

## Gastric Cancer: Descriptive Epidemiology, Risk Factors, Screening, and Prevention

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### Abstract

Less than a century ago, gastric cancer was the most common cancer in the United States and perhaps throughout the world. Despite its worldwide decline in incidence over the past century, gastric cancer remains a major killer across the globe. This article reviews the epidemiology, screening, and prevention of gastric cancer. We first discuss the descriptive epidemiology of gastric cancer, including its incidence, survival, mortality, and trends over time. Next, we characterize the risk factors for gastric cancer, both environmental and genetic. Serologic markers and histological precursor lesions of gastric cancer and early detection of gastric cancer using these markers are reviewed. Finally, we discuss prevention strategies and provide suggestions for further research. *Cancer Epidemiol Biomarkers Prev*; 23(5); 700–13. ©2014 AACR.

### Introduction

Less than a century ago, gastric cancer was the most common cancer in the United States and perhaps throughout the world. Although it is no longer the most common cancer worldwide, gastric cancer remains the second leading cause of cancer-related mortality worldwide and the most prevalent cancer in Eastern Asia (1). This article discusses the epidemiology and prevention of gastric cancer, reviewing both classic studies and the new findings that have been added to the literature over the past few years.

### Some Terminology

The large majority (approximately 90%) of gastric cancers are adenocarcinomas, which arise from the glands of the most superficial layer, or the mucosa, of the stomach. Therefore, if not specified otherwise, our discussion of gastric cancer mainly pertains to adenocarcinomas. There are, however, other types of cancer arising from the stomach, including mucosa-associated lymphoid tissue lymphomas, which originate from the lymphoid tissue of

the stomach, and leiomyosarcomas, which arise from the muscles surrounding the mucosa.

A popular classification by Lauren stratifies gastric cancer adenocarcinomas into two major histologic types: diffuse and intestinal (2). These two types not only look different under the microscope, but also differ in gender ratio, age at diagnosis, and other epidemiologic features (3).

The stomach is divided into several anatomic subsites, including the cardia (roughly the top inch of the stomach), fundus, body, pylorus, and the antrum. These areas are distinguished by anatomic demarcations, histologic differences, or both. Most relevant to this paper is the distinction between adenocarcinomas arising from the cardia (cardia gastric cancer) and other parts of the stomach (noncardia gastric cancer), as they have different epidemiologic patterns and causes.

### Incidence, Mortality, and Burden

Each year approximately 990,000 people are diagnosed with gastric cancer worldwide, of whom about 738,000 die from this disease (4), making gastric cancer the fourth most common incident cancer and the second most common cause of cancer death (5). Gastric cancer also causes one of the highest cancer burdens, as measured by disability-adjusted life years lost (6).

Gastric cancer incidence rates vary wildly between men and women and across different countries. Rates are 2- to 3-folds higher in men than women (4). Comparing nations, the highest incidence rates are observed in East Asia, East Europe, and South America, whereas the lowest rates are observed in North America and most parts of Africa (7). For example, the annual age-standardized gastric cancer incidence rates per 100,000 in men are 65.9 in Korea versus 3.3 in Egypt (5). In the United States, the incidence is relatively low, particularly in Whites, with an estimated incidence rate per 100,000 of 7.8 and 3.5 in

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non-Hispanic White men and women, respectively (8). Rates also vary across races. For example, in the United States, rates are higher in Latinos (13.9 per 100,000 in men and 8.2 per 100,000 in women) than in non-Hispanic White populations (8). Indigenous populations, particularly Inuits in circumpolar region and Maoris in New Zealand, suffer from high rates of gastric cancer (9).

### Trends

Gastric cancer incidence rates have been on the decline in most parts of the world (10, 11). In United States, for example, the incidence rates decreased by 1.7% for men and 0.8% for women annually from 1992 to 2010 (12). A major exception to these decreasing trends is that cardia gastric cancer rates have remained stable or increased (13, 14), at least in Western countries. Such contrasting trends for cardia and noncardia gastric cancer may result from distinct etiologies. Unlike for noncardia gastric cancer, *Helicobacter pylori* does not seem to be a risk factor for cardia gastric cancer in Western countries (15), so its decline in prevalence would not be expected to affect cardia gastric cancer rates. In contrast, obesity and gastroesophageal reflux seem to be the risk factors for cardia but not noncardia gastric cancer. Obesity has been increasing in prevalence in Western countries (16), which may contribute to the rates of cardia gastric cancer. Finally, improvements in classification of tumors of the stomach might have contributed to an apparent increased rate of gastric cardia adenocarcinoma (17).

Other exceptions to the overall decreasing rates of gastric cancer have been recently noted. For example, an increased incidence among young White populations in the United States has been recently reported (18) but these findings may need further confirmation.

