**REVIEW**

**Molecular epidemiology, pathogenesis and prevention of gastric cancer**

Christian T.K.-H.Stadtländer and John W.Waterbor

Department of Epidemiology and International Health, University of Alabama at Birmingham, School of Public Health, 220F Ryals Building, 1665 University Boulevard, Birmingham, AL 35294-0022, USA

To whom correspondence should be addressed
Email: h2bor@uab.edu

Cancer of the stomach is one of the most commonly diagnosed malignancies and remains an important cause of mortality world wide. This type of cancer is not uniformly distributed among populations but shows a marked variation in both incidence and mortality. Although gastric cancer is declining in many parts of the world, the reasons for this decline are not well understood and its etiology remains unclear. Several factors are suspected to play a role in gastric carcinogenesis, including the effects of diet, exogenous chemicals, intragastric synthesis of carcinogens, genetic factors, infectious agents and pathological conditions in the stomach (such as gastritis). A new look at the results of epidemiological and experimental studies is important for the establishment of strategies for control. Since cancer of the stomach has a very poor prognosis in its more advanced stages, such a control program must have its main focus on primary prevention. This review describes our knowledge about cancer of the stomach regarding epidemiology, pathogenesis and prevention.

**Introduction**

Gastric cancer is a global health problem of major proportions. In 1980, cancer of the stomach was the most frequent neoplasm in the world, comprising 10.5% of the major cancers with ~669 400 incident cases per year (1). In the mid 1980s, gastric cancer was surpassed by lung cancer, with stomach comprising 9.9 and lung 11.8% of estimated incident cases (755 000 and 896 000, respectively) (2). Gastric cancer ranked second in males (after lung cancer) and fourth in females (after malignancies of the breast, cervix uteri and colon/rectum) (2). Cancer of the stomach remains the most common malignancy in many countries of the world, although it is declining in frequency in almost all populations.

In recent years, research on gastric cancer has concentrated primarily on identifying environmental and genetic risk factors. Studies have shown that high intake of smoked, salted and nitrated foods, high intake of carbohydrates and low intake of fruits, vegetables and milk significantly increase the risk for stomach cancer (3.4). Clinical and epidemiological studies have suggested a link between gastric cancer and concurrent or previous infection with a bacterium or virus. *Helicobacter pylori* is believed to play a role in ~60% of gastric cancer cases (5) and multiple studies have demonstrated that *H.pylori* infection is associated with a 2.7- to 12-fold increased risk of gastric cancer (6). On the other hand, investigations of stomach cancers by PCR and *in situ* hybridization have shown the presence of Epstein–Barr (EB) virus-specific genetic material in gastric cancer cells (7). In addition, recent molecular genetic studies have provided evidence that genetic alterations of the human genome play important roles in the multistage process of gastric carcinogenesis (8).

The purpose of the present review is to provide an updated, comprehensive summary of the epidemiological, clinical, histopathological, molecular genetic and microbiological features of gastric cancer. An important aspect of this review is to provide an insight into stomach cancer etiology important for the development of prevention strategies.

**Epidemiology**

**Gastric cancer in the USA**

In 1930, cancer of the stomach was the leading cause of cancer death in American males and ranked third in females, after malignancies of the uterus and breast (9). The incidence and mortality rates of gastric cancer have been declining in the USA for more than 50 years. The age-adjusted mortality rate has decreased from 28.8 per 100 000 population in 1930 to 13 per 100 000 population in 1955 (10). From 1969 to 1971, gastric cancer ranked eighth among different cancer sites in incidence and accounted for 3.5% of all malignant neoplasms (11). According to the population-based Surveillance, Epidemiology and End Results (SEER) Program of the National Cancer Institute, which began in 1973 and covers an estimated 9.5% of the USA population, the age-adjusted incidence rate of gastric cancer across all races has decreased by 33.5% in males and 36.8% in females between 1973 and 1996, while the age-adjusted mortality rates decreased by 41.2 and 41.3%, respectively (12). The incidence rates for stomach cancer for all races between 1992 and 1996 fell to 10.4 per 100 000 population for males and 4.4 per 100 000 population for females. The highest incidence rates were observed in black males (17.2), while white males, black females and white females had considerably lower incidence rates (9.0, 7.0 and 3.7, respectively). Within the same time frame, the mortality rates for gastric cancer were estimated at 6.1 per 100 000 population for males and 2.8 per 100 000 population for females. The ranking for mortality by race was similar to that for incidence: black males had the highest mortality rates (12.1), followed by white males (5.4), black females (5.4) and white females (2.5) (12). Interestingly, the same ranking by race was noted for stomach cancer mortality by Haenszel in 1958 (10). This shows that over a period of nearly 40 years black males maintained the highest risk in the USA of dying from gastric cancer. The 5 year relative probabilities of survival of gastric cancer across all races between 1989 and 1995 were estimated at 18.6% for males and 25.2% for females (12). White females had the highest 5 year relative survival probabilities of survival.
probability (23.6%), while for black females survival was 23.2% for black males 20.6% and for white males 16.7% (12).

Strategies for gastric cancer control depend on the age at which the disease is detected. In the USA, most incident cases of gastric cancer occur between the ages of 65 and 74 years (12). The median age of gastric cancer patients at diagnosis among all races is 70 in males and 74 in females. Black males are diagnosed at a median age of 68 while white males, black females and white females are diagnosed at older median ages (at ages 71, 73 and 75, respectively). The median as a measure of central tendency is, unlike the mean, not affected by extreme values and thus often much more representative. Most deaths due to stomach cancer occur between the ages of 65 and 84, with a median age at death among all races of 71 in males and 76 in females. The median age at death is lowest in black males (69 years), followed by white males (72 years), black females (74 years) and white females (77 years) (12). Among primary cancer sites in the digestive system, gastric cancer currently ranks number 2 in males and number 3 in females by incidence rates, number 4 in males and 3 in females by mortality rates and number 6 both in males and females by 5 year relative survival rates (Table I). Although colorectal cancer has the highest incidence and mortality rates of all cancers of the digestive system, the 5 year survival probability for colorectal cancer is 61.2% in males and 60.8% in females and thus much higher than that of stomach cancer (18.6 and 25.2%, respectively) (12).

