

Molecular Pathological Epidemiology in Helicobacter Pylori Infection and Risk of Chronic Atrophic Gastritis

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ABSTRACT

Helicobacter pylori (*H. pylori*) infects more than 50% of the global population and has been identified as the most important risk factor (cause) of chronic atrophic gastritis (CAG), the main precursor lesion of gastric cancer (GC). Regular endoscopic examination and worry of development of GC bring these CAG patients serious physical, psychological and economic burden. However, most of the *H. pylori*-infected patients will not progress to the development of CAG, not to speak of GC, through their lives. Therefore, if we can classify all the *H. pylori*-infected patients according to the risk of CAG, most of them would be relieved from their burden. Molecular pathological epidemiology (MPE) is a new interdisciplinary, transdisciplinary

and multidisciplinary study field, which has emerged as an integrated approach of molecular pathology and epidemiology, and investigates the relationships between molecular characteristics or molecular changes, exogenous and endogenous exposure factors, and initiation, evolution, progression, and response to treatment of diseases. According to the principle and methods, MPE may be a promising approach to achieve our purpose. Moreover, the MPE can provide some very important insights on the molecular mechanisms, personalized prevention and treatment for the study field of *H. pylori* infection and CAG.

Key words: Molecular pathological epidemiology; *Helicobacter pylori*; Chronic atrophic gastritis; Risk factor; Molecular mechanism

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HELICOBACTER PYLORI (*H. PYLORI*) INFECTION AND CHRONIC ATROPHIC GASTRITIS (CAG)

Helicobacter pylori (*H. pylori*), which was isolated for the first time in the year of 1982 by Australian scientists Marshall and Warren^[1], infects more than 50% of the global population^[2]. In developing countries, the prevalence of *H. pylori* infection is very high and it has been found in the stomachs of 70 to 90% of the total population, whereas in developed countries, 25 to 50% of the people carries *H. pylori* and the prevalence is relatively lower^[3]. As early as 1984, it had been very clear that the infection of *H. pylori* was strongly associated with the inflammation of gastric mucosa tissues, especially the polymorphonuclear cell infiltration^[4]. Until now, it is well known that *H. pylori* infection plays an important etiologic role in many of the most common gastroduodenal diseases, including chronic

atrophic gastritis^{5,6}).

Chronic atrophic gastritis (CAG) is the long-term inflammation of epithelial lining of the stomach mucosa, leading to the loss of gastric glands and replacement by fibrous and intestinal tissues⁷. According to one recent meta-analysis, which included 14 studies and was published in 2010, the incidence rates of CAG ranged from 0% to 10.9% per year⁸. *H. pylori* infection has been identified as the most important risk factor (cause) of CAG⁷. Compared to patients without *H. pylori* infection, those patients with *H. pylori* infection have a higher incidence rate of CAG. A meta-analysis reported that the rate ratios were in a range from 2.4 to 7.6, and the summary estimate was 5.0 (95% confidence interval [CI], 3.1 to 8.3)⁸. Because many and many studies have confirmed CAG as the main precursor lesion of gastric cancer (GC), *H. pylori* eradication and regular endoscopic examination (screening for early detection of GC) are recommended for those with CAG, to prevent and reduce the prevalence of GC⁷, although some misunderstandings exist in the risk of GC and *H. pylori* infection⁹.

Regular endoscopic examination and worry of development of GC bring these CAG patients serious physical, psychological and economic burden. Moreover, in the face of the alarming rise of antibiotic resistance, *H. pylori* eradication is very difficult for some patients¹⁰. However, according to the published epidemiological data, most of the *H. pylori*-infected patients will not progress to the development of CAG, not to speak of GC, through their lives^{11,12}. For example, one population-based German cohort study included 9953 person and found that 51.9% of them had *H. pylori* infection and 5.7% were diagnosed with CAG¹². Another study which was conducted in the Cameroon included 139 dyspeptic patients and found that the prevalence of *H. pylori* infection and CAG were 79.82% and 6.6%, respectively¹¹. In addition, among all the *H. pylori*-infected patients, only 1 to 2% will develop gastric cancers^{7,13}.

