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The Impact of Host Genetic Susceptibility and *Helicobacter pylori* Infection on the Development of Chronic Atrophic Gastritis and Gastric Cancer

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Despite a worldwide decline in incidence and mortality, gastric cancer (GC) is still the fourth most common cancer and the second most common cause of cancer death. It is widely accepted that *Helicobacter pylori* infection, which is prevalent in about half of the world's population, causes chronic gastric inflammation that progresses to chronic atrophic gastritis (CAG), metaplasia, dysplasia and GC. However, only a small fraction of infected people develop GC or its precursors. Such clinical diversity suggests that factors other than bacterial infection alone determine carcinogenesis. Apart from lifestyle factors such as diet and smoking, virulence factors of the pathogen and host genetic susceptibility, are likely to contribute to the development of GC and its precursors.

The objectives of this project were to assess the impact of host genetic susceptibility and *H. pylori* infection on the development of CAG and GC in large population-based studies from Saarland, Germany. Additionally, the associations between GC and carcinogenesis related non-inflammatory genetic polymorphisms were systematically summarized by means of literature review.

The MEDLINE database was searched for articles on the associations between GC and carcinogenesis related genetic polymorphisms published until 15 September 2008. For data analyses to assess the impact of *H. pylori* infection and host genetic susceptibility

on the development of CAG and GC, data of the ESTHER and the VERDI studies, two large population-based studies conducted in the entire state of Saarland, were combined. A total of 534 serologically defined CAG cases (all from ESTHER) and 123 GC cases (81 from ESTHER and 42 from VERDI), together with a total of 1068 controls without a history of GC (frequency matched on sex and 5-year age group) were included. Information on potential risk factors and medical history were obtained through a questionnaire. A commercial screening ELISA was used to assess *H. pylori* infection and *H. pylori* multiplex serology was used to determine the serostatus of 15 specific *H. pylori* antigens for all included subjects. Eight selected inflammatory single nucleotide polymorphisms in 7 cytokine genes (*IL1A* C-889T, *IL1B* C-511T, *IL1RN* A9589T, *IL8* T-251A, *IL10* T-819C/A-1082G, *LTA* C+80A and *TNFA* G-308A) were genotyped for CAG cases and controls.

The systematic literature search identified 82 articles on the associations between carcinogenesis related genetic polymorphisms and GC susceptibility. Based on their biological roles, the involved genetic polymorphisms were categorized in two groups: cell proliferation (n=53) and tumor invasion (n=29) related polymorphisms. Meta-analyses were performed for three of the most well studied polymorphisms (*TP53* Pro72Arg, *L-myc* *Eco*RI and *CDH1* C-160A). Twenty one cell proliferation-related and 14 tumor invasion-related polymorphisms significantly related to GC in at least one published study were identified, which suggests that polymorphisms in genes implicated in carcinogenesis could be candidate biomarkers of GC risk. However, current evidence for the use for risk stratification is still very limited. Heterogeneity is common among previous studies which chould at least in part be explained by the selection of study populations and subtypes of GC.

A pro-inflammatory genetic profile was associated with increased risk of CAG in our study subjects. A significant inverse association of the pro-inflammatory genetic profile with seroprevalence of *H. pylori* was found among CAG cases, which seems to be independent of a potential impact on severity of the disease and may point to

enhanced elimination of the infection during disease progression.

All 15 specific antibodies against *H. pylori* measured by multiplex serology were shown to be significantly associated with CAG, with odds ratios (ORs) ranging up to 4.5. The exclusion of severe cases of CAG substantially increased the observed associations, with OR then ranging up to 10.0. The associations remained significant for all but two antibodies when restricting the analyses to subjects that had been classified as *H. pylori* positive by a commercial screening ELISA. CagA, VacA, HcpC and GroEL were identified as independent virulence factors for CAG with adjusted ORs (95% CI) of 3.52 (2.01-6.10), 3.19 (1.44-7.05), 4.03 (1.53-10.65) and 2.65 (1.06-6.62) respectively. In combination, these four virulence factors were associated with an 18-fold risk of CAG. Eight of the specific antibodies against *H. pylori* were shown to be significantly associated with GC, and the risk increased with the number of seropositivities. The associations were more pronounced for noncardia GC. Seropositivities for CagA and GroEL were identified as independent risk predictors, which were strongly related to GC risk in a dose-response manner.

In conclusion, carcinogenesis related non-inflammatory polymorphisms could be candidate biomarkers for GC. The association between a pro-inflammatory genetic profile and CAG support the hypothesis that inflammatory polymorphisms may exert their impact on gastric carcinogenesis since the very early precancerous stage. Considering that such a pro-inflammatory profile may also favor the elimination of *H. pylori* independent of disease severity, it could be an important candidate as biomarkers for GC risk stratification especially among those with past infection of *H. pylori*. HcpC and GroEL were identified as new independent virulence factors of *H. pylori* and, in combination with the established virulence factors CagA and VacA, were strongly associated with CAG. GroEL was also identified as a new independent risk marker for GC which may be indicative of both current and past *H. pylori* infection.