Biomarkers in clinical practice: a tool to find subjects at high risk for stomach cancer. A personal view

*Sipponen P**

HUSLAB, Helsinki University Central Hospital (HUCH), Division of Pathology, Jorvi Hospital, Espoo, Finland

Direct diagnosis of gastric cancer with a single laboratory test is impossible. Gastric biomarkers assayed from a blood sample provide, however, a tool to diagnose patients at particularly high risk for gastric malignancy. This possibility is commonly neglected although the biomarkers provide a handy and inexpensive way to rationalize the clinical practices, and to identify the subjects most likely to have a gastric neoplasia, and in whom a careful immediate diagnostic endoscopy is most beneficial.

Helicobacter pylori gastritis and atrophic gastritis precede gastric cancer in 50-80% of the cases, and atrophic gastritis is inevitably the most important single risk condition of gastric cancer known and identified so far [1,2]. Strategies intended to find the subjects with this preceding condition with blood tests followed by diagnostic endoscopy have provided promising results in early diagnosis of the gastric malignancy [3]. Subjects with atrophic gastritis have a 2-90-fold risk of gastric cancer compared to subjects with normal and healthy stomach (normal gastric mucosa: no inflammation, no atrophy, no *H. pylori*) [2-4].

The risk of gastric cancer increases with increasing grade and extent of atrophic gastritis in the stomach, and is highest in those with severe atrophy [1,2]. Assays of the levels of serum pepsinogen I (S-PGI) and II (S-PGII), and gastrin-17, as well as *H. pylori* – antibodies provide a possibility to diagnose the subject with atrophic gastritis, and to establish with high sensitivity and specificity in which part of the stomach the atrophic alterations are, and how extensive the atrophy is. On the other hand, the blood test with biomarkers also reveals with high accuracy those who have a normal and healthy stomach and in whom the cancer risk, correspondingly, is practically nil [5-8].

* CORRESPONDING AUTHOR:
DR. PENTTI SIPPONEN IS A SCIENTIFIC ADVISER OF BIOHIT, PLC,
A FINISH COMPANY THAT SELLS AND DEVELOPES DIAGNOSTIC TESTS
Prof. Pentti Sipponen, M.D., Head of Division
HUSLAB, Helsinki University Central Hospital (HUCH)
Division of Pathology, Jorvi Hospital, Espoo, Finland
Tel.: +358-9-861 2671; Fax: +358-9-861 5912
e-mail: pentti.sipponen@hus.fi (Pentti Sipponen)

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In two Finnish cross-sectional population-based studies on "asymptomatic" subjects, gastric cancer or its early stage was found in 4-6% of the 50-65 year-old men who showed a moderate or severe atrophy of the corpus mucosa with the S-PGI test [3]. The atrophy was diagnosed by screening more than 20,000 men and the gastroscopy was performed to 1,344 men who had a low serum level of PGI (S-PGI <25 μg/l). Of these, 80% had *H. pylori* antibodies, and 63 out of 1,344 men had gastric cancer or cancer preceding lesion (dysplasia, intramucosal neoplasia). The study demonstrated further that approximately 70% of the cancers identified in the screening program were at early stage ("early cancers"), all of which patients could be curatively healed by the surgery or endoscopic mucosectomy. As compared to findings in endoscopy and histology, the sensitivity and specificity of the low PG I level (<25 microg/l) were 78% (95% confidence interval 75-80%) and 98% (95-100%) for advanced (moderate or severe) atrophic gastritis.

