Metachronous gastric cancer occurs frequently following endoscopic removal of an early gastric cancer. H. pylori eradication significantly reduces that risk. While, the pathogenesis of this phenomenon remains unclear, it is clear that following H. pylori eradication the natural history of metachronous gastric cancer is altered. Gastric cancer is fundamentally a disease associated with progressive genetic instability leading to autonomous growth and suppression of the local immune response. Genetic instability of gastric cells can be induced by inflammation, H. pylori, host or environmental factors resulting in the production of malignant cells. H. pylori eradication reduces and reverses the inflammation caused by the presence of the bacteria which can also result in reversal of epigenetic damage and abnormal expression of miRNA’s. Fundamentally, H. pylori eradication stops the progression of changes and may reverse some of the damage to the mucosa. Any resulting improvement in acid secretion can change the gastric microbiome and reduce carcinogen production. Because the risk of developing metachronous cancer varies among patients, prospective research is needed to identify reliable biomarkers to predict the risk of development of metachronous cancer as well as to define surveillance methods, intervals, and duration. Some candidate examples of prognostic or predictive biomarkers for the prediction of subsequent risk include the presence or absence, titers, and changes in anti-H. pylori IgG and or anti-CagA antibodies, serum pepsinogens, gastrin, and miRNAs.