H. pylori atrophic gastritis in the pathogenesis of gastric cancer

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Precancerous gastric lesions are adenomas and dysplastic changes of various cross-morphological type and form. Proper diagnosis of the precancerous lesions requires biopsy sampling of endoscopically visible mucosal lesions such as tumors, polyps, ulcers, folds, erosions, discoloured spots of the mucosa, etc. Dysplastic lesions are rarely diagnosed by random biopsy sampling of the stomach. In analysis of 63 cases with gastric cancer or definite dysplasia (of low or high grade) among 1.344 patients with advanced atrophic gastritis (serum pepsinogen I ≤25μg/L), all except one of the neoplastic lesions were found to occur in visible mucosal alterations in a recent Finnish study.[1]

Helicobacter pylori (*H. pylori*) infection and subsequent atrophic gastritis are precancerous conditions in which the risk of preneoplastic lesions is increased.[2] This risk increases exponentially with increasing grade and extent of atrophic gastritis and intestinal metaplasia in the stomach, the risk being approximately 90 times higher in patients with multifocal severe atrophic gastritis affecting both gastric antrum and corpus compared to the cancer risk in subjects with normal, non-atrophic gastric mucosa.[2] The cancer to be developed in these cases is usually of intestinal subtype. No reliable precancerous states are identified so far for gastric cancer of the diffuse type but also the risk of this cancer subtype is increased in subjects with *H. pylori* infection and gastritis, suggesting that the *H. pylori* gastritis is a premalignant condition for both intestinal and diffuse types of diffuse types of gastric cancer.

Association of the gastric cancer of intestinal subtype with atrophic gastritis provides some possibilities to identify or to screen subjects with an increased risk of gastric cancer. Serum pepsinogen I (SPGI) is a direct measure and a "serum biopsy" of multifocal atrophic gastritis, and of atrophic gastritis that particularly affects the gastric corpus. The SPGI level linearly decreases with increasing atrophy and loss of oxyntic glands, and is very low (≤25μg/L) typically in subjects with severe corpus atrophy and hypochlorhydria, or achlorhydria. The SPGI screen has been succesfully used in Japan and Finland to improve the early diagnosis of gastric cancer and precancerous lesions.[1,3]

The recent Finnish approach[1] included 22.000 middle-aged (55-69 years) men who at first were screened with the SPGI. Approximately 2.000 men were found who did fulfil the screening criterium (SPGI ≤25μg/L), and 1.344 were subsequently be endoscopically examined. Among the 63 cases with cancer or definite dysplasia found in the endoscopy of these 1.344 men, 11 and 7 were asymptomatic men with cancer or dysplasia of high grade, respectively. Of the 11 cancer cases, 7 were sc "early cancers" (invasion of the cancer is limited to submucosa at most). A further analysis of approximately 80 consecutive gastric cancer patients revealed that a low SPGI level (SPGI ≤25μg/L) occurs in 23%, suggesting that one fourth of all gastric carcinomas in Finland can be disclosed at early, curable stage with the SPGI-endoscopy procedure. The diagnosis of 18 cases with either cancer or high grade dysplasia in the Finnish project indicates that the SPGI-endoscopy procedure improves the cancer diagnosis at least 3-5-fold (this is because the expected annual incide of new gastric cancers among 22.000 men of age 65 is 20 of which 5 are correspondingly such which associate with a low SPGI level, and can be identified with the SPGI-endoscopy procedure). This intensification of cancer diagnosis with the SPGI-endoscopy procedure seems to be based on diagnosis of cancers and precancerous lesions at asymptomatic phase, obviously 3-5 years earlier than the case is with tumours diagnosed in the connection with ordinary clinical diagnostic routine.

Intestinal (IGCA) and diffuse (DGCA) types of gastric adenocarcinoma are the main microscopical subtypes that markedly differ from each others regarding epidemiology and demographic characteristics. Both of these tumor types comprise approximately 40% of all gastric adenocarcinomas. The DGCA's are tumors that more often occur in young age groups than the IGCA's, and they are less infrequently associated with atrophic gastritis and intestinal metaplasia of the underlying mucosa than the IGCA tumors. The risk of both DGCA and IGCA is, however, increased by the presence of *H. pylori* infection and gastritis, and it is likely that the development of most (up to 80%) of DGCA and IGCA tumors can be prevented with early eradication of the *H. pylori* infection.

