Gastric Breast Cancer 2002; 1(1): 4-6

MINI-REVIEW

Gastric Cancer Causation

Niki J. Agnantis M.D., and Dimitrios H.Roukos M.D.

Gastric cancer is the end result of a multifactorial, multigenetic, multistep process.[1] Environmental exposures and genetic factors have been reported to cause gastric cancer but the debate about whether environment or heritability plays the principal role continuous. The knowledge of factors that influence gastric carcinogenesis is determinant for the development of strategies effective for prevention and treatment.[2]

Over the past decades various conditions and risk factors have been identified to predispose to cancer development (Table 1). However, now most clinical and research attention has been focused on Helicobacter pylori infection, the preneoplastic lesions chronic atrophic gastritis and intestinal metaplasia, the free-radicals[1,2] and on familial gastric cancer predisposition.

- Helicobacter pylori (Hp) infection

An unbelievably large number of reports is increasingly publishing for the association of Hp and gastric cancer. That is not unexpected if we think that estimates suggest that about half of the world population is infected by this bacteria.[3] Previous epidemiological studies have consistently demonstrated an association between H. pylori infection and the risk of gastric cancer. Prospective serological studies have reported that H. pylori carriers are 3 to 6 times more likely to develop gastric cancer than those without infection[4-6] but most recent data estimate this risk much lower, about 2-fold.[7] Several questions about the role of Hp in gastric cancer remain to be elucidated. Until now is unclear why a very small percentage among Hp carriers will develop gastric cancer. This fact can not support the aspect that Hp is the causative and single factor for gastric cancer. The precise role of H. pylori infection in gastric carcinogenesis remains unclear and the effect of anti-Hp treatment on the prevention of gastric cancer are still unknown.[7,8]

- Chronic atrophic gastritis and intestinal metaplasia:

These two lesions are most closely linked to an increased risk of gastric cancer, specifically the intestinal type.[9] Atrophic gastritis begins as a multifocal process in the distal stomach. The state of reduced gastric acid (achlorhydria), as a result of gastritis, may progress to intestinal metaplasia, dysplasia, and ultimately carcinoma is thought to represent progress of the atrophic gastritis. Several investigators suggest that atrophic gastritis and intestinal metaplasia represent an important intermediate step in the pathogenesis of endemic, intestinal type gastric cancer. Pathological studies indicate that both conditions have been reported in otherwise healthy adults who do not subsequently have gastric cancer, indicating that neither atrophic gastritis nor achlorhydria alone is sufficient to cause gastric carcinoma.

- Family history of gastric cancer:

Clustering of gastric cancer within families has been reported for centuries, most notably in the Bonaparte family.[10] Napoleon, his father Charles and his grandfather Joseph all died of the disease, as did several of Napoleon's siblings. Case control studies indicate that first-degree relatives (e.g. parent or sibling) of patients with gastric cancer have two to threefold increase in the risk of contracting the disease.[11] Of the other condition and factors included in Table 1, an increased risk for gastric cancer has been reported for a history of partial gastrectomy for benign disease, the Barrett's oesophagus and a consumption of salted, smoked, or poorly preserved foods. This latest factor may partially explain the declining incidence of the disease in the latest decades.

- Pernicious anemia:

Studies of patients with this condition have demonstrated that is associated with two- to threefold excess risk of stomach cancer. In such patients an excess risk of gastric carcinoid tumors, may be the result of prolonged acid suppression, hypergastrinemia and

From the Departments of Pathology (NJA) and Surgery (DHR) at the Ioannina University School of Medicine, GR-45110, Ioannina, Greece. Correspondence to: Dimitrios H. Roukos M.D., Ioannina University School of Medicine, GR 45110, Ioannina, Greece, e-mail: droukos@cc.uoi.gr

neuroendocrine hyperplasia. Many observations that there has been a concern that iatrogenic achlorhydria may result in an increase in the incidence of intestinal type gastric cancer and gastric carcinoids, but up to date no study has reported an increased risk in patients with long term drug induced achlorhydria.[12, 13]

Partial gastrectomy for benign disease
Distal gastrectomy for benign disorders, particularly peptic ulcer disease, is associated with an increased risk of gastric cancer, although an association between gastric ulcer and gastric cancer has been alleged. Recent meta-analyses indicate that the previous relative risk remains low until 15 to 20 years after resection of distal stomach but increases steadily thereafter to the range approximately 1.5 to 3.0. The delay in the development of gastric cancer may reflect the time required for a gradual progression of normal mucosal to intestinal metaplasia to dysplasia and ultimately cancer.[14, 15]

- Menetrier's disease
There is numerous case reports link gastric cancer with Menètrier's disease, although the rarity of this disease has made it difficult to determine the strength of this association. [16, 17]

- Gastric adenomatous polyps
Similarly Menètrier's disease, considerable evidence indicates an increased risk of gastric cancer among patients with adenomatous polyps of the stomach. The malignant potential of adenomas appears to be directly related to the size of the polyp and the degree of the dysplasia.[18]

- Barrett's oesophagus
Studies demonstrate that the marked rise in the incidence of adenocarcinoma of gastric cardia and distal oesophagus appears to be strongly correlated with an increase in the incidence of Barrett's oesophagus. The incidence of cancer in patients with Barrett's oesophagus has been estimated to be 0.8% per year.[19]

- Blood type A:
Several studies reporting an increased risk of gastric cancer among persons with blood type A. The risk appears to be more pronounced for diffuse lesions than for the intestinal type.[20]

- Hereditary nonpolyposis colon cancer syndrome:
Patients with hereditary nonpolyposis colorectal cancer (i.e. Lynch syndrome II), an autosomal dominant disorder with a high degree of penetrance, are at increased risk for gastric cancer.[21]

- Low socio-economic status:
Although the link between a higher risk of gastric cancer is inversely associated with socio-economic status appears to be independent of occupational exposure, it is difficult to ascertain the relative contribution of other potential confounding factors, such as overcrowding, poor sanitation, inadequate preservation of food and poor nutrition.[22, 23]

- Low consumption of fruits and vegetables:
Studies have generally demonstrated that diets rich in fruits and vegetables are associated with a reduced risk of gastric cancer. Studies in Japan suggest that the recent decline in deaths from gastric cancer has been accompanied by a parallel decline in per capita consumption of salted and dried foods, as well as a parallel increase in the consumption of fresh fruits and vegetables.[24,25]

- Consumption of salted, smoked, or poorly preserved foods:
Studies have generally demonstrated that excessive dietary salt has been associated with gastric atrophy in animals and with atrophic changes in gastric mucosal in humans. Consumptions of highly salted and pickled foods over a long period may therefore lead to atrophic gastritis, making gastric mucosal more susceptible to the development of gastric carcinoma.[26,27]

- Cigarette smoking:
Several cohort and case-control studies have shown a [1, 5] to 3,0-fold increase in the risk of gastric cancer among smokers, although most studies have failed to demonstrate a clear dose-response relation.[28,29]

Precursor conditions

Chronic atrophic gastritis and intestinal metaplasia
Pernicious anemia
Partial gastrectomy for benign disease
Helicobacter pylori infection
Menètrier' s disease
Gastric adenomatous polyps
Barrett's oesophagus

Genetic and environmental

Family history of gastric cancer
Blood type A
Hereditary nonpolyposis colon cancer syndrome
Low socio-economic status
Consumption of salted, smoked, or poorly preserved foods
Cigarette smoking

REFERENCES

1. Correa P. Human gastric carcinogenesis: A multistep and multifactorial process. First American Cancer Society Award Lecture on Cancer Epidemiology and Prevention. *Cancer Res* 1992;52:6735-40
2. You Wc, Zhang L, Gail MH, etal. Dysplasia and Gastric Cancer: Helicobacter pylori, Serum Vitamin C, and Other Risk Factors. J *Natl Cancer Inst* 2000 Oct 4; 92(19):1607-1612.

3. Tytgat GN. Helicobacter pylori: where we are and where are we going?. *Aliment Pharmacol Ther* 2000 Oct;14 Suppl 3:55- 58.
4. Parsonnet J, Friedman GD, Vandersteen DP, et al. Helicobacter pylori infection and the risk of gastric carcinoma. N Engl J Med 1991;325:1127-31.
5. Forman D, Newell DG, Fullerton F, et al. Association between infection with Helicobacter pylori and risk of gastric cancer: evidence from a prospective investigation. BMJ 1991;302:1302-5.
6. The Eurogast Study Group. An international association between Helicobacter pylori infection and gastric cancer. Lancet 1993;341:1359-62. [Erratum, Lancet 1993;341:1668.]
7. Huang JQ, Hunt RH. Helicobacter pylori and gastric cancer - the clinicians' point of view. Aliment Pharmacol Ther 2000 Oct;14 Suppl 3:48-54.
8. Kandel G. Helicobacter and disease: still more questions than answers. Can J Surg 2000 Oct;43(5):339-46.
9. Kitahara F, Shimazaki R, Kojima Y, Morozumi A, Fujino MA. Severe atrophic gastritis with Helicobacter pylori infection and gastric cancer. Gastric Cancer 1998;1:118-24.
10. Sokollof B. Predisposition to cancer in the Bonaparte family. Am J Surg 1938;40:673-8.
11. La Vecchia C, Negri E, Franceschi S, Gentile A. Family history and the risk of stomach and colorectal cancer. Cancer 1992;70:50-5
12. Brinton L, Gridley G, Hrubec Z, Hoover R, Fraumeni JF Jr. Cancer risk following pernicious anaemia. Br J Cancer 1989;59:810-3.
13. Hsing AW, Hansson LE, McLaughlin JK, et al. Pernicious anemia and subsequent cancer: a population-based cohort study. Cancer 1993;71:745-50.
14. Tersmette AC, Offerhaus GJ, Tersmette KW, et al. Metaanalysis of the risk of gastric stump cancer: detection of high risk patient subsets for stomach cancer after remote partial gastrectomy for benign conditions. Cancer Res 1990;50:6486-9.
15. Dubrow R. Gastric cancer following peptic ulcer surgery. J Natl Cancer Inst 1993;85:1268-70.
16. Menetrier P. Des polyadenomas gastriques et de leurs rapports avec le cancer de l'estomac. Arch Physiol Norm Pathol 1888;1:322-36.
17. Matzner MJ, Raab AP, Spear PW. Benign giant gastric rugae complicated by submucosal gastric carcinoma: report of case. Gastroenterology 1951;18:296-302.
18. Nakamura T, Nakano G. Histopathological classification and malignant change in gastric polyps. J Clin Pathol 1985;38:754-64.
19. Spechler S. Barrett's asophagus. Semin Oncol 1994;21:431- 7.
20. Haenszel W, Kurihara M, Locke F, Shimuzu K, Segi M. Stomach cancer in Japan. J Natl Cancer Inst 1976;56:265-74.
21. Lynch HT, Smyrk TC, Watson P, et al. Genetics, natural history, tumor spectrum, and pathology of hereditary nonpolyposis colorectal cancer: an updated review. Gastroenterology 1993;104:1535-49.
22. Barker DJ, Coggon D, Osmond C, Wickham C. Poor housing in childhood and high rates of stomach cancer in England and Wales. Br J Cancer 1990;61:575-8.
23. Correa P, Cuello C, Duque E. Carcinoma and intestinal metaplasia of the stomach in Colombian migrants. J Natl Cancer Inst 1970;44:297-306.
24. Butiatti E, Palli D, Decarli A, et al. A case-control study of gastric cancer and diet in Italy. 1. Association with nutrients. Int J Cancer 1990;45:896-901.
25. Coggon D, Barker DJ, Cole RB, Nelson M. Stomach cancer and food storage. J Natl Cancer Inst 1989;81:1178-82.
26. Chyou P, Nomoura A, Hankin J, Stemmermann GN. A casecohort study of diet and stomach cancer. Cancer Res 1990;50:7501-4.
27. Nomura A, Grove J, Stemmermann G, Severson R. A prospective study of stomach cancer and its relation to diet, cigarettes, and alcohol consumption. Cancer Res 1990;50:627-31.
28. Kneller RW, McLaughlin JK, Bjelke E, et al. A cohort study of stomach cancer in a high-risk American population. Cancer 1991;68:672-8.
29. Kneller R, You W, Chang Y, et al. Cigarette smoking and other risk factors for progression of precancerous stomach lesions. J Natl Cancer Inst 1992;84:1261-6.