### Survival

Since 1970s, there have been notable improvements in the relative 5-year survival rates for gastric cancer, for example, from 15% in 1975 to 29% in 2009 in the United States (8). However, survival rates remain dismal (19). The overall 5-year relative survival rate is about 20% in most areas of the world, except in Japan, where 5-year survival rates of above 70% for stages I and II of gastric cancer have been reported (20). Such high survival rates may be due to effectiveness of mass screening programs in Japan or, alternatively, perhaps due to overdiagnosis, that is, the identification of localized cancers by screening programs which would not have progressed to invasive cancer or caused mortality (21).

Recent studies suggest that survival may be better in patients with gastric cancer tumors that harbor Epstein-Barr virus, which constitute approximately 9% of tumors (22). Survival is poorer among smokers, as they are more likely to develop subsequent primary cancers of the stomach (23) and may also die of other complications of smoking (24).

**Table 1.** Some prominent risk factors for gastric cardia and noncardia cancers

| Risk factors for gastric cancer |  |
|---------------------------------|--|
| Cardia                          | Noncardia                                |
| Age                             | Age                                      |
| Male sex                        | Male sex                                 |
| Tobacco smoking                 | Tobacco smoking                          |
| Race                            | Race                                     |
| Family history                  | Family history                           |
| Low physical activity           | Low physical activity                    |
| Fiber intake                    | Fiber intake                             |
| Radiation                       | Radiation                                |
| —                               | <i>H. pylori</i>                         |
| —                               | Low socioeconomic status                 |
| —                               | High intake of salty and smoked food     |
| —                               | Low consumption of fruits and vegetables |
| Obesity                         | —  |
| GERD                            | —  |

### Demographic and Environmental Risk Factors

Gastric cancer is a multifactorial disease, and both environmental and genetic factors have a role in its etiology. Some of these risk factors, such as age and sex are not modifiable, whereas others such as smoking and *H. pylori* infection potentially are.

Risk factors for cancers arising from cardia and noncardia regions of the stomach may be different (Table 1). Common risk factors for both cardia and noncardia gastric cancer include older age, male sex, tobacco smoking, radiation, and family history. Intake of aspirin and statins may prevent against both of these cancers. Although race is a risk factor for each, the direction differs by site. In the United States, Whites are more likely to acquire cardia gastric cancer, whereas Hispanics are more likely to be diagnosed with noncardia gastric cancer. Factors associated with cardia gastric cancer, but not noncardia gastric cancer, include obesity and gastroesophageal reflux disease (GERD). On the other hand, risk factors that are exclusive for noncardia gastric cancer include *H. pylori* infection (at least in Western countries), low socioeconomic status, and perhaps dietary factors such as low consumption of fruits and vegetables and high intake of salty and smoked food.

### Age

The incidence rate of gastric cancer rises progressively with age. Of the cases diagnosed between 2005 and 2009 in the United States, approximately 1% of cases occurred between the ages of 20 years and 34 years, whereas 29% occurred between 75 years and 84 years (25). During this period, the median age at diagnosis of gastric cancer was 70 years (25).

### Male sex

Compared with females, males have a higher risk of both cardia (5-fold) and noncardia gastric cancer (2-fold; ref. 26). The reasons for such differences are not clear. Environmental or occupational exposures may play a role. For example, men have been historically more likely to smoke tobacco products, although elevated rates in men seem to persist even in countries where men and women have similar smoking patterns (27). Alternatively, sex differences may reflect physiologic differences. Estrogens may protect against the development of gastric cancer. In women, delayed menopause and increased fertility may lower the risk of gastric cancer, whereas anti-estrogen drugs, for example tamoxifen, may increase the rates of gastric cancer (28, 29). These hormones may provide protection against gastric cancer during the fertile years of women but their effect is diminished after menopause, such that females develop gastric cancer in a manner similar to males, albeit with a 10- to 15-year lag after their male counterparts (30, 31).

### Cigarette smoking

Although the role of smoking in causing several other cancers has long been established, it was not until 2002 that the International Agency for Research on Cancer concluded that there was "sufficient" evidence of causality between smoking and gastric cancer (32). The reason for such delay is, in part, that the association between smoking and gastric cancer has not been consistent across studies, and that the association is not strong. A meta-analysis of cohort studies showed that the risk of gastric cancer is increased by only 60% (RR:1.6) in male smokers and 20% (RR:1.2) in female smokers compared with never smokers, and the associations are even weaker in former smokers (33). Although studies vary, overall the accumulated data suggest that smoking is a risk factor for both cardia and noncardia gastric cancer (33–35). Other forms of tobacco use, such as hookah use, have also been associated with higher risk of gastric cancer (36), although these associations have not been found in other studies (37) and need further confirmation.