The decline in incidence and mortality rates of gastric cancer is believed to be partly due to an increase in incidence of and mortality from other cancers, in particular lung cancer, as well as secular changes in diet and the increasing availability of refrigeration for food (3). Despite the decrease in incidence and mortality, gastric cancer remains a disease with significant impact on the USA health system: it has been estimated that in 1999 there would be 21 900 new gastric cancer cases and 13 500 people would die due to this disease (12).

Gastric cancer in Europe

The International Agency for Research on Cancer (IARC), an independently financed organization within the World Health Organization (WHO), noted in 1993 that incidence and mortality rates for gastric cancer were lower in countries belonging to the European Community than elsewhere in Europe, although a decline from 1970 to 1985 was observed in all parts of the continent (13). In central Europe, mortality rates for males between 1983 and 1987 were highest in Poland, with 26.8 per 100 000 population, followed by Hungary (25.9), Bulgaria (22.1) and the former Czechoslovakia (22.1), while in females, the highest rates were observed in Bulgaria (12.1) and Hungary (11.4) (14). In 1990, stomach cancer mortality ranked fourth among different cancer sites in the European Union and accounted for 7% of cancer deaths in males and 5% in females (15). The incidence rates were highest in Portugal, with 31.9 per 100 000 population in males and 14.6 per 100 000 population in females, followed by Austria (21.6 and 11.3), Italy (20.7 and 9.4) and Germany (18.6 and 9.0), respectively. The fourth rank by incidence in females was tied between Germany and Finland. The ranking for mortality by sex was similar to that for incidence: Portugal had the highest mortality rates, with 26.2 per 100 000 population in males and 12.2 per 100 000 population in females, followed by Austria (16.5 and 8.0), Italy (17.0 and 8.0) and Germany (14.5 and 7.6), respectively (15).

An earlier study of the Nordic Cancer Union, which includes the cancer registries of Denmark, Finland, Iceland, Norway and Sweden, revealed that the age-adjusted incidence rates between 1970 and 1979 were 19.9 per 100 000 population for males and 10.4 per 100 000 population for females (16). The highest incidence rates were observed in Iceland (34.7 for males and 15.6 for females) and the lowest in Denmark (17.0 for males and 8.8 for females). There was a high risk area for gastric cancer incidence stretching from northern Norway to western and southern Finland while low risk areas were found in the central parts of Scandinavia and in the eastern islands of Denmark. The reasons for the observed geographical variations in gastric cancer incidence and mortality among European populations are believed to be linked to differences in the available technology of food preparation and storage, excessive intake of salt, access and consumption of fresh
Gastric cancer: a review

vegetables and fruits and *H. pylori* infection (14–16). It was observed in Sweden that cancer of the gastric cardia has been rising in incidence since 1970, with a mean annual increase of 2.5% (17). A recent study by Ekström *et al.* (18) indicates that misclassification and an increase in diagnostic awareness are responsible for the observed increase in adenocarcinomas of the cardia. The authors suggested that the accuracy of site classification should also be estimated in other countries in which an increase in this type of gastric cancer was noted.

The EUROCARE project, aimed at estimating and comparing the survival of cancer patients in different European populations, showed that the age-adjusted relative 5 year survival rates among adult Europeans diagnosed between 1978 and 1985 were highest in Switzerland (23%), Germany (19%) and The Netherlands (18%) and lowest in England (8%), Scotland (7%) and Poland (7%) (19). The survival rates in Switzerland are believed to be slightly overestimated because of the censoring of foreign residents who emigrate after diagnosis. Access to specialized care (such as endoscopy), disease stage at diagnosis, quality of treatment and (in)completeness of epidemiological data were suggested as explanations for the observed differences among European populations (19).

Gastric cancer in Asia

Asian countries have high stomach cancer incidence and mortality rates. World wide, Japan ranks first in incidence for both sexes (20). Highest incidence rates were recorded in the prefectures Yamagata, with 93.3 per 100 000 population, and Osaka (73.6). Between 1986 and 1988, mortality rates reached 37.9 in Japanese males and 17.2 in Japanese females. The northeastern parts of Japan have higher stomach cancer incidence and mortality rates than does the rest of Japan (20). Surprisingly, Japan does not rank first in stomach cancer mortality, as the incidence data might suggest. The Japanese population ranks fourth by mortality in males and females after South Korea (54.6 in males and 23.7 in females), Costa Rica (49.9 for males and 23.1 for females), the former Soviet Union (38.4 for males) and Ecuador (19.1 for females). This indicates that survival of gastric cancer is substantially better in Japan than in the other listed countries (20). Mortality rates are also high in China. Between 1986 and 1988, China ranked sixth in mortality both for males and females, with rates of 31.2 and 15.6, respectively (20). Kurotachi *et al.* (21) compiled and calculated cancer mortality statistics in 33 countries which allowed examination of secular trends in cancer mortality by site in each country. An international comparison of gastric cancer mortality rates by sex for selected countries is displayed in Figure 1.

Dietary factors, such as the consumption of salted and nitrated food, are believed to be primarily responsible for the high incidence and mortality rates of stomach cancer observed in Asian countries. A high intake of salt (NaCl) can cause stomach irritation which, in turn, can lead to the development of atrophic gastritis. Salt also causes excessive cell replication and increases the mutagenicity of nitrosated foods (7,22). On the other hand, heavily nitrated food can be harmful because nitrate when reduced to nitrite can react with other nitrogen-containing substances to form *N*-nitroso compounds (NOC), which are known mutagens and carcinogens (7,22).

Migrant studies revealed that Japanese who migrated to the USA experienced a significant decrease in mortality rates of gastric cancer when compared with Japanese who continued to live in Japan (23,24). The risk for developing gastric cancer was even further reduced in sons of migrants, but not in daughters (24). Changes in traditional food habits (females may adhere more closely to traditional food than males), changes in the risk from other (competing) causes and differences in diagnosing and reporting the causes of death were discussed as possible explanations for the observed differences in cancer mortality for men and women between home and adopted country (24).