Therefore, if we can classify all the *H. pylori*-infected patients according to the risk of CAG and/or GC, most of them would be relieved from their physical, psychological and economic burden. Molecular pathological epidemiology (MPE) was introduced for the first time in 2010 and may be a promising approach to achieve this goal¹⁴⁻¹⁷.

INTRODUCTION OF MOLECULAR PATHOLOGICAL EPIDEMIOLOGY (MPE)

Molecular pathological epidemiology (MPE) was consolidated and introduced for the first time by Professor Shuji Ogino and Professor Meir Stampfer in 2010, mainly based on their researches of colorectal cancers¹⁴. Molecular pathology investigates the molecular characteristics in cells, tissues, organs or bodily fluids¹⁸. Epidemiology studies the endogenous and exogenous exposure factors, including lifestyle, dietary, environmental or genetic factors, in defined populations¹⁹. Currently, molecular pathology and epidemiology have converged and created a new interdisciplinary, transdisciplinary and multidisciplinary study field, which has been introduced as “molecular pathological epidemiology”^{14,15}. In the field of MPE, investigators study the relationships between (A) molecular characteristics or molecular changes of cells, tissues, organs or bodily fluids; (B) exogenous and endogenous exposure factors, including lifestyle, dietary, environmental or genetic factors; and (C) initiation, evolution, progression, and response to treatment of diseases, such as tumors^{16,17}.

For better understanding of the concept and basic approach of MPE, we would describe briefly the prototypical study in the evolving

field of MPE, which was one case-control study and conducted in the USA by Professor Peter T. Campbell and others²⁰. It was designed to determine the relationships between tumor microsatellite instability (MSI) status, body mass index (BMI) and risk of colorectal cancers (CRC). The authors found the positive relationship between BMI and CRC risk, but this relationship was modified by the status of MSI²⁰. For patients with MS-stable CRC, the adjusted odds ratio (OR) was 1.38 (95% CI, 1.24 to 1.54) with an increment of 5 kg/m² of BMI, and that value was 1.33 (95% CI, 1.04 to 1.72) for those with MSI-low colorectal tumors. However, no significant difference was found for those patients with MSI-high tumors (OR, 1.05; 95% CI, 0.84 to 1.31)²⁰.

According to the principle of MPE, this case-control study addressed the relationships between molecular change (MSI status of CRC), endogenous exposure factor (high BMI) and tumor initiation (risk of CRC). However, the MPE approach can be applied to not only neoplastic diseases but also non-neoplastic diseases, such as this study field of *H. pylori* infection and CAG^{16,17}. In this research field, the investigators will study the relationships between molecular characteristics, *H. pylori* infection, and development and progression of CAG. If the risk of CAG associated with *H. pylori* infection can be determined by using some certain molecular changes or biomarkers, the *H. pylori*-infected patients can be classified and most of them would be relieved from their serious physical, psychological and economic burden. Moreover, the MPE can provide some very important insights on the molecular mechanisms, personalized prevention and treatment for the study field of *H. pylori* infection and CAG.

MPE IN *H. PYLORI* INFECTION AND RISK OF CAG

Until now, according to our current knowledge and previously published studies, very few MPE researches can be available for the relationship between *H. pylori* infection and risk of CAG²¹⁻²³. The term of MPE had not been adopted by these studies and they were usually performed under the umbrella of molecular epidemiology. However, based on the objectives and methods, they can be treated as MPE researches.

The “first” MPE study was conducted in the Netherlands and published in the Journal of the National Cancer Institute in 1995²¹. The purpose of this study was designed to determine the relationships between the status of CagA (cytotoxin-associated gene A), *H. pylori* infection and development of CAG. Fifty-eight *H. pylori*-infected patients were included and they had been followed up for a mean period of 11.5 years²¹. Twenty-four (41%) of them were CagA positive and at the initial visit, 14 patients had been diagnosed with moderate to severe CAG. During the follow-up, among the 44 initially atrophy-negative patients, eight (50%) developed CAG in the 16 patients with CagA-positive *H. pylori* infection, however, in the 28 CagA-negative *H. pylori*-infected patients, 29% (8/28) of them developed CAG. The value of relative risk (RR) was calculated as 1.75 (95% CI, 0.82 to 3.76)²¹. The authors concluded that these CagA-positive *H. pylori*-infected patients had an increased risk of CAG development.