### Race

Comparing Whites to other racial groups, cardia gastric cancer is approximately twice as common (26), whereas noncardia gastric cancer is approximately half as common (38). The risk of noncardia gastric cancer in the United States is highest among Asians/Pacific Islanders, Blacks, followed by Hispanics, and is least common in Whites (26). The association of race with the incidence of gastric cancer seems to be mediated mostly via environmental effects, rather than genetic variations. Japan has one of the highest rates of gastric cancer incidence in the world (10). After the Japanese migrate to the United States, they maintain very high rates in their first generation. However, their rates decline and become similar to those of Americans of European lineage after two generations (39).

### *Helicobacter pylori*

In their pivotal letter published in Lancet, the two discoverers of the *H. pylori* presciently noted that: "[the bacteria] may have a part to play in other poorly understood, gastritis-associated diseases (i.e., peptic ulcer and gastric cancer)" (40). Significant research over the ensuing two decades established *H. pylori* as an incontrovertible cause of gastric cancer (41), with relative risks of approximately 6 for noncardia gastric cancer (42). Certain *H. pylori* types, particularly those positive for the virulence factor cytotoxin-associated gene A (*cagA*), are more likely to cause gastric cancer (43–45). *H. pylori* is estimated to cause 65% to 80% of all gastric cancer cases, or 660,000 new cases annually (42, 46). These numbers may be underestimated, as most epidemiologic studies have used ELISA to assess *H. pylori* infection, a method that is insufficiently sensitive for this purpose. More recent studies that have used the Western blot assay have found relative risk closer to 21 (47). It has to be noted that, at least in Western countries, *H. pylori* is a major risk factor for only noncardia gastric cancer but not for cardia gastric cancer (42). Decreasing *H. pylori* prevalence (48, 49), perhaps due to better sanitation and extensive use of antibiotics, may be a major reason for rapid decline in the incidence of noncardia gastric cancer. It is not entirely clear how *H. pylori* causes gastric cancer. Two potential pathways are most considered: indirect action of *H. pylori* on gastric epithelial cells by causing inflammation and direct action of the bacteria on epithelial cells. *H. pylori* could also directly modulate epithelial cell function through bacterial agents, such as CagA. Although the relationship between the two pathways is unclear, both pathways seem to work together to promote gastric cancer development (50).

### Low socioeconomic status

At least since the studies of Villermé (51) and Chadwick (52) in the first half of the 19th century, we have known that lower socioeconomic status is associated with higher risk of total and cause-specific mortality, including mortality from most cancers (53, 54). Gastric cancer and its precursor lesions have been associated with markers of low socioeconomic status, including low education and low income (55–57). Higher rates of *H. pylori* infection, higher intake of starchy food, or lower access to fresh food and vegetables may be responsible for the association between low socioeconomic status and higher risk of gastric cancer (58). The prevalence of *H. pylori*, particularly CagA-positive strains, is substantially higher in low-income African Americans (59) and may contribute to higher risks in this group.

### Intake of salty and smoked food

The World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) has concluded that: "Salt, and also salt-preserved foods, are probably causes of [gastric cancer]" (60). A 1965 study showed a strong correlation between mortality from stroke and gastric cancer across geographic areas and over time, which

suggested salt as a risk factor for both (61). Epidemiologic and experimental studies supported this hypothesis. A recent meta-analysis of 11 case-control and cohort studies showed that higher intake of salt increases the risk of gastric cancer by 22% (62). Also, large cohort studies in Korea have shown that people who tend to prefer salty food have higher risk of gastric cancer (63). Salt may increase the risk of gastric cancer through direct damage to the gastric mucosa resulting in gastritis or other mechanisms (64).

The role of smoked food in gastric carcinogenesis was suggested in the early 1960 (65). Studies in Europe at the time showed that gastric cancer rates were highest in Finland and Iceland, where smoked fish and meat use was very high, which led to a further examination of smoked food and their polycyclic aromatic hydrocarbon (PAH) content in gastric carcinogenesis (66). Since then, benzo[a]pyrene and other PAHs formed in smoked food have been incriminated in many areas of the world with high gastric cancer rates (67).

In addition, certain cooking practices may be associated with increased risk of gastric cancer. These include broiling of meats, roasting, grilling, baking, and deep frying in open furnaces, sun drying, curing, and pickling, all of which increase the formation of N-nitroso compounds (68).