Clinico-histopathology

Tumors of the stomach may be either malignant (cancerous) or benign (non-cancerous). They can be classified based on gross morphological and histopathological features. Almost all malignant tumors of the stomach are epithelial in origin and can thus be classified as adenocarcinomas (4). Histological typing and histopathological grading allows the clinician to more specifically characterize gastric cancer and to arrive at a prognosis. Rules for typing and grading must be periodically updated to maintain uniform data collection over long periods and to allow inclusion of new approaches (25). The classification developed by Laureñ in 1965 has been used most often during the past several years (26). It distinguishes gastric carcinomas by dividing them into two types. The intestinal (or well-differentiated) type of tumor consists of large and irregular nuclei in large and distinct cells. These cells retain sufficient cell cohesion allowing the formation of gland-like tubular structures. The diffuse (or undifferentiated) type of gastric cancer contains small solitary cells or small cell clusters which are arranged in a non-polarized pattern. This type can lead to early metastasis and generally shows a more aggressive clinical course (26–28). Hermanek and Wittekind (25) pointed out that the Laureñ classification became important because the intestinal and diffuse types of gastric cancer differ with regard to epidemiology, etiology, pathogenesis and behavior. This classification also appears to be useful in planning the surgical procedure, especially regarding the extent of safety margins when tumor resection is indicated (25).

Clinico-epidemiological studies showed that the intestinal (epidemic) type is commonly found in countries with high incidence rates of gastric cancer (e.g. Japan, China and the former Soviet Union) and appeared to be more common in males and in the elderly than in females and younger individuals. In contrast, the incidence of the diffuse (endemic) type tumor appeared similarly high in most populations, without preference for either sex, occurring at a younger age on average than observed in cases with the intestinal type (28,29). Muñoz and Matko (30) reported that the intestinal type of gastric cancer is found in association with intestinal metaplasia. Based on a currently accepted model of human gastric carcinogenesis, first described by Correa *et al.* in 1975 (31) and subsequently updated (22,32), it is believed that the successive tissue changes displayed in Figure 2 occur in the development of the intestinal type of human gastric cancer.

Besides adenocarcinomas, other gastric malignancies which contribute to gastric cancer statistics are lymphomas and leiomyosarcomas. These tumors, however, represent only a few percent of all gastric cancer cases (4).

Genetic factors

Observational studies are useful to determine whether heredity plays a role in gastric cancer and molecular epidemiological
studies can be used to identify factors involved in cancer development, progression and metastasis. Studies aimed at determining the role of heredity in stomach cancer include family pedigree reports, twin studies, family aggregation studies and blood typing studies. As discussed by Nomura (33), it has been shown that gastric cancer can be present in families over two to three generations and family members of a stomach cancer case have two to three times the risk than does
the general population of developing gastric cancer. Studies involving family members are methodologically limited, however, because they do not distinguish genetic from environmental factors, as family members tend to share a common environment (33). The results of blood typing studies indicate that blood group A is associated with gastric cancer more frequently than are the other blood groups. The association is stronger in males and for diffuse type gastric cancer as compared with intestinal type gastric cancer (4,33).

Molecular genetic studies have provided evidence that genetic alterations play a role in the multistage process of carcinogenesis and tumor progression. Effects of oncoproteins, inactivation of tumor suppressor genes by mutation, loss of heterozygosity (LOH) of chromosomes carrying tumor suppressor genes and errors in the replication of DNA, particularly in simple repeated sequences, have been discussed in the context of gastric malignancies. Mutations and/or amplification/overexpression of the oncoproteins c-Ki-ras, c-erbB-2, K-sam, hstl-1, c-met and c-myc and inactivation of the tumor suppressor genes p53, APC (adenomatosis polyposis coli), DCC (deleted in colorectal carcinomas) and RB1 (retinoblastoma), as well as LOH in one or more chromosomes including 1p, 5q, 7q, 12q, 13q, 17p, 18q and Y, are believed to play a role in gastric carcinogenesis (8,34–36). Wu et al. (37) showed that overexpression of p53 was more frequent in early intestinal type than in early diffuse type gastric cancer and was expressed in tumor stage progression of the diffuse type but not intestinal type of gastric cancer. Overexpression of c-erbB-2 was more common in intestinal type gastric cancer and in advanced gastric cancer of both histological types while overexpression of c-met was greater in diffuse type gastric cancer, particularly at advanced tumor stages. In addition, it was noted that LOH of APC was more common in the intestinal type irrespective of the stage but rarely in diffuse type gastric cancer while LOH of DCC occurred primarily in advanced intestinal type gastric cancer and infrequently in early gastric cancer or advanced diffuse type gastric cancer (37).

With regard to cancer invasion and metastasis, suppression of E (epithelial)-cadherin activity is believed to support the dissociation and release of gastric cancer cells from their primary cancer nests and integrins (e.g. β1-integrin) seem to play a role in tissue attachment, migration and invasion of gastric cancer cells (38). In addition, the CD44 receptor and E-selectin are currently potential candidates for study of the extravasation process of gastric tumor cells, which include the lodging of malignant stomach cells between endothelial cells and subsequent adhesion to the extracellular matrix of host tissues leading to the manifestation of metastatic nodules (38). The catalog of gene alterations in human cancer grows rapidly. Major genes and chromosomes altered in gastric carcinogenesis and metastasis are described in Table II.

