "death sits in the bowels" and "bad digestion is the root of all evil". These statements highlight what we believe today, namely the diet, the bowel, and overall health are intimately linked! The term "microbiome" was actually coined in 2001 by Joshua Lederberg to emphasize that microorganism inhabiting the body influence mammalian cellular processes and must be considered part of the genome [1].

The human microbiome, which contains more than 100 trillion bacteria, fungi, and viruses, has a significant impact on physiological processes. About 90% of bacteria reside in the gastrointestinal tract in intimate contact with the human body, and they are influenced, both in composition and metabolism, by the foods eaten. Since the skin and intestinal microbiome contain greater than 100 fold genes than are present in mammalian cells, humans are literally sandwiched between layers of microbes that can influence our metabolism, and likely our health and lifespan. Knowledge about the importance of the microbiome is only beginning to emerge, although early studies of constituent microorganisms trace back to Antonie Philips van Leeuwenhoek (1632-1723), a Dutch scientist and tradesman known for improving the microscope lenses and establishing the science of microbiology.

Microorganisms are involved in interrelationships with the human body: mutualism (win-win), commensalism (win-neutral), parasitism/predation (win-lose), amensalism (neutral-lose), or competition (lose-lose). More than a century ago, Metchnikoff observed for the first time that intestinal microbes are influenced on food intake, and it is possible to adopt dietary measures to modify microbial populations and to replace harmful microbes with useful microbes.

Probiotics have been described as "good-for-you" bacteria. The World Health Organization defines probiotics as "living microorganisms that provide a health benefit to the host when ingested in adequate amounts". In 2002 a *Joint FAO/WHO Expert Consultation on Evaluation of Health and Nutritional Properties of Probiotics in Food* recommended that specific health claims for probiotics in foods be allowed if there is sufficient scientific evidence according to the guidelines set forth in the report [2]. Nevertheless, there are concerns that under certain conditions even these "good" organisms may have adverse consequences in some individuals. In 2012 Mendoza reported two cases of a severe eosinophilic syndrome [3] in subjects with no prior history of autoimmune disease who was taking an "extra strength concentration", of a new brand of probiotics. The patients responded to immunosuppressive therapy, but the cause of these eosinophilic syndromes remains unclear. The high concentration of probiotics, an excipient added to them, and the quality control of manufacturing practice were raised as possible causes since other over- the-counter supplements also have produced eosinophilic syndromes. A recent European randomized controlled study using probiotics concluded that *L. rhamnosus* can safely be administrated to healthy subjects at a daily dose 1×1011 colony forming units [4]; however these results cannot be extended to all probiotics without further research.

Martin et al. [5] demonstrated significant metabolic changes in the microbiome when the microbial population changed only "a little bit" [6]. Therefore, the metabolic activity of microbiome is likely key to its interrelationship with health, and it can change under the influence of multiple factors, with the diet as the primary modulator. Dr. J. Nicholson has emphasized the importance of learning what the microbes are actually doing versus learning what they can do [6]. Although health benefits of probiotics are widely accepted in principle, the necessary conditions for each microorganism to produce a beneficial response remain largely unknown in terms of the concentration, interaction with the host genome, complementary and antagonistic relations with other components of the microbiome, impact of foods and their components, as well as temporal or adaptive linkages with health and/or disease risk.

Evidence for the role of probiotics has surfaced in studies using germ-free animals. Interestingly, microbiota transplanted to lean germ-free mice from mice with diet-induced obesity promoted weight gain in previously lean mice. Thus, organisms can have a profound impact on overall bioenergetics, weight, and presumably susceptibility to obesity-related diseases. It is known that diet-induced obesity produces a bloom in a single uncultured clade within the Mollicutes class of the Firmicutes, which can be diminished by subsequent dietary manipulations that limit weight gain [7]. Whether or not the response is due to a decrease, an increase, or balance between Mollicutes/Firmicutes and Bacteroidetes remains to be determined.