#### **Low consumption of fruits and vegetables**

The WCRF/AICR in 2007 commented that: "Non-starchy vegetables, including specifically allium vegetables, as well as fruits probably protect against gastric cancer" (60). In this report, a 50 g/day intake of allium vegetables was associated with a 23% reduction in risk of gastric cancer, a number that was confirmed in a recent meta-analysis (69). Such an association is plausible, as fruit and vegetables are rich sources of vitamin C, folate, carotenoids, and phytochemicals, which may inhibit carcinogenesis by modulating xenobiotic-metabolizing enzymes.

However, despite many years of research and a plausible hypothesis, the epidemiologic literature remains inconsistent (70, 71). WCRF/AICR's 2007 position of "probable" protection of gastric cancer by fruit and vegetables was a withdrawal from its 1997 position, which concluded that there was "convincing" evidence. This change was largely because cohort studies published between the two reviews did not replicate the strong protections that were mostly found in earlier case-control studies. Since the publication of WCRF/AICR report, the results of other large cohort studies have been conflicting, too. Although the one large cohort study found no evidence for protection (72), another one found a statistically significant inverse association (73). The results are also mixed for cardia and noncardia gastric cancer. In a high-risk Chinese population, a randomized trial of 7.3 years of supplementation with garlic extract and oil resulted in a statistically nonsignificant reduction in gastric cancer incidence or mortality (74).

#### **Antioxidant use**

Although intake of vitamin and antioxidants was once considered to be effective to prevent cancers, well-conducted randomized trials have generally shown very little or no benefit from their use to prevent gastric cancer or to promote overall health (75, 76). However, dietary supplementation may play a preventive role in populations with high rates of gastric cancer and low intake of micronutrients (74, 77).

#### **Other dietary factors**

Several other dietary factors or patterns have been studied in relation to gastric cancer. Studies have suggested that adherence to Mediterranean diet (78), diets that may be titled prudent or healthy (79), diets with high antioxidant capacity (80), and diets with high fiber content (81) are associated with lower gastric cancer risk. Conversely, diets that have a Western pattern (79) may increase gastric cancer risk. However, these findings need to be confirmed in future studies.

#### **Nonsteroidal anti-inflammatory drugs**

Current evidence suggests that intake of nonsteroidal anti-inflammatory drugs (NSAID) may have an inverse association with gastric cancer risk. Two meta-analyses of observational studies have shown an inverse association between aspirin or any other NSAIDs and cardia and noncardia gastric cancer (82, 83), whereas another one reported an inverse association of aspirin use with noncardia gastric cancer but not with cardia gastric cancer (84). The two most-updated meta-analyses (one with 13 and the other with 15 studies) reported an inverse association between aspirin use and all gastric cancer (OR = ~0.65), with little difference between case-control and cohort studies in this regard (85, 86). These two studies did not report the results by subsites of gastric cancer. On the other hand, in a pooled analysis of seven clinical trials of daily aspirin use (done originally for prevention of vascular events), the risk of death from gastric cancer in the aspirin taking group was not lower than in the control group: the HR (95% confidence interval; CI) was 1.85 (0.81–4.23) for 0 to 5 years of follow-up and 3.09 (0.64–14.9) for longer follow-up. These estimates were, however, based on 36 gastric cancer deaths only (87).

#### **Statins**

Two recent meta-analyses (88, 89) suggested that statin intake was associated with an approximately 30% reduced risk of gastric cancer. However, when a study with outlier results was excluded, the risk reduction was approximately 15%, which was homogeneous across studies. Statins have been associated with reduced risk of some other cancers, such as esophageal adenocarcinoma (90), and a host of mechanisms has been suggested for a lower risk of cancer associated with statin use (91). Nevertheless, statins are not associated with a reduced risk of all cancer incidence or mortality, particularly in randomized trials (92). As such, the reduced risk of gastric

cancer associated with statin use needs to be further investigated.

### Obesity

Obesity is a growing problem in modern societies and has been associated with a range of diseases, including the cardia gastric cancer. Compared with individuals with body mass index (BMI) of <25, individuals with BMIs of 30 to 35 have a 2-fold, and those with a BMI of >40 have a 3-fold risk of cancers of the esophagogastric junctional, including the cardia gastric cancer (93). In contrast, obesity is not a risk factor for noncardia gastric cancer (94). Several mechanisms have been proposed. Abdominal fat may directly cause GERD, a risk factor for esophageal cancer and cardia gastric cancer. Moreover, fat is metabolically active and produces numerous compounds that circulate in the body. These metabolic products, such as insulin-like growth factor and leptin, have been associated with malignancies, possibly through the induction of progrowth changes in the cell cycle, decreased cell death, and proneoplastic cellular changes (95, 96).

