Potential Impact of Active *Helicobacter pylori* Infection with or without Concomitant Metabolic Syndrome on Colorectal Cancer Invasion and Mortality

To the Editor:

Based on serology, Shmuely and colleagues [1] concluded that *Helicobacter pylori* infection (*Hp*-I) may be a risk factor for all-cause mortality among colorectal cancer (CRC) patients who are evaluated by positron emission tomography/computed tomography imaging.

However, the serological test does not discriminate between current and past infections. Apart from past infection that might even be more applicable for oncogenesis, such a distinction is crucial because only current *Hp*-I induces humoral and cellular immune responses that provoke or perpetuate chronic inflammatory processes in gastrointestinal tract with potential oncogenic sequelae including metastases and mortality. Many neoplasms, such as CRC, arise at the sites of chronic inflammation and infection; and chronic inflammation via the nuclear factor kappa B pathway promotes CRC invasion, metastasis, and mortality.

Our studies [2,3] comprised 50 CRC patients, 25 patients with colorectal adenomas (CRA), and 10 controls. Based on histology, the practical gold standard for current *Hp*-I diagnosis, our research showed significantly higher presence of *Hp*-I in the CRA (68%) group and CRC (84%) group compared to controls (30%). With regard to the features of histological severity in CRA group, presence of *Hp*-I was observed in 50% of patients with mild dysplasia and 80% of patients with moderate/severe dysplasia. Likewise, presence of *Hp*-I in the CRC group was observed in 89% of patients with mild and 83% with moderate/severe grade (including stage IV) dysplasia, also mentioned by the authors [1]. Noteworthy, *H. pylori* presence was documented by immunohistochemical stain in CRA and CRC tissues. In addition, presence of *Hp*-I with accompanying immunohistochemical expression of CD44, which is an indicator of cancer stem cells (CSCs) and/or bone marrow-derived stem cells (BMDSCs), in biopsy specimens was found in a high proportion of CRA patients accompanied with moderate/severe dysplasia (88%) and CRC patients with moderate/severe degree of malignancy (91%) [3]. CD44 plays a critical role in oncogenesis, differentiation, and lymph node metastasis and is predictive of the prognosis and mortality for various carcinomas including gastric cancer and CRC. Comparable pictures were also obtained for proliferation marker Ki-67 (Ki-67 correlates with the degree of malignancy, CRC invasiveness, metastatic behavior, patient survival, and the risk of relapse), anti-apoptotic Bcl-2 (Bcl-2 polymorphism could be a risk factor of CRC poor prognosis), and CD45 (assessing mainly T and B lymphocytes locally) immunohistochemical expressions [2,3].

Metabolic syndrome (MetS) is closely related to insulin resistance, and *Hp*-I has been proposed to be a contributing factor [2]. In a systematic review, we reported an association between *Hp*-I and insulin resistance, the major underlying mechanism responsible for the MetS. Both *Hp*-I and MetS are widespread globally and there is growing evidence for a potential association between *Hp*-I and insulin resistance syndrome or MetS and its related morbidity [2]. In Israel, the probability of MetS appears to be significantly increased in relation to *Hp*-I and upper gastrointestinal pathologies, thereby suggesting that long-term gastric inflammation caused by *H. pylori* could play a role in metabolic homeostasis and oncogenesis [4]. Specifically, the risk of synchronous CRC is considerably increased by gastric cancer occurrence, especially in MetS patients; and screening for synchronous CRC is highly recommended for gastric cancer patients with MetS [2]. MetS is significantly associated with overall and advanced CRC. It also confers an increased risk of CRC incidence and mortality in both genders [2]. Moreover, relative data indicate that *Hp*-I with concomitant MetS could further increase the risk of colorectal neoplasms. The occurrence of MetS is associated with a twofold increased risk of CRC mortality and tumor recurrences. Preoperative MetS is a strong predictor for CRC mortality. MetS appears to be an independent predictor for CRC recurrence, and is associated with an increased recurrence risk equally in non-metastatic CRC.

Thus, casting additional light in the uncertain pathophysiological mechanisms underlying *H. pylori* with or without concomitant MetS in CRC invasion and mortality, our results, as well as those of others, have indicated that *Hp*-I impacts colorectal oncogenesis and progression by causing a possible chronic inflammatory mucosal damage, comparable to upper gastrointestinal tract (UGT) infections, thereby promoting CRC invasion, metastasis, and mortality [3]; inducing an exaggerated gastrin and progastrin release that may be predictive of aggressive CRC behavior (progastrin expression by stage IV tumors is considerably greater than stage IIa tumors); stimulating CSCs or recruiting BMDSCs, similar to UGT *Hp*-I-associated chronic inflammation, atrophic gastritis, hyperplasia, metaplasia, dysplasia, and BMDSCs recruitment that may facilitate tumor progression, lymph node metastasis, and mortality [3]; and affecting MetS parameters, oncogenes, and immune surveillance processes that may be involved in CRC invasiveness, metastatic behavior, mortality, and the risk of relapse [2,3] .

Therefore, because active *Hp*-I, with or without concomitant MetS, might be involved in all-cause invasion and mortality among CRC patients, *H. pylori* eradication might inhibit or delay CRC progression and thus large-scale studies are required.

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