The exact pathogenesis of DGCA is unknown but the pathogenesis of IGCA includes identifiable precancerous conditions such as atrophic gastritis and intestinal metaplasia, and the process results in appearance of dysplastic precancerous lesions,[4-8] and finally in overt cancers. Atrophic gastritis, on the other hand, is a direct result of the *H. pylori* infestation and, for unknown reasons, will appear in more than half of the infected subjects.[5-8]

Gastric cancer is known to be approximately twice as common in males than in females. This male predominance cannot be explained with the *H. pylori* infection, gastritis, atrophic gastritis, or intestinal metaplasia, which all occur as often in males as in females. The analysis of the male-to-female ratio (M/F ratio) of the incidences of gastric cancer provides new views of the gender-related differences in the pathogenesis of gastric cancern.[9] The M/F ratio of GCA rises with increasing age and reaches a peak at age of 60, after which the ratio decreases again. The form and magnitude of this "reversed V-shape" of the age-specific curve of the M/F ratio is independent of the incidence of gastric cancer or of the prevalence of *H. pylori* gastritis of the population. The curve is similar in countries with low (such as developed countries) and high (Japan, developing countries) gastric cancer incidence. The further analysis have indicated that the high M/F ratio of the cancer incidence concerns tumours of the IGCA type but those of the DGCA type. It seems that the incidence of IGCA begins to increase in males at earlier age than in females, and, correspondingly, there is a delay of 10-15 years between males and females in getting of the IGCA tumours. Among women, the IGCA tumours begin to progressively increase in prevalence at and after the age of 60 (menopause), resulting in a decrease of the M/F ratio of the cancer incidences. The most logical explanation for this gender-related difference is that the sex hormones, possibly estrogens, protect women for IGCA, and this type of gastric tumour begin to be common in females only after the menopause. It is conceivable that the appearance and development of the IGCA type tumours is somehow inhibited in female subjects by estrogens even though the *H. pylori* infection and atrophic gastritis occur equally often, and appears at same age in both gender.

REFERENCES

1. Varis K, Taylor PR, Sipponen P, Samloff IM, Heinonen OP, Albanes D, Harkonen M, Huttunen JK, Laxén F, Virtamo & The Helsinki Study Group. Gastric cancer and premalignant lesions in atrophic gastritis: A controlled trial on the effect of supplementation with alpha-tocopherol and beta-carotene. Scand J Gastroenterol 1998;33:294-300.

2. Sipponen P, Kekki M, Haapakoski J, Ihamäki T, Siurala M. Gastric cancer risk in chronic atrophic gastritis: statistical calculations of cross-sectional data. Int J Cancer 1985;35:173-7.
3. Miki K, Ichinose M, Ishikawa KB, Yahagi N, Matsushima M, Kakei N, Tsukada S, Kido M, Ishihama S, Shimizu Y. Clinical application of serum pepsinogen I and II levels for mass screening to detect gastric cancer. Jpn J Cancer Res 1993;84:1086-90.
4. Morson BC, Sobin LH, Grundmann E, Johansen AA, Nagayo T, Serck-Hanssen A. Precancerous conditions and epithelial dysplasia in the stomach. J Clin Pathol 1980;33:711-21.
5. Siurala M, Sipponen P, Kekki M. Chronic gastritis: dynamic and clinical aspects. Scand J Gastroenterol 1985;20(suppl 109):69-6.
6. Kuipers EJ, Uyterlinde AM, Pena AS. Long-term sequelae of *Helicobacter pylori* gastritis. Lancet 1995;55:2111-5.
7. Valle J, Kekki M, Sipponen P, Ihamäki T, Siurala M. Long-term course and consequences of *Helicobacter pylori* gastritis. Results of a 32-year follow-up study. Scand J Gastroenterol 1996;31:546-50.
8. Correa P. The epidemiology and pathogenesis of chronic gastritis: three etiologic entities. Front Gastrointest Res 1980;6:98-108.
9. Sipponen P, Hyvärinen H, Seppälä K, Blaser MJ. Review article: pathogenesis of the transformation from gastritis to malignancy. Alim Pharmacol Ther 1998;12(Suppl 1):61-71.