The results of this study were subsequently confirmed by a few other studies^{22,24}. Sozzi *et al* described the difference in the prevalence of atrophy between patients with CagA-positive and CagA-negative *H. pylori* infection²⁴. They included 80 *H. pylori*-infected patients and found that 53 (66%) were CagA seropositive, and CagA-positive patients had an increased prevalence of atrophy²⁴.

Another population-based study which was conducted in the Japan included 738 subjects and showed that the ORs for development of CAG were 4.26 (95% CI, 2.22 to 8.17) and 3.87 (95% CI, 1.95 to 7.68) respectively for CagA-positive and CagA-negative *H. pylori*-infected subjects in males, and the corresponding ORs were 4.92 (95% CI, 3.06 to 7.92) and 3.02 (95% CI, 1.69 to 5.41) respectively for females with *H. pylori* infection^[22].

However, in these studies, the numbers of included subjects are very limited, and the values of RR/OR and selected molecular biomarker are not satisfactory. It isn't nearly enough for our purpose of classification or stratification of the *H. pylori*-infected subjects according to the risk of development of CAG. More and more well-designed MPE researches are required. Some previously published associated studies can provide certain clues or indications for the design of such MPE researches, including molecular epidemiology studies, molecular pathology studies, analyses of genomic expression profiles, and comparative proteomics analyses^[17].

For virulence factors of *H. pylori*, some studies found that vacuolating toxin (VacA), the chaperonin GroEL, and helicobacter cysteine-rich protein C (HcpC) were strongly associated with CAG^[25,26]. The concept of "serological gastric biopsy" for diagnosis of CAG^[27-29], which composed of serum pepsinogen I (PGI), PG II, PG I /PG II ratio (PGR), and protein stimulated gastrin-17 (G-17), has been widely used by some studies, but they are not perfect for *H. pylori*-induced CAG^[27, 29, 30]. For example, one recent study was designed to determine the optimal serum pepsinogen cut-off value for prediction of CAG^[30]. The authors found that patients with CAG had the lower serum PGR than those without CAG, and the optimal PGR cut-off values for predicting CAG of the antrum and of the corpus were 4.9 and 3.5, respectively^[30].

One comparative proteomics analysis showed that up-regulation of ribosomal protein S12 (RPS12) and down-regulation of proteasome activator subunit 1 (PSME1) were involved in the development of CAG^[31]. Another analysis of genomic expression profiles found that five genes were associated with *H. pylori*-related CAG, including ATP6V0B, ATP6V1G1, ATP6V1F, NDUFV2 and NDUFS5^[32]. In addition, the epigenetic markers including methylation levels of the gastric mucosa have been associated with the development and prognosis of CAG^[33,34]. Zhao *et al* observed that the aberrant methylation levels of Runx3 in the peripheral blood could be used to predict the prognosis of CAG^[33]. Han *et al* described that promoter methylation of RNF180 was associated with *H. pylori* infection and could be used as the marker for development of CAG and GC^[34]. These molecular changes or biomarkers can be used in the design and performance of future MPE researches.

FUTURE PERSPECTIVES

H. pylori infection has been identified as the most important risk factor of CAG, the main precursor lesion of GC. Regular endoscopic examination and worry of GC development bring these CAG patients serious physical, psychological and economic burden. However, most of the *H. pylori*-infected patients will not progress to the development of CAG, not to speak of GC. Therefore, if we can classify all the *H. pylori*-infected patients according to the risk of CAG, most of them would be relieved from their burden. MPE is an interdisciplinary, transdisciplinary and multidisciplinary study field, which may be a promising approach to achieve this goal. Moreover, the MPE can provide some important insights on the molecular mechanisms, personalized prevention and treatment for the study field of *H. pylori* infection and CAG.

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