Natalia Zumkeller
Dr. med.

Helicobacter pylori and the risk of colorectal carcinoma: case-control study under consideration of potential pathomechanisms

Geboren am 12.10.1965 in Perm, Russland
Staatsexamen am 26.06.90 am Staatlichen Medizinischen Institut in Perm, Russland

Promotionsfach: Epidemiologie
Doktorvater: Prof. Dr. med. Dietrich Rothenbacher

The role of *H. pylori* in the development of chronic gastritis, gastric and duodenal ulcer disease and gastric cancer is meanwhile proven. It has been suggested that both, bacterial virulence factors as well as host genetic polymorphisms, together with different environmental and lifestyle factors determine the spectrum of clinical outcomes of *H. pylori* infection. Some authors reported also an increased prevalence of *H. pylori* infection in patients with colorectal carcinoma or colorectal adenoma compared to other subjects and concluded that *H. pylori* infection may also be a potential risk factor for colorectal cancer (CRC). The possible association between *H. pylori* infection and CRC seems to be biological plausible, since *H. pylori* is known to cause hypergastrinemia in most infected persons, and gastrin is known to be a trophic factor for the colonic mucosa. However, epidemiological evidence investigating this relationship is limited and inconsistent in results.

In this large case-control study the association between *H. pylori* seroprevalence (alone and in combination with CagA status) and CRC risk, after adjustment for the effects of potential confounding variables was investigated. In addition, the association between IL-1RN and Il-1B pro-inflammatory gene profiles and colorectal cancer risk was considered. Furthermore,

evaluation of the combined effects of *H. pylori* infection and the pro-inflammatory IL-1 gene profiles in determining of the individual predisposition to CRC was performed.

H. pylori-serostatus (IgG) and CagA-serostatus were determined in serum of 386 patients with incident, histological confirmed colorectal adenocarcinoma, aged between 30 and 75 years, and 467 population-based control subjects matched on age, gender and area of residence. Recruitment took place between January 2003 and June 2004. Information was obtained by means of a standardized questionnaire during a personal interview, performed by a team of specially trained interviewers.

The *H. pylori*-seroprevalence was overall higher in patients (51%) than in control subjects (44%), in men and in women, and a weak positive association between *H. pylori* infection and colorectal adenocarcinoma risk was found, that persisted even after adjustment for known potential confounders (OR of 1.48; 95% CI, 1.11-1.98). The observed risks appeared slightly greater for cancer of the rectum and colorectal cancer in females. Presence or absence of *H. pylori* CagA did not significantly affect the observed risks. Additional assessment of the combined effects of *H. pylori* infection and hosts genetic polymorphisms on CRC risk provided some indication of possible effect modification by pro-inflammatory gene profiles of the IL-1RN gene (especially for the rectum cancer risk) and of the IL-1B gene in females: *H. pylori*-positive subjects carrying the pro-inflammatory polymorphisms had a lower risk.

In conclusion, the results of this research demonstrate a weak though statistically significant increased risk of CRC associated with a positive *H. pylori* serostatus, even after adjustment for other known or suspected risk factors for CRC, which is in line with the results of a concurrently performed own meta-analysis. The observed risks appeared slightly greater for cancer of the rectum and colorectal cancer in females. In contrast to results for gastric cancer,

a pro-inflammatory genotype of IL-1 gene cluster does not increase the risk for CRC associated with *H. pylori* infection. Further studies on even larger populations are needed, as well as plausible explanations of possible pathomechanisms.