### Physical activity

A recently published meta-analysis (97) showed a 21% reduction in gastric cancer risk, comparing individuals who are most active with those who are least active. This risk reduction was seen for both cardia gastric cancer (20% risk reduction) and noncardia gastric cancer (37% risk reduction). However, risk reductions were less strong in high-quality studies. Furthermore, because all included studies were observational, the potential for confounding should be considered.

### Gastroesophageal reflux disease

GERD is strongly associated with risk of esophageal adenocarcinoma, with approximately 5- to 7-fold increase in the risk (98). Several studies have also reported statistically significant associations between GERD and cardia gastric cancer (99–103), with increased risks of 2- to 4-folds in the majority of studies, although not all studies agree (104–106).

Some investigators have suggested that there might exist two distinct forms of cardia gastric cancer: one similar to esophageal adenocarcinoma and associated with GERD and one similar to noncardia gastric cancer and associated with severe atrophic gastritis and *H. pylori* infection (103, 107, 108). This pattern, if it truly exists, could explain the null association observed in some populations. If the association between GERD and cardia gastric cancer is real, then the mechanism might be similar to those for the association between GERD and esophageal adenocarcinoma: GERD may cause columnar and intestinal metaplasia with potential progression to adenocarcinoma (109). Alternatively, however, esophageal adenocarcinomas are adjacent to and often cross the upper border of the stomach, thus may be misclassified as cardia cancers (93, 102).

A null or an inverse association has been reported for GERD and noncardia gastric cancer (100, 101, 104, 106, 110). This may be explained, at least partly, by the association between atrophic gastritis and noncardia gastric cancer. Severe atrophic gastritis may be associated with decreased secretion of gastric acid and lower risk of GERD (106).

### Radiation

Long-term follow-up of survivors of Hiroshima and Nagasaki established radiation as a risk factor for gastric cancer (111). A recent study of survivors of Hodgkin's lymphoma also showed that radiation to the stomach had a dose-response association with higher risk of gastric cancer (112). This effect was particularly pronounced in those who concomitantly received procarbazine as the chemotherapeutic agent, such that those who received both high-dose radiation and procarbazine had a 77-fold increased risk of subsequent gastric cancer (112). Little information is available for cardia and noncardia gastric cancer.

### Other potential risk factors

A number of other risk factors have been investigated in relation to gastric cancer but the results are not convincing, at least as of yet. Among these risk factors are poor oral hygiene and tooth loss (37, 113, 114), opium use (36, 115–117), infection with Epstein-Barr virus (118, 119), and eating pickled vegetables (120).

### Familial Aggregation

A positive family history (having a first-degree relative with gastric cancer) is a risk factor for gastric cancer (121). The magnitude of the relative risk differs by country and study, ranging from 2 to 10 (122). Positive family history could be a risk factor as a result of shared environment, for example, passing of *H. pylori* from parents to children, or because of shared genetic factors (123).

Studies have shown two patterns of risk change after migration. First, the risk of gastric cancer in migrants gets closer to that of the population of origin but does not reach the risk of the host population in the immigrant or the first-generation postmigration; it takes at least two generations to reach the risk levels of the adopted country (123–125). Second, place of birth is perhaps a stronger predictor of gastric cancer risk than current place of residence (126, 127). These findings show the importance of childhood exposure in the etiology of gastric cancer, such that migrants do not lose their risk in the generation who migrated or their children who migrated with them early in their life. One example of a risk factor that could take a couple of generations to modify is that *H. pylori* infection usually happens before the age of 10 years (48, 128), typically before one migrates. Even when children are born in the adopted country, they are likely to contract *H. pylori* from parents, older siblings, or other people who have migrated from their native country (129).

## Genetic Risk Factors

Only 1% to 3% of gastric cancer cases arise as a result of inherited syndromes (130), which are briefly discussed in the "Hereditary syndromes" section. The rest are sporadic gastric cancer cases, for whom no major high-penetrance genes have been discovered. Investigation of genetic risk factors for sporadic cases is discussed under "Single-nucleotide polymorphisms."

### Hereditary syndromes

These syndromes include hereditary diffuse gastric cancer (HDGC), familial adenomatous polyposis (FAP), and Peutz–Jeghers syndrome (PJS).

HDGC is a rare, autosomal dominant inherited form of gastric cancer, usually with a highly invasive diffuse type tumor, a late presentation, and a poor prognosis (131). These cancers display a prominent molecular abnormality, defective intercellular adhesions, which might be the result of loss of expression of the cell adhesion protein E-cadherin (132). Approximately 25% of families with HDGC have inactivating CDH1 germline mutations (132). The penetrance of CDH1 gene mutations is high, with an estimated risk of >80% for both men and women by the age of 80 years, and the median age at diagnosis of 38 years.