The increase in cell number and metabolic activity of one or more bacterial strain in the colon also can be affected by prebiotics, non-digestible food ingredients that beneficially affect the host by altering colonic flora to a healthier composition. In 2007 the United Nations Food and Agriculture Organization defined prebiotic as "a non-viable food component that confers a health benefit on the host associated with modulation of the microbiota". Proposed prebiotics include inulin, fructo-oligosaccharides (FOS), galactooligosaccharides, soya-oligosaccharide, xylo-oligosaccharides, osomalto-oligosaccharides, and pyrodextrines. Some prebiotics can increase the abundance of probiotics (ex: *Bifidobacterium spp*). Other prebiotics decrease harmful organisms; for example, inulin and FOS to reduce Clostridium cluster XI and *Clostridium difficile* toxin gene expression and associated incidence of chronic intestinal inflammation in transgenic rats [8]. It should also be noted that possibly detrimental compounds may arise

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from microbial metabolism. Recently it was proposed trimethylamine-N-oxide (TMAO) arising from dietary lecithin to be and associated with an increased risk of major adverse cardiovascular events [9] but TMAO comes also from other sources besides lecithin, like fish and meat. While increased red meat consumption is associated with increased risk of cardiovascular events, fish i s k nown t o l ower t he cardiovascular risk.

Bioactive food components likely have a major role in non-communicable disease prevention, including cancer, and it is clear that not everyone responds identically, offering protection to some while being detrimental to others. Recent studies suggest that microbially produced metabolites may have a stronger effect than t he parent compound from which they are produced. For example, women with microbes that produce equol following soy consumption have a lower risk of breast cancer than women who are unable to produce this metabolite [10]. The ability to produce equol or the equol itself is also closely related to the lower incidence of prostate cancer in Japanese and Korean residents compared to Americans [11]. Likewise, urolithins produced by microbial metabolism of lignans in berries are associated with an increased population of *Bifidobacteria spp*. and *Lactobacillus spp*., which suggests the microbiota-modulating capacities of these compounds [12]. In addition, urolithin B effectively i nhibits aromatase activity in live cell assay, therefore suggesting potential for the prevention of estrogen-responsive breast cancers [13]. Thus, the overall response to berries may be partially explained by individuals being high-or low-urolithin producers based on microbial bacteria and genetics (polymorphisms, etc.). Collectively, this combined information should help explain the inter-individual variability when it comes to health benefits of the ability of equol and urolithins to influence human estrogenic activity may be a plausible explanation for influencing the risk of estrogen influenced types of cancers.

These findings provide compelling evidence about the importance of microbe-host interactions, there is a dearth of information about the amounts of specific microbes or balances that are needed to bring about a change in health, as well as how an individual's genetics influence t he overall relationship. I ncorporating k nowledge a bout nutrigenomics makes the interrelationship between the host and the microbiome even more complex. Since microorganisms share some common as well as unique genetic material, it is logical to believe dynamic interrelationships exist with the genetics of the host. Thus, it is also logical to assume that not all individuals will respond similarly to the same population of microbes.

Although there is much excitement about the potential use of probiotics to promote health, and probiotics are qualified GRAS by the FDA, more research is needed before they can be incorporated into widespread public health approaches. It is critical to have adequate information to predict who will benefit from the use of probiotic preparations, and who might possibly expect adverse effects related to these intervention strategies.

The characteristics of a "normal" or "healthy" microbiome remain ill defined, but this is an area of active investigation. Despite the efforts of the NIH Human Microbiome Project to define the microbiome in healthy individuals, little is known about the influence of age, ethnicity, eating behaviors, or other variables. We do recognize, however, there is variation in response in different populations. Th e interaction between one's microbiome and microbiota with particular genetic background and diet makes nutrition a fascinating science. The result of these interactions likely has a crucial effect in disease prevention, aging, and increase healthy lifespan. The Division of Cancer Prevention at the National Cancer Institute recognizes the importance of the microbiome in cancer risk and prevention; there are several research awards in its portfolio to examine the effects of individual differences in gut bacterial community composition, genes and race on hormone metabolism after dietary intervention, and how the gut microbiome influences gene expression in relation to cancer prevention.

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