### Infectious agents

**Bacteria**

An acidic environment is necessary for the protein digestion that occurs in the stomach and for killing invading microorganisms. A loss of gastric acid (achlorhydria) would raise the pH of gastric juice to 4 and above, at which level bacteria from the oropharyngeal, nasal passages and intestinal regions may establish themselves as resident flora in the stomach (39,40). In the presence of gastric acid, however, only those bacteria that tolerate the low pH of the gastric juice will survive. At the beginning of the 1980s, a bacterium from gastric biopsy specimens of patients with gastritis and peptic ulceration was successfully cultured (41). The bacterium was initially designated *Campylobacter pyloridis* (42) and later *C. pylori* to conform to the rules of scientific nomenclature (43). It is now called *Helicobacter pylori* (44). This Gram-negative and spiral-shaped bacterium utilizes a variety of strategies to survive in the acidic environment of the stomach. Its urease enzyme can neutralize gastric acidity and induce inflammation. Motility allows the bacterium to reach the gastric epithelium and adhesions promote attachment to gastric epithelial cells. Superoxide dismutase and catalase make *H. pylori* resistant to phagocytic killing and vacuolating cytotoxin (VacA) and cytotoxin-associated protein (CagA) may be used to produce damage to the gastric epithelium (6,45). It was shown by Blaser et al. (46) that CagA-positive strains of *H. pylori* have a stronger pathogenic activity and increase the risk for development of intestinal type gastric cancer. Censini et al. (47) reported that the cagA gene resides within a pathogenicity island, a DNA segment which contains ~40 genes encoding bacterial virulence factors. The cagA gene is a marker for enhanced pathogenicity and serological detection of infection with cagA-positive strains is currently considered the best test for *H. pylori* virulence (48).

Infection with *H. pylori* leads to gastric inflammation. The immune response to *H. pylori* involves a complex network of inflammatory mediators including chemokines [e.g. interleukin (IL)-8], pro-inflammatory cytokines (e.g. IL-1, IL-6, tumor necrosis factor α) and immunosuppressive peptides (e.g. IL-10) (49). It is believed that chronic infection with *H. pylori* leads to alterations of the cell cycle, including increased epithelial cell replication, increased rate of cell death (apoptosis) and production of oxidants. This, in combination with depletion of antioxidant defenses, may predispose to carcinogenesis by increasing the likelihood of DNA mutagenesis. The accumulation of mutations may then lead to metaplasia, dysplasia and gastric cancer (22,50–53).

*Helicobacter pylori* is known as the main cause of chronic (type B) gastritis and duodenitis, leading to gastric and duodenal ulcers (6). It has been estimated that 6–20% of infections with *H. pylori* result in peptic ulceration, but <1% lead to gastric cancer (54). These bacteria play a role in 53% of gastric cancer cases in developing countries and in 60% in developed countries (55). *Helicobacter pylori* has been linked to adenocarcinomas and lymphomas (56,58). Gastric lymphoma is, unlike gastric adenocarcinoma, a relatively rare disease comprising ~3–6% of all gastric malignancies (57). *Helicobacter pylori* infection has been associated with low grade B cell lymphomas that arise from lymphoid infiltrates which accumulate in the gastric mucosa in response to the infection and which can progress to a mucosa-associated lymphoid tissue (MALT) lymphoma (56,58).

Sero-epidemiological studies provided evidence of a strong worldwide association between *H. pylori* and gastric cancer, as was summarized by O’Connor et al. (5) and Taylor and Blaser (59). Recent results of a nested case–control study involving 84 stomach cancer patients identified from the Cancer Registry in Finland and 146 controls revealed an odds ratio (OR) of 2.52 [95% confidence interval (CI) 1.14–5.57] for elevated anti-*H. pylori* immunoglobulin A (IgA) levels (60). It was also observed that low levels of serum pepsinogen I (PG I) (which has been linked to atrophic gastritis) together with high anti-*H. pylori* IgA antibody levels resulted in an OR
Helicobacter pylori was recently classed as a Group 1 carcinogen by the IARC and WHO, suggesting that there is sufficient evidence in humans for the carcinogenicity of infection with *H. pylori* (62). Despite numerous studies providing the evidence for the *H. pylori*–gastric cancer link, there are also data indicating that peptic ulcers can protect patients infected with *H. pylori* from developing gastric malignancies, as summarized by Parsonnet et al. (63).

Another helicobacter has been associated with gastric cancer: a bacterium originally called *Gastrospirillum hominis* (64), for which the name *Helicobacter heilmannii* was recently proposed (65). Yang et al. (66) investigated 2943 patients by endoscopy for upper gastrointestinal diseases and detected 51 additional cases with *H. heilmannii* infection, which is not yet widely available (61). Bacteria other than *Helicobacter* spp. have also been described in gastric carcinomas. Sasaki et al. (71) reported the detection of a *Mycoplasma* infection in 11 (48%) out of 23 DNA samples of gastric cancer patients by PCR amplification using *Mycoplasma*-specific primers. They also described infection with *Streptococcus* in nine (20%) out of 43 gastric cancer samples, using Southern blot analysis and PCR. Sipponen and Stolte (72) suggested that an increased number of routine collections of biopsies from patients who undergo gastroscopy for abdominal complaints may lead to the detection of additional cases with *H. heilmannii* infection, which is necessary to determine whether *H. heilmannii* gastritis is more commonly associated with a MALT lymphoma or gastric carcinoma. In addition, the use of a variety of isolation media and procedures as well as PCR, in situ hybridization and immunoelectron microscopy should increase the chances of detecting and identifying bacteria in cancerous lesions of the stomach.

**Viruses**

In 1964, the EB virus, an icosahedral herpesvirus containing linear double-stranded DNA, was discovered (73). It was, however, not until 1990 that the virus was linked to gastric cancer. EB virus is ubiquitous in all human populations. It has been associated with gastric cancer both infections. They observed that colonization with *H. heilmannii* was mainly (91.2%) focal and for the most part restricted to the antrum (only 29.1% concurrent colonization of the corpus) while *H. pylori* showed a more diffuse pattern of colonization. In addition, the *H. heilmannii* gastritis was significantly milder than the *H. pylori* gastritis. In the same study, one case of *H. heilmannii* gastritis with concurrent gastric carcinoma and seven cases of low grade gastric MALT lymphoma were reported (68). Regimbeau et al. (69) reported a case of low grade gastric MALT lymphoma associated with *H. heilmannii* in the absence of *H. pylori*. They observed regression of endoscopic and histological lesions after eradication of *H. heilmannii*, indicating its role in gastric lymphoma. Hilzenrat et al. (70) evaluated 1223 gastric biopsies from 1042 upper endoscopies with biopsies performed over 1 year and found histological evidence of *H. pylori* and *H. heilmannii* in 59 and 0.5%, respectively, of 912 endoscopies. This suggests that infection with *H. heilmannii* in the stomach is much less common than infection with *H. pylori*.