FAP is an autosomal-dominant colorectal cancer syndrome, caused by a mutation in the adenomatous polyposis coli gene (133). Patients with FAP carry a 100% risk of colorectal cancer by the age of 35 to 40 years, as well as a high risk of other malignancies, including gastric cancer.

PJS is a rare autosomal dominant inherited condition, characterized by hamartomatous gastrointestinal polyposis, and melanin spots on the lips and buccal mucosa (134). Germline mutation of the *LKB1* gene, which encodes a serine/threonine kinase that acts as a tumor suppressor, is a cause of PJS.

### Single-nucleotide polymorphisms

Before the advent and wide use of genome-wide scans, hundreds of case–control studies examined candidate polymorphisms (mostly chosen based on biologic plausibility) in relation to gastric cancer. Although some of these associations showed promise, nearly all failed to replicate. For example, the initially exciting associations found for polymorphisms in inflammatory genes, in particular *interleukin-1B* polymorphisms, were not replicated in future studies (135), including in genome-wide association studies (GWAS).

In contrast with candidate studies, results from very large GWAS seem to be reproducible (refs. 136–139; Table 2). So far, all GWAS results are from East Asians, including Japanese, Korean, and Chinese populations. However, results from other populations are expected in the next few years.

A significant association between single-nucleotide polymorphisms (SNP) located in the prostate stem cell antigen (*PSCA*) gene and gastric cancer has been reported by three independent GWAS: one in Japanese

and Korean (136) and two in Chinese (137, 138) populations. In both Japanese and Korean populations, this association was much stronger with the diffuse type of gastric cancer than with the intestinal type (Table 2). In one of the Chinese studies, a SNP in *PSCA* was associated with noncardia gastric cancer but not with cardia gastric cancer (138). The other Chinese study that reported a positive association included noncardia gastric cancer cases only (137).

Significant associations between SNPs at 1q22, located in *Mucin 1*, cell surface-associated (*MUC1*) gene, and gastric cancer were reported in the GWAS of Japanese and Korean (136) and two independent GWAS of Chinese populations (137, 138). Meta-analysis of the results from Japanese and Korean populations identified several other SNPs in *MUC1* that were significantly associated with gastric cancer risk (140). These SNPs had stronger associations with diffuse type than with intestinal type of gastric cancer. In one of the GWAS in Chinese population, positive associations between SNPs in *MUC1* and cardia and noncardia cancers were similar (138). The other Chinese study that reported a positive association included noncardia gastric cancer cases only (137). *MUC1* encodes mucin glycoproteins expressed in most epithelial cells, including gastric epithelium.

Additional loci have been identified. Two independent GWAS in Chinese reported associations between multiple variants at 10q23, located in gene *PLCE1*, and cardia gastric cancer risk (138, 139). One of these GWAS did not include noncardia gastric cancer cases (139). The other one did not find any association between SNPs in *PLCE1* region and noncardia gastric cancer (138). Other loci were found in the *Chromosome 20 open reading frame 54* (*C20orf54*) gene (137, 139), the first intron of *PRKAA1* (encoding protein kinase, AMP-activated,  $\alpha$ -1 catalytic subunit, AMPK) and adjacent to *PTGER4* (encoding prostaglandin E receptor 4), and the second SNP located in the intron of *ZBTB20* (encoding zinc finger and BTB domain containing protein 20; ref. 137).

The mechanism of action is not yet clear for any of these polymorphisms. Hopefully, however, these findings will lead to mechanistic insights into gastric carcinogenesis.

## Screening

Screening to detect gastric cancer at its early stages can be done for large masses of the population (mass screening) or for individuals at high risk (opportunistic screening). Although the value of screening mass populations for gastric cancer remains controversial (141), it has been provided in some countries with high incidence of gastric cancer, such as Japan, Venezuela, and Chile. In contrast, in countries with low incidence of gastric cancer, such as the United States, this strategy is costly and unwarranted. In low-risk regions, only people with certain conditions may benefit from gastric cancer screening, including older individuals with chronic gastric atrophy or pernicious anemia, and patients who have had gastric polyps, partial

