Editorial Commentary

Interplay of homologous-recombination genes and *Helicobacter pylori* in gastric cancer susceptibility

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Gastric cancer (GC) ranks as the 5th most prevalent neoplasm and the 4th primary contributor to cancer-related fatalities worldwide (1). Despite a global reduction in GC incidence, the year 2020 marked the diagnosis of 1.1 million individuals and the unfortunate occurrence of 770,000 subsequent fatalities due to this disease. Furthermore, the overall 5-year relative survival rate for individuals with GC remains diminished (2). Looking ahead to 2040, recent projections indicate a significant surge of 62% in case numbers, reaching a staggering 1.77 million, should the current rates persist (3).

In light of the well-documented correlation between *Helicobacter pylori* (*H. pylori*) infection and GC development, the International Agency for Research on Cancer (IARC) Working Group, a subsidiary of the World Health Organization (WHO), has categorized *H. pylori* as a Group 1 carcinogen (4). This decision was grounded in both compelling epidemiological data and solid biological plausibility (5). Despite advancing insight into the virulence factors of this bacterium, the specific causes behind differing individual susceptibilities to GC remain elusive. Among these mechanisms, *cagA*, a prominent gene encoding an oncogenic protein, emerges as a key factor in the context of *H. pylori*-related gastric carcinogenesis (6). Biological differences between the Eastern Asian and Western variants of *cagA* have been suggested as potential factors explaining the highest age-standardized global incidence rate of cancer attributed to *H. pylori* infection, particularly prevalent in East Asia (7,8). However, uncertainty remains concerning whether the factors contributing to this variation in GC incidence are solely confined to microbial biology.

Certainly, over the past few years, a growing body of evidence has emphasized the significant contribution of genetic predisposition when combined with *H. pylori* infection, towards influencing the risk of GC (9). In their groundbreaking publication in *The New England Journal of Medicine*, Usui *et al.* [2023] ratificate that the presence of pathogenic variants in homologous-recombination (HR) genes, combined with *H. pylori* infection, significantly amplifies the risk of GC in individuals with both risk factors (10). This research not only deepens our understanding of the intricate interaction but also provides valuable insights into the multifaceted etiology of GC.

Germline pathogenic variants in cancer-predisposing genes play a significant role in familial cancer risk syndromes (11). For instance, the inclination towards diffuse gastric cancer (DGC) is currently attributed to the presence of pathogenic and likely pathogenic variants (P/LP) in genes such as *CDH1* and *CTNNA1*, resulting in the development of hereditary diffuse gastric cancer (HDGC) (12,13). Families meeting specific criteria for HDGC are recommended to undergo genetic testing. Subsequently,

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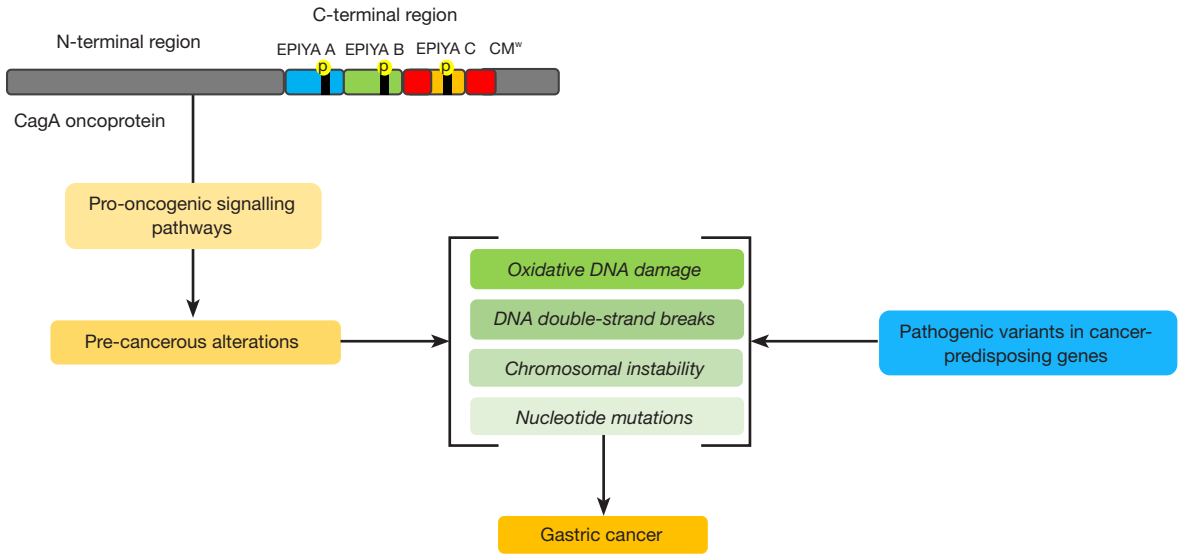

Figure 1 Basic illustration: how homologous recombination genes and *H. pylori* interact in gastric cancer susceptibility. Phosphorylation-triggered translocation of CagA to the inner lipid layer of the plasma membrane is depicted. Functioning as a versatile scaffold or hub protein, CagA simultaneously disrupts multiple host signaling pathways. These pathways play a pivotal role in regulating various cellular processes including proliferation, differentiation, and apoptosis. The resultant incongruent interaction between CagA and host proteins leads to oncogenic alterations in cells. The potential link between the alignment of pro-oncogenic insults and variations in cancer-predisposing host genes is proposed to be connected with the progression to gastric cancer. *H. pylori*, *Helicobacter pylori*.

individuals carrying deleterious alterations in the *CDH1* gene are considered potential candidates for preventive gastrectomy (14). This example illustrates how targeted screening for germline pathogenic variants in cancer-predisposing genes can identify high-risk individuals, facilitating early intervention and surveillance.

Additionally, apart from *CDH1*, Usui *et al.* identified eight genes—*BRCA1*, *BRCA2*, *APC*, *ATM*, *MLH1*, *MSH2*, *MSH3*, and *PALB2*—each harboring distinct pathogenic variants intricately linked to GC predisposition (10). These findings hold considerable significance, as targeted screening for germline pathogenic variants in cancer-predisposing genes could aid in identifying high-risk individuals who might benefit from early intervention and surveillance (15). Nevertheless, the realization of this hypothesis remains uncertain, prompting the need for subsequent clinical investigations and comprehensive cost-effectiveness analyses of these strategies.

Thereafter, the authors intriguingly demonstrated an association between *H. pylori* infection and pathogenic variants in HR genes regarding the susceptibility to GC [relative excess risk attributed to this interaction: 16.01; 95% confidence interval (CI): 2.22 to 29.81; P=0.02] (10). Notably, pathogenic variants within HR genes can impede DNA repair efficacy, predisposing to pro-oncogenic genetic modifications (16). In this context, the authors propose that the underlying mechanism driving this elevated risk entails genome instability induced by *H. pylori* infection, thereby contributing substantively to the progression of gastric carcinogenesis (10).

Indeed, upon translocation and subsequent tyrosine phosphorylation at EPIYA (Glu-Pro-Ile-Tyr-Ala) motifs, the oncogenic protein CagA relocates to the cell membrane, serving as a pathological scaffold. It disrupts various intracellular signaling pathways, leading to disturbances in cell proliferation, differentiation, and apoptosis (17). In turn, these alterations elevate the likelihood of cells acquiring pro-oncogenic genetic mutations. For instance, CagA inhibits PAR1b kinase activity, impacting the phosphorylation status of the *BRCA1* gene (18,19). Consequently, this alteration contributes to an increased frequency of DNA double-strand breaks (DSBs). The observed phenotype thus underscores the potential linkage between CagA-mediated signaling disturbances and heightened genetic instability (*Figure 1*).

Based on these findings, the authors propose that addressing the susceptibility to GC in individuals with germline pathogenic variants in cancer-related genes

could be effectively achieved through the eradication of *H. pylori* (10). As a result, this approach holds the potential for tailored interventions encompassing prophylactic antibiotic regimens, adjustments in lifestyle factors, and vigilant surveillance. Furthermore, these potential benefits may extend to immediate family members of individuals carrying HR gene variants or those affected by GC. This cohort could benefit from proactive screening for *H. pylori* infection, especially considering that relatives of GC patients are commonly colonized by the most virulent *H. pylori cagA* genotypes, potentially elevating the risk of gastric carcinogenesis (20,21).

However, as underscored by the authors, although randomized controlled trials represent the ultimate approach for addressing these inquiries, the ethical complexities associated with the implementation of such trials within the context of *H. pylori* eradication and its potential impact on GC prevention warrant significant attention (10). Considering the potential contributions of the study, integrating its outcomes into clinical practice guidelines demands a rigorous assessment by experts, who must scrupulously evaluate the strengths, limitations, and applicability of the findings.

In line with any pioneering study, novel inquiries inevitably arise, prompting the need for subsequent investigations to directly address these emerging questions. Future research should delve into the precise molecular pathways and interactions that underlie the synergy between germline pathogenic variants and *H. pylori* infection in influencing susceptibility to GC. Additionally, exploring the role of other genetic factors and their interactions with *H. pylori* could provide a more comprehensive understanding of the disease's complexity.

It is noteworthy that Usui *et al.* highlighted they could not accurately detect copy-number variants (CNVs) using amplicon-target sequencing and available single-nucleotide polymorphism (SNP) array data. This limitation is particularly significant due to the pivotal role CNVs can play in cancer development and predisposition (22,23). Such structural variations can cause changes in the copy count of specific genes, potentially altering gene dosage and expression levels, which in turn contribute to GC risk (24). Therefore, this aspect should be addressed in future studies.

Given the distinct variations between Western and Eastern *H. pylori* strains, it is crucial to initiate similar research efforts specifically focused on Western populations. In a recent genotype-driven study by Garcia-Pelaez *et al.*, the links between CDH1 germline variations and GC were explored, revealing significant associations (25). However, there remain unexplored aspects concerning how pathogenic gene variants interact with *H. pylori* infection to influence cancer susceptibility. Furthermore, a noticeable gap exists in assessments in regions with lower GC rates, such as African nations, and a lack of comparative studies among East Asian countries. Conducting cross-population comparisons can significantly enhance our understanding of the interplay between HR genes and *H. pylori* in the context of GC development.

In conclusion, the paper "*Helicobacter pylori*, Homologous Recombination Genes, and Gastric Cancer" ratificate a compelling interplay between germline pathogenic variants in cancer-predisposing genes and the presence of *H. pylori* infection. This association significantly heightens the susceptibility to GC, indicating a prospective era wherein tailored preventive and therapeutic approaches could transform the approach to addressing this lethal ailment. The findings emphasize the vital role of interdisciplinary investigation, amalgamating genetics, microbiology, and gastrointestinal oncology, to lay the groundwork for enhanced patient outcomes. However, given the limitations of the study, the need for subsequent clinical investigations and comprehensive cost-effectiveness assessments of these approaches is underscored.

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