<table>
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<tr>
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<th>Chromosomal locus</th>
<th>Massa (kDa)</th>
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| Loss of heterozygosity of chromosomes | 1p, 5q, 7q, 12q, 13q, 17p, 18q, Y | LOH |

kb, kilobase; kDa, kilodalton; gp, glycoprotein; LOH, loss of heterozygosity.

*aAdapted from Ochiai and Hirohashi (8) and Hesketh (36).

*bPredicted/expressed.

cNo data available.

of 5.96 (95% CI 2.02–17.57) while low serum PG I levels alone showed only an OR of 1.50 (95% CI 0.70–3.22) (60). Serological tests (e.g. ELISA and latex agglutination tests) are commercially available. However, molecular biological assays (e.g. PCR), although evaluated for diagnostic use for *H. pylori* infection, are not yet widely available (61).

**Table II. Genes and chromosomes altered in gastric carcinogenesis and metastasis**

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used PCR, DNA and EB virus-encoded RNA in situ hybridization and detected the virus in 22 out of 138 cases (16%) of gastric adenocarcinoma. Tokunaga et al. (76) detected the virus in 9.2% of males and 3.1% of females in a study involving 999 cases in Japan. Thus, EB virus appears to be about three times more prevalent in male than in female Japanese diagnosed with gastric cancer.

The number of reports on the detection of EB virus in gastric cancer cases is rapidly increasing. However, the mechanism of EB virus-induced gastric carcinogenesis remains to be elucidated. The virus replicates in epithelial cells of the pharynx and salivary glands and then typically infects B lymphoid cells. B cell infection is mediated by the viral envelope glycoprotein gp350 with the receptor for the C3d complement component CR2 (CD21) (74). After binding of the virus to the host cell and fusion of the viral envelope with the host cell membrane, involving viral glycoproteins gp85, gp25 and gp42, the virus may persist in a latent state in the host for life. Upon triggering of the EB virus-infected host cells, the lytic cycle is initiated and shedding of infectious virus can occur (74).

It appears that in gastric carcinoma, EB virus infection precedes malignant transformation in a significant fraction of cases, but neither bcl-2 expression (an inhibitor of apoptosis) nor p53 accumulation was found to be consistently associated with the presence of the virus (84). Ojima et al. (87) studied 412 patients with gastric adenocarcinoma and detected EB virus-specific RNA in tumor cell nuclei of 83 patients (20.1%), of which 60 were histologically subclassified as gastric carcinoma with lymphoid stroma. Overexpression of p53 was demonstrated in only seven (8.4%) of 83 EB virus-positive gastric carcinomas, but in 31 (34.4%) of 90 randomly selected EB virus-negative gastric carcinomas. The authors of this study believed that EB virus-associated gastric carcinomas may arise through a different mechanism from other types of gastric carcinomas without EB virus infection (87).

**Fungi**

The importance of fungal infection in gastric disease is not well understood. Wu et al. (88) evaluated, in a prospective study, the prevalence of fungal infection in gastric ulceration and its effects on ulcer healing in 178 benign and 97 malignant gastric ulcers. Fungal material (spores and/or hyphae) was microscopically detected in 36 (20.2%) patients with benign gastric ulcers and 26 (26.8%) patients with gastric cancers. The difference between the two groups was, however, statistically insignificant ($P > 0.2$). Kimura et al. (89) reported the isolation of Rhizopus microsporus var. rhizopodiformis from gastric biopsy specimens of a single case with gastric ulcer and adenocarcinoma. The authors indicated that small biopsies may not be enough to identify a fungus. Instead, the collection of multiple biopsy specimens should be reserved not only for histopathology but also for culture. This allows identification of the fungus as well as determination of whether the fungus colonized or invaded gastric tissue. Colonization with a fungus often does not influence the prognosis while invasion is usually fatal (89). Future studies should also reveal which fungi are primary pathogens and which act as opportunists.

**Parasites**

There are several reports describing gastric disease associated with the nematode Anisakis. In 1960, van Thiel (90) reported that Anisakis parasitic in herring caused acute abdominal syndromes in humans. Sugimachi et al. (91) analyzed 178 cases treated for acute anisakiasis between 1969 and 1984. The patients complained about acute and severe epigastric pain after eating raw fish. One hundred and fifty-five of the patients (87.1%) ate raw mackerel, seven horse mackerel, three bream and five squid, sardines or bonito, while 18 patients did not remember the species of fish they had eaten. All 178 patients underwent gastroscopy and worms were removed with endoscopic forceps. Local or generalized mucosal edema, with or without erosions, was endoscopically observed in 86% of the patients, while tumor formation was seen in 43% of the patients. Kakizoe et al. (92) studied the hospital records of 87 cases with anisakiasis who had been treated between 1989 and 1993. Moderate to severe gastric mucosal edema occurred within 1 or 2 days after infection with Anisakis larvae, accompanied by leukocytosis. In 55% of the cases, penetration of Anisakis was found in the greater curvature with severe mucosal edema. Petithory et al. (93) described a case of a 32-year-old female with Anisakis simplex. Histopathological examination revealed polyadenomas infiltrated with eosinophils. Since polyadenomas are considered to be precancerous lesions, the authors believed that A. simplex may be a cofactor for certain forms of gastric cancer. However, Tamura (94) suggested that the adenoma–carcinoma sequence appears to be relatively rare in gastric carcinogenesis. As reviewed by Kakizoe et al. (92), cases of anisakiasis have been reported in Japan, The Netherlands, England and the USA. Most cases of anisakiasis occurred in Japan, probably because the Japanese eat a great deal of raw fish. The risk of anisakiasis is, however, increasing throughout the world since traditional Japanese food has become popular worldwide (92). A list of infectious agents which have been linked to gastric malignancies is displayed in Table III.

### Table III. Infectious agents associated with gastric cancer

<table>
<thead>
<tr>
<th>Infectious agent</th>
<th>Histological type</th>
</tr>
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<tbody>
<tr>
<td>Bacteria</td>
<td></td>
</tr>
<tr>
<td><em>Helicobacter pylori</em></td>
<td>Adenocarcinoma, lymphoma</td>
</tr>
<tr>
<td><em>Helicobacter heilmannii</em></td>
<td>Adenocarcinoma, lymphoma</td>
</tr>
<tr>
<td><em>Mycoplasmas</em></td>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td><em>Streptococci</em></td>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td>Viruses</td>
<td></td>
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<tr>
<td>Epstein–Barr virus</td>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td>Fungi</td>
<td></td>
</tr>
<tr>
<td><em>Rhizopus microsporus var. rhizopodiformis</em></td>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td>Parasites</td>
<td></td>
</tr>
<tr>
<td>Anisakis simplex</td>
<td>Polyadenoma</td>
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</table>

**Experimentally induced gastric cancer**

Gastric carcinogenesis is a multistage and multifactorial process (22). Factors responsible for initiating or contributing to this chain of events can be tested in a variety of assay systems, such as animal tests, cell transformation assays, bacterial mutagenesis assays and DNA binding studies. Each of these assays has advantages and disadvantages with regard to expense, time and interpretation (40). Chemical agents have been evaluated for their carcinogenic properties for several decades. The addition of N-methyl-N’-nitro-N-nitrosoguanidine (MNNG) to the drinking water induced adenocarcinomas in rats, mice, hamsters, ferrets, rabbits and dogs (95–97). MNNG is a potent mutagen which causes methylation of nucleic acids and proteins. Sodium
chloride enhances the initiation of gastric carcinogenesis induced by MNNG in rats and apparently also acts as a tumor promoter because the enhancing effect was observed when it was given to rats after the treatment with MNNG was stopped. In contrast, ascorbate, selenium, β-carotene and calcium chloride in the diet of rats decreased the incidence of gastric adenocarcinomas induced by MNNG (98–101). Ascorbic acid (vitamin C) is believed to protect against gastric cancer by scavenging reactive radical species formed in the gastric mucosa, resulting in a reduced level of radical-mediated DNA damage (102). Nitric oxide (NO), a component of combustion processes and a product of macrophages in vivo in response to an infection, enhanced mutation in a Salmonella mutagenicity assay. The mutagenicity of NO was inhibited by β-carotene and α-tocopherol (vitamin E) but not ascorbate (103). β-Carotene also decreased the induction of 3-methylcholanthrene-induced transformation of 10T1/2 cells (104). Catechol, a component of cigarette tar, induced gastric adenocarcinomas in rats (105). It was shown that catechol inhibits DNA synthesis (106) and interferes with the elimination of transformed cells by normal cells (107). N-methyl-N-nitrosourea (MNU) has been found to be a gastric carcinogen in mice and rats after administration in the drinking water (97). Finally, N-ethyl-N′-nitro-N-nitrosoguanidine induced stomach cancer in rats, hamsters, dogs and non-human primates (96,97).

Investigations of gastric cancer experimentally induced by infectious agents depend on the availability of suitable animal models. Most studies with Helicobacter spp. focused on attempts to induce gastritis and evaluate vaccine candidates for eradication of the bacteria from gastric mucosa. Natural or experimental models included rodents, ferrets, guinea pigs, cats, dogs, piglets and non-human primates (108–110). There are, however, no suitable models of ulceration or gastric cancer because data from long-term infected animals are not available in sufficient numbers. The lack of a suitable animal model of gastric cancer is the reason why the IARC stated in its 1994 report that there is inadequate evidence in experimental animals for the carcinogenicity of infection with H. pylori (62). The most promising models of infectious etiology are those with Helicobacter felis, H. heilmannii, Helicobacter mustelae and H. pylori (108,109). It was shown that H. felis infection in mice can result in chronic gastritis followed by atrophy in the antrum and fundus after 1.5 years (111). Infection of mice with a gastric homogenate from a H. heilmannii-infected mouse induced gastric atrophy and some dysplasia (108). Fox et al. (112) showed that nine out of 10 animals naturally infected with H. mustelae and receiving MNNG developed an adenocarcinoma. Finally, a cat colony with H. pylori infection having chronic gastritis was detected (113).

More recently, a gerbil model was described which appears to be useful for gastric cancer research. In 1996, Hirayama et al. (114) reported the development of a successful Mongolian gerbil model of persistant H. pylori infection. The animals exhibited a slowly progressive gastritis and superficial erosions and lymph follicles were observed in the gastric submucosa at 42 days after inoculation. Ikeno et al. (115) inoculated gerbils with H. pylori and observed that these animals developed chronic active gastritis, intestinal metaplasia and gastric ulceration. Honda et al. (116) reported that gerbils inoculated with H. pylori developed atrophic gastritis, intestinal metaplasia and dysplasia. Two of five infected animals exhibited well-differentiated gastric carcinomas at 18 months. The gerbil model was also used to study the effects of chemical mutagens in the presence or absence of H. pylori. It was observed by Sugiyama et al. (117) that when comparing effects of inoculation with H. pylori before and after continuous MNU administration, only the H. pylori inoculation groups with MNU exposure developed adenocarcinomas while animals in the MNU alone group and H. pylori inoculation alone group did not show neoplastic lesions. Tatematsu et al. (118) induced gastric cancer in H. pylori-sensitive Mongolian gerbils treated with MNU and MNNG. It was shown by Zhang et al. (119) that ascorbate (10 mg/animal/day for 7 days) decreased H. pylori colonies in the stomach of gerbils and inhibited the growth of H. pylori in vitro. There are also reports describing experimentally induced lymphomas. Enno et al. (120) reported that long-term infection of BALB/c mice resulted in the development of lymphoid aggregates with lympho-epithelial lesions similar in appearance to those seen in human H. pylori-associated low grade B cell lymphoma. Shomer et al. (62) reported that experimental infection with H. pylori induced antral gastritis and MALT in guinea pigs. More data from long-term infected animals are expected in the near future which will help to answer questions about the development of gastric adenocarcinomas and lymphomas associated with a helicobacter infection (108,109). The availability of genetically modified knockout or transgenic animals are expected to provide additional data important for our understanding of events occurring in gastric carcinogenesis (97,109).