**Table 2.** Susceptibility loci associated with higher risk of gastric cancer identified in GWAS

| SNPs by nearest gene (locus)   | Study                              | Ethnicity             | Subtype        | Case/control   | Allele-specific OR (95% CI) | P                     |                       |
|--------------------------------|------------------------------------|-----------------------|----------------|----------------|-----------------------------|-----------------------|-----------------------|
| <i>PSCA</i> (8q24.3)           |                                    |                       |                |                |                             |                       |                       |
| rs2294008 (T>C)                | Sakamoto et al. (136)              | Japanese              | —              | 749/750        | 1.58 (1.35–1.85)            | $6.3 \times 10^{-9}$  |                       |
|                                | —                                  | —                     | Diffuse        | 925/1,396      | 1.67 (1.47–1.90)            | $2.2 \times 10^{-15}$ |                       |
|                                | —                                  | —                     | Intestinal     | 599/1,396      | 1.29 (1.11–1.49)            | $6.0 \times 10^{-4}$  |                       |
|                                | —                                  | Korean                | Diffuse        | 454/390        | 1.91 (1.57–2.33)            | $6.3 \times 10^{-11}$ |                       |
|                                | —                                  | —                     | Intestinal     | 417/390        | 1.37 (1.12–1.69)            | 0.0017                |                       |
|                                | Abnet et al. (138)                 | Chinese               | Cardia         | 1,213/3,302    | —                           | 0.53                  |                       |
|                                | —                                  | —                     | Noncardia      | 917/3,302      | 1.27 (1.09–1.47)            | $1.63 \times 10^{-3}$ |                       |
|                                | Shi et al. (137)                   | Chinese               | Noncardia      | 4,294/5,882    | 1.36 (NR)                   | $2.1 \times 10^{-7}$  |                       |
|                                | rs2976392 (A>G)                    | Sakamoto et al. (136) | Japanese       | — <sup>a</sup> | 749/750                     | 1.62 (1.38–1.89)      | $1.1 \times 10^{-9}$  |
|                                |                                    | —                     | —              | Diffuse        | 926/1,397                   | 1.71 (1.50–1.94)      | $1.5 \times 10^{-16}$ |
| —                              |                                    | —                     | Intestinal     | 926/1,397      | 1.29 (1.12–1.49)            | $5.0 \times 10^{-4}$  |                       |
| —                              |                                    | Korean                | Diffuse        | 449/390        | 1.90 (1.56–2.33)            | $8.0 \times 10^{-11}$ |                       |
| —                              |                                    | —                     | Intestinal     | 416/390        | 1.37 (1.12–1.68)            | 0.0017                |                       |
| Shi et al. (137)               |                                    | Chinese               | Noncardia      | 4,294/5,882    | 1.35 (NR)                   | $3.7 \times 10^{-7}$  |                       |
| <i>MUC1</i> (1q22)             |                                    |                       |                |                |                             |                       |                       |
| rs4072037 (A>G)                | Abnet et al. (138)                 | Chinese               | Cardia         | 1,213/3,302    | 0.75 (0.62–0.87)            | $9.5 \times 10^{-5}$  |                       |
|                                | —                                  | —                     | Noncardia      | 917/3,302      | 0.72 (0.62–0.85)            | $5.7 \times 10^{-5}$  |                       |
|                                | —                                  | —                     | Total          | 2,240/3,302    | 0.75 (0.67–0.84)            | $4.2 \times 10^{-7}$  |                       |
|                                | Shi et al. (137)                   | Chinese               | Noncardia      | 4,294/5,882    | 0.73 (NR)                   | $1.0 \times 10^{-4}$  |                       |
| rs4460629 (C>T)                | Abnet et al. (138)                 | Chinese               | Cardia         | 1,213/3,302    | 0.74 (0.64–0.86)            | $1.3 \times 10^{-4}$  |                       |
|                                | —                                  | —                     | Noncardia      | 917/3,302      | 0.75 (0.64–0.88)            | $5.4 \times 10^{-4}$  |                       |
|                                | —                                  | —                     | Total          | 2,240/3,302    | 0.75 (0.67–0.85)            | $2.3 \times 10^{-6}$  |                       |
| rs2070803 (A>G)                | Sakamoto et al. (136) <sup>b</sup> | Japanese              | — <sup>a</sup> | 749/750        | 1.62 (1.33–1.98)            | $1.2 \times 10^{-6}$  |                       |
| rs2075570 (G>A)                | Sakamoto et al. (136) <sup>b</sup> | Japanese              | — <sup>a</sup> | 749/750        | 1.65 (1.34–2.02)            | $9.2 \times 10^{-7}$  |                       |
| <i>PLCE1</i> (10q23)           |                                    |                       |                |                |                             |                       |                       |
| rs2274223 (A>G)                | Wang et al. (139)                  | Chinese               | Cardia         | 2,766/11,013   | 1.55 (1.45–1.66)            | $1.7 \times 10^{-39}$ |                       |
|                                | Abnet et al. (138)                 | Chinese               | Cardia         | 1,213/3,302    | 1.57 (1.40–1.76)            | $4.2 \times 10^{-15}$ |                       |
|                                | —                                  | —                     | Noncardia      | 917/3,302      | 1.02 (0.86–1.22)            | 0.15                  |                       |
| rs3765524 (C>T)                | Abnet et al. (138)                 | Chinese               | Cardia         | 1,213/3,302    | 1.56 (1.40–1.75)            | $7.4 \times 10^{-15}$ |                       |
|                                | —                                  | —                     | Noncardia      | 917/3,302      | 1.03 (0.87–1.22)            | 0.16                  |                       |
| rs3781264 (T>C)                | Abnet et al. (138)                 | Chinese               | Cardia         | 1,213/3,302    | 1.60 (1.41–1.81)            | $1.1 \times 10^{-13}$ |                       |
|                                | —                                  | —                     | Noncardia      | 917/3,302      | 1.18 (0.97–1.42)            | 0.25                  |                       |
| rs11187842 (C>T)               | Abnet et al. (138)                 | Chinese               | Cardia         | 1,213/3,302    | 1.63 (1.42–1.87)            | $7.1 \times 10^{-12}$ |                       |
|                                | —                                  | —                     | Noncardia      | 917/3,302      | 1.17 (0.97–1.42)            | 0.26                  |                       |
| rs753724 (G>T)                 | Abnet et al. (138)                 | Chinese               | Cardia         | 1,213/3,302    | 1.63 (1.42–1.87)            | $8.0 \times 10^{-12}$ |                       |
|                                | —                                  | —                     | Noncardia      | 917/3,302      | 1.19 (0.99–1.44)            | 0.16                  |                       |
| <i>C20orf54</i> (20p13)        |                                    |                       |                |                |                             |                       |                       |
| rs13042395 (C>T)               | Shi et al. (137)                   | Chinese               | Noncardia      | 4,294/5,882    | 0.80 (NR)                   | $6.9 \times 10^{-4}$  |                       |
|                                | Wang et al. (139)                  | Chinese               | Cardia         | 2,766/11,013   | 0.91 (0.85–0.97)            | $3.0 \times 10^{-3}$  |                       |
| <i>PRKAA1, PTGER4</i> (5p13.1) |                                    |                       |                |                |                             |                       |                       |
| rs13361707 (T>C)               | Shi et al. (137)                   | Chinese               | Noncardia      | 4,294/5,882    | 1.41 (1.32–1.49)            | $7.6 \times 10^{-29}$ |                       |
| <i>ZBTB20</i> (3q13.31)        |                                    |                       |                |                |                             |                       |                       |
| rs9841504 (C>G)                | Shi et al. (137)                   | Chinese               | Noncardia      | 4,294/5,882    | 0.76 (0.69–0.83)            | $1.7 \times 10^{-9}$  |                       |

Abbreviation: NR, not reported.

<sup>a</sup>Only participants included in a part of the study (stage II of the screening study).

<sup>b</sup>Another gene in the original paper was mentioned as the nearest gene. Further fine mapping showed that the SNP was located in *MUC1* gene (140). Meta-analysis of the results from Japanese and Korean populations in this study showed more significant associations between rs2075570 (OR = 1.71;  $2.3 \times 10^{-12}$ ) and rs2070803 (OR = 1.71;  $4.3 \times 10^{-13}$ ) and gastric cancer (140).

gastrectomy, FAP, and hereditary nonpolyposis colon cancer (142).

Screening may be done using markers of atrophy in the stomach (a precursor lesion of gastric cancer), such as serum pepsinogens or serum ghrelin; or serum antibodies to *H. pylori*, the main risk factor for gastric cancer; or examining the stomach mucosa using methods such as barium photofluorography or endoscopy (143). We have reviewed these approaches below.

### Photofluorography

Barium studies, including photofluorography, have been used for gastric cancer screening in Japan since the 1960s (143). The Japanese Guidelines for Gastric Cancer Screening, which used data from five case-control and two cohort studies, recommended photofluorography for both mass screening and opportunistic screening (143). Several studies have shown that the 5-year survival using these methods could increase approximately from 50% to 80%.

Despite the fact that photofluorography has the best evidence among all methods used to screen for gastric cancer, there is no published randomized trial to assess its efficacy. Observational studies used to determine the efficacy of photofluorography may be subject to biases (144). For example, participants in Japanese national mass screening programs were more likely to consume more vegetables, milk, and dietary fiber, and were less likely to smoke than the general population (145). When such healthier volunteers choose to screen, the results will favor screening regardless of its real effect.

### Serum pepsinogens

Pelayo Correa has suggested a progression model for intestinal type of gastric cancer (146). In this model, intestinal type gastric cancer develops after a prolonged latency period and is preceded by several precancerous stages, namely superficial gastritis, atrophic gastritis, small intestinal metaