

Merging *Helicobacter pylori* eradication and family history-based genetic counseling in patients with gastric cancer: towards an overarching approach in clinical practice

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Helicobacter pylori (*H. pylori*) represents the prototype chronic infection of the gastric and potentially the gastrointestinal system, and it is a key model for studying microbially-induced oncogenesis in humans [1,2]. *H. pylori* is now a well-established risk factor for gastric cancer [3], especially through the action of certain microbial genes, such as CagA [4], whereas its eradication has been robustly linked to gastric cancer reduction, especially for those harboring non-atrophic or atrophic gastritis as precancerous lesions [5]. Although perhaps not oft-discussed in daily practice, a family history of gastric cancer is also a major contributing factor [6].

A recent study by Choi *et al* assessed whether *H. pylori* eradication can reduce the risk for gastric cancer in individuals with a family history of this cancer type in first-degree relatives [7]. The study built upon previous systematic findings that first-degree relatives of patients with gastric cancer present with a higher risk of developing gastric cancer themselves, as evidenced both by *H. pylori* prevalence rates *per se* and by markers of gastric atrophy and intestinal metaplasia [8]. In that novel study, the authors showed a statistically significant difference in the proportion of patients developing gastric cancer between those treated for *H. pylori* and those who did not receive any treatment (1.2% vs. 2.7%, hazard ratio 0.45, 95% confidence interval 0.21-0.94; P=0.03) [7]. These results imply that the risk posed by having a family history of gastric cancer can be mitigated by addressing an environmental (in this case, microbial) factor [7]. Nonetheless, they should be interpreted with caution, especially upon considering some methodological caveats in this study, which diminish their broader clinical usefulness (as observed in other *H. pylori*-related studies [9]). Specifically, the family history of gastric cancer was defined as *having at least one first-degree relative with gastric cancer whose diagnosis had been histologically confirmed* [7]. However, no search for variants in well-

established oncogenes and tumor suppressor genes and, in turn, no stratification based on such genetic biomarkers (e.g., *E-cadherin* or *ARID1A*) were performed in that study. Doing so would have allowed a more robust genetic confirmation of gastric cancer predisposition [10-12].

Moving forward, a broader question arises, important for clinical practice and clinical cancer genetics counseling: is having a first-degree relative with gastric cancer a sufficient criterion for family history? This question is crucial, not only from a clinical, cancer genetics viewpoint, but also when viewed in the context of *H. pylori*. In many family settings, previous studies have observed the intrafamilial presence of phylogenetically identical *H. pylori* strains (as assessed by rRNA gene patterns, called *ribopatterns*) [13]. Regardless of whether these findings are explained by person-to-person transmission or, alternatively, by the presence of a common source of infection, they collectively highlight the potential for intrafamilial transmission of *H. pylori* [13]. Mother-to-child and sibling-to-sibling transmission have also been reported [14]. Therefore, could this intrafamilial transmission of *H. pylori* strains contribute to the family history of gastric cancer?

On this basis, future studies considering the ties between a family history of gastric cancer and *H. pylori* eradication should also assess the molecular subtypes (e.g., analysis of CagA and the CagA-associated EPIYA polymorphisms [15]) and potential clonality of *H. pylori* strains, both in the examined individuals and in their first-degree affected relatives. Such study designs could ultimately contribute to a *precision oncomicrobiology* approach (for further description, see [1]) and could have far-reaching implications.

H. pylori infection is a communicable disorder (i.e., an infectious disease), whereas gastric cancer is considered a chronic, non-communicable disease. Thus, the suggestion that intrafamilial transmission of *H. pylori* contributes to shared strain-induced common gastric cancer needs to be validated in independent settings before concrete clinical guidelines are formulated; nevertheless, the *margins* between the notion of *communicable* and *non-communicable* diseases would become looser if that scenario is validated. Besides, the idea that non-communicable diseases may in fact be *communicable* is not novel; this notion has been previously suggested in different contexts and settings [16,17].

In conclusion, the study by Choi *et al* highlights that *H. pylori* eradication is of merit even in the presence of a family history of cancer; however, the methodological criteria implemented in this study should be viewed with caution

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before conclusive clinical guidelines are established. More importantly, clinical gastroenterologists should work closely with both clinical molecular geneticists and clinical molecular microbiologists to offer an *overarching* approach in clinical practice, by concurrently considering: (a) the family's genetic predisposition to gastric cancer; and (b) oncogenesis-related microbial genetic features of *H. pylori* strains isolated from these patients.

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