Information is lacking regarding experimentally induced gastric cancer associated with EB virus infection. This is probably due to the fact that EB virus has been linked to gastric cancer only within the last decade. Therefore, most studies have focused on providing epidemiological evidence for an association between EB virus and gastric cancer. Previous experimental studies concentrated on inducing cancers other than gastric cancer, primarily in non-human primates and rodents (74). The establishment of EB virus-negative and EB virus-positive human gastric cancer cell lines (121–123) could provide useful models for analyzing the molecular mechanisms of neoplastic transformation by EB virus in gastric epithelial cells (123).

Prospects for prevention of gastric cancer

Over the last decades, numerous risk factors and protective factors for gastric cancer have been identified. These include genetic, infectious, dietary, environmental and proneoplastic factors. The aim of a successful control program is to reduce morbidity and mortality of gastric cancer by applying our current knowledge about these factors. The prevention of gastric cancer may include a combination of approaches: preservation of a good nutritional status, cessation of smoking, education in hygiene, eradication of infectious agents, control of occupational exposures and risk assessment of genetic disorders with the prospect of gene-directed therapy. At present, however, not all of the above approaches are possible. Vaccination against infectious agents such as H. pylori or EB virus are not available yet. Also, treatment of EB virus infection with cytotoxic T lymphocytes is currently not feasible. Risk assessment of genetic alterations in gastric cancer patients and subsequent gene-directed therapy are also unavailable at the present time.

Diet plays an important role in gastric carcinogenesis. Carcinogens can be present in food, introduced during food preparation or synthesized by interaction of food items (e.g. during
cooking). In addition, the absence of protective factors in food can result in cancer promotion (124). Breslow et al. (125) examined food intake trends in the US population by analyzing data from the 1987 and 1992 National Health Interview Survey. The results indicate that Americans did not adopt behaviors consistent with national guidelines recommending the increased consumption of vegetables and fruits. In contrast, they adopted behaviors for the reduction of dietary fat, probably because this campaign more strongly emphasized the benefits of eating less fat (125). Thus, it appears important and feasible to develop better dietary guidelines for the population. Dietary changes are important and should include the regular consumption of fresh vegetables, fruit and milk to provide vitamins and antioxidants important to maintain a good nutritional status. Pool-Zobel et al. (126) showed in a human intervention study that supplementation of the diet with tomato, carrot or spinach products resulted in a significant decrease in endogenous levels of DNA strand breaks in peripheral blood lymphocytes while carrot juice significantly reduced base oxidation. Inoue et al. (127) reported that intake of green tea protects from developing gastric cancer: the OR of stomach cancer decreased to 0.69 (95% CI 0.48–1.00) with a high intake of green tea (7+ cups/day). On the other hand, the intake of smoked and heavily salted, nitrated and carbohydrate food should be avoided. High salt consumption has been associated with atrophic gastritis, while nitrates when reduced to nitrites can lead to the subsequent synthesis of carcinogenic NOC (124). Smoked fish contain polycyclic aromatic hydrocarbons which, when administered in an edible oil vehicle, induced forestomach cancer in mice and rats (128). Thus, there is reason to limit consumption of such foods. Food stored under unsatisfactory conditions should also be avoided because spoiled food can contain microorganisms which may have converted nitrate to nitrite, with subsequent endogenous nitrosation (129). Smoking should be stopped because tar contains carcinogenic substances such as catechol. Finally, education and promotion of hygiene, particularly in children, is important because infectious agents have been associated with gastric cancer.

Diagnosis of *H. pylori* infection and appropriate treatment may become important components of a gastric cancer control program. Diagnosis depends on the availability of suitable tests. Glupczynski (61) recently discussed that endoscopic tests, rapid urease tests and serological tests are useful for detection of *H. pylori* while urea breath tests and PCR are not yet widely available. Culture is useful for determining susceptibilities to antibiotics but is not recommended in a prevention program because it can easily lead to false-negative results (61). Eradication of *H. pylori* infection in order to avoid gastric cancer would include the use of antibiotics and/or vaccines (130,131). Vaccination against *H. pylori* recently became important because conventional treatment does often not completely eradicate *H. pylori*. From the numerous experimental vaccines, which include whole cells and cell sonicates of *H. pylori* as well as subunit vaccines (132), one antigen of *H. pylori* (i.e. urease) currently appears to be the most promising candidate. Kleanthous et al. (133) recently summarized the preclinical data and results of early stage clinical trials of a recombinant *H. pylori* urease vaccine. Such a vaccine may be used for prophylactic and/or therapeutic immunization in a prevention program.

Immunization against *H. pylori* appears to be useful in developing countries because of the high infection rates as well as in developed countries to reduce the costs of conventional treatments of gastrroduodenal diseases (132). It is, at present, not clear whether global eradication of *H. pylori* will become part of a prevention program in the future. In fact, in 1994, a consensus panel of the National Institutes of Health did not recommend *H. pylori* eradication for the purpose of preventing gastric cancer but recommended eradication of *H. pylori* in ulcer patients (134). Although treatment of *H. pylori* could reduce premature mortality and reduce the costs of treatment of *H. pylori*-induced diseases (135), it was more recently suggested that we eradicate *H. pylori* only in those patients who are infected with clearly pathogenic strains of *H. pylori* and who have developed or can be expected to develop a clinical disease (136).

In the case of EB virus, similar considerations to those discussed for *H. pylori* may be made in the future if more epidemiological evidence can be provided for a strong association between EB virus infection and gastric cancer. Diagnostic tests for EB virus are available, including serological and molecular biological tests (74). Treatment of EB virus infections is difficult because only a few drugs (e.g. acyclovir) prevent replication and even fewer are clinically useful due to the unacceptable side-effects (i.e. toxicity). Vaccine development showed that attenuated and killed EB virus variants cannot be used because of their oncogenic potential. However, gp350-based EB virus vaccines currently have the greatest potential. Finally, passive immunotherapy may be an alternative to control EB virus infection. The treatment of patients with cytotoxic T lymphocytes may be used to maintain control of latently infected cells, but cannot eliminate EB virus from the body (74).