Approximately 5-10% of Finnish males at age over 50 have an advanced (moderate or severe) atrophic gastritis of the corpus which may lead, in addition to gastric cancer, to low output of intrinsic factor and consequently to malabsorption of vitamin B_{12} [9,10]. Of the patients with advanced atrophic corpus gastritis, 30% have an exceptionally low (<170 pmol/l) levels of vitamin B_{12} in serum, and 50% have the vitamin levels <220 pmol/l that typically associates with increased serum levels of homocysteine [10]. On the basis of the available prevalence rates of atrophic gastritis and vitamin B_{12} deficiency in subjects with corpus atrophy, it can be estimated that there are thousands of elderly people in Finland (total population approximately 5 millions) who have or who are at high risk for the deficiency of vitamin B_{12} caused by the atrophic gastritis, in the majority of whom (80% at least) the atrophic gastritis is initiated by *H. pylori* infection, and who still have an undiagnosed ongoing *H. pylori* infection.

H. pylori test alone is not enough to diagnose the patients at risk for gastric cancer.

Breath test and antigen stool tests are commonly used to diagnose *H. pylori* infection in the general practice. Both tests

Table 1. **Diagnostic algorithms based on biomarker tests (GastroPanel) from a blood sample**

Biomarker test result	Interpretation and conclusions
Normal (healthy) stomach	Risk of cancer and peptic ulcer is practically nil (except in users of NSAID and aspirin). Consider other examinations first than gastroscopy. Colonoscopy, abdominal ultrasound and other examinations may be more beneficial than gastroscopy. PPI may be helpful in cases with reflux symptoms, or if gastrin-17 is very low – stomach is hyperchlorhydric – there is a risk of acid related damages in esophagus and cardia in patients with gastroesophageal reflux [34].
Non-atrophic *H. pylori* gastritis	Risk of gastric cancer is low whereas the risk of peptic ulcer may be considerable. Gastroscopy may be of low diagnostic help. Consider the treatment of *H. pylori* (prevention of gastric cancer and peptic ulcer).
Atrophic gastritis irrespective whether *H. pylori* (+) or (-)	Cancer risk is considerable. Careful diagnostic gastroscopy is mandatory to diagnose a possible cancer or precancer lesion (occur in up to 5% of cases). Treatment of *H. pylori*, if present, is recommended (cancer prevention). Test serum B_{12} if corpus is atrophic. No need for PPI, if corpus mucosa is atrophic (endogenous acid secretion is low). No risk of peptic ulcer if corpus mucosa is atrophic (endogenous acid secretion is low) but the ulcer risk, the risk of gastric ulcer in particular is high, if the atrophic gastritis is limited to antrum alone.

are reliable in cases with florid and extensive infection but are handicapped in cases with severely atrophic and hypochlorhydric stomach, as often is the case in patients with high cancer risk [11-14]. These direct tests only address an answer as to whether the patient has an *H. pylori* infection – nothing else. They are, however, unable to answer the question whether the patient has atrophic gastritis, and whether the patient is, therefore, at risk for gastric neoplasia. These direct tests, also including endoscopic biopsy urease test, can neither provide reliable evidence of whether the gastric mucosa is certainly normal and healthy. Particularly in the elderly, the negative breath test does not exclude the possibility that the stomach is severely sick, or that the patient would not have, for example, a severe *H. pylori* – negative atrophic gastritis. The direct tests often give false negative results particularly in patients with atrophic gastritis, hypochlorhydria and intestinal metaplasia, obviously due to reduction in *H. pylori* load in the gastric mucosa. This low colonization of bacteria is also the cause for common false negative results by breath test, or by antigen stool test, in subjects under the PPI treatment [15-18]. In fact, if one relies only on direct *H. pylori* tests, the risk of false negative test result, and the consideration that the patients has a healthy stomach, tends to be highest just among the subjects with highest cancer risk.

How to interpret the blood biomarker tests?

My personal view and advices to interpret the biomarker tests are presented in *Tab. 1* [see also refs 18-34]. It gives some personal suggestions only. It should be noticed, however, that all patients with severe and alarming symptoms (severe pain, bleedings, weight loss, etc.) must always be referred to immediate gastroscopy and endoscopic biopsies, without any prior tests. The suggestions given are advisable and valid only with tests of high quality that include assays of *H. pylori*, pepsinogens I and II, as well as gastrin-17 (GastroPanel).

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