Occupational risk factors for gastric cancer also need to be considered in a control program. Several factors have recently been described by Cocco et al. (137) and Parent et al. (138). Although data are limited, it appears that limitation of exposure to NOC and their precursors nitrate and nitrogen oxides, γ-radiation, crystalline silica, organic and inorganic dusts, glycol ethers, hydraulic fluids and leaded gasoline should be included.

| Table IV. Possible gastric cancer prevention approaches |
|-----------------|-----------------|-----------------|
| Risk factors | For prevention of gastric cancer | Feasibility |
| **Diet and behavior** | | |
| Fruits | Increase | Yes |
| Vegetables | Increase | Yes |
| Milk | Increase | Yes |
| Green tea | Increase | Yes |
| Smoked, salted and nitrated foods | Reduction | Yes |
| High carbohydrate | Reduction | Yes |
| Contaminated and spoiled food | Avoidance | Yes |
| Smoking | Prevention; cessation; Yes; yes |
| **Infectious agents** | | |
| *Helicobacter pylori* | Antibiotic treatment of infection; Vaccination; CTL therapy | Yes; no; no |
| Epstein–Barr virus | Occupational | |
| **Carcinogens** | | |
| Genetic | | |
| Alterations | Risk assessment; gene-directed therapy | No; no |

**CTL.** cytotoxic T lymphocyte.

*Not yet available.*
in a prevention program. Strategies of prevention should include a ban on these carcinogens in the workplace, removing carcinogens, reducing exposure levels and hazardous activities, increasing personal protection and conducting surveillance and education (139).

Finally, the identification of genetic alterations and subsequent gene-directed therapy may be incorporated into a gastric cancer prevention program in the future. Suppression of oncogene activity, replacement of defective tumor suppressor genes, enhancement of immune responses to tumor cells and destruction of tumor cells directly with cytotoxic agents may be part of such therapy (36). Table IV gives an overall summary of possible prevention approaches which target gastric cancer.

Conclusions

The present review demonstrates that gastric cancer remains one of the major health burdens in the world today but that this cancer is not uniformly distributed throughout the world’s populations. There are geographical variations both among and within countries. Populations with a high incidence and high mortality rates can be found in Asian countries (e.g. Japan, China and South Korea), European countries (e.g. the former Soviet Union, Finland, Iceland, Poland, Hungary and Portugal) and Latin American countries (e.g. Costa Rica and Ecuador). In the USA, the non-white population has the highest risk among all races to develop gastric cancer.

Much research has been done to identify factors and events which influence the initiation, promotion and progression of gastric cancer. It is clear that stomach cancer is a disease of complex etiology involving multiple risk factors including dietary, infectious, occupational, genetic and preneoplastic factors. In the past, two types of flowcharts have been used to describe the events occurring in gastric carcinogenesis: the ‘arrow path model’ (5,22,59) and the ‘staircase model’ (7). Both models are useful as they describe the sequence of steps important in gastric carcinogenesis. However, these models do not sufficiently show that the time an individual requires to move from one phenotypic stage to the next can vary depending on the accumulation of risk and protective factors. Thus, gastric carcinogenesis appears to be a very dynamic process, i.e. a process in which individual events can lengthen or shorten the development (induction period) of gastric cancer. We, therefore, propose a ‘spiral model’ of human gastric carcinogenesis (Figure 2). It shows that risk factors can compress the spiral and reduce the time until development of gastric cancer while a decrease in duration or intensity of exposure to these factors can expand the spiral and lengthen the induction time of gastric carcinogenesis. Helicobacter pylori infection and an excessively salty diet cause gastritis and atrophic changes in the gastric mucosa. The transition from atrophic gastritis to small intestine metaplasia is believed to be caused by NOC. Atrophic gastritis leads to higher gastric pH due to loss of acid-secreting parietal cells. This allows the growth of anaerobic bacteria which reduce nitrate (NO3−) abundant in many foods) to nitrite (NO2−). Nitrite then reacts with other nitrogen-containing compounds (from foods and drugs) to form mutagenic–carcinogenic nitroso compounds (N=O). Vitamin C acts as a blocker of the nitrosation reaction. On the other hand, β-carotene opposes the effects of dietary salt, especially in late events in gastric carcinogenesis (i.e. dysplasia and early invasive carcinoma). Substances in tobacco tar (such as catechol) support the development of preneoplastic lesions. A diet rich in vegetables and fruit, containing antioxidants and radical scavengers, supports the maintenance of a healthy gastric mucosa.

Based on current knowledge about risk and protective factors, we present numerous prevention strategies for gastric cancer and describe which of them are currently feasible (Table IV). Since cancer of the stomach must be considered, at least in part, as a consequence of lifestyle, changes in dietary habits and behavior could reduce morbidity and mortality. Watanabe et al. (7) estimated that such changes in lifestyle may prevent at least half of the gastric cancers in high prevalence areas. Since infectious components are also involved in the development of gastric cancer, strategies of eradication (antibiotic treatment and vaccination) have been discussed. Control of occupational risk is another important part of the proposed prevention program. Finally, approaches to risk assessment of genetic alterations and possibilities of gene-directed therapy can be considered. It must be kept in mind that elimination of one risk factor may not be sufficient to fully eliminate the disease because gastric cancer occurs through a multifactorial process.

The study of gastric cancer control depends on the interaction between investigators with different backgrounds and expertise. Incorporation of epidemiological, clinical, histopathological, molecular genetic, microbiological, occupational and behavioral assessments have had a major impact on our understanding of gastric cancer today. In the future, collaboration of scientists from different disciplines will be even more critical because it can lead to the identification of previously unrecognized factors relevant to gastric carcinogenesis as well as to the further development and subsequent implementation of a successful prevention program.

In 1986, Howson et al. (3) called the observed decline in gastric cancer an ‘unplanned triumph’. A carefully planned prevention program would allow us to ‘plan the next triumph’, i.e. to further reduce gastric cancer in human populations. In the USA, such a program could save the lives of ~13 500 people per year.

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References


Gastric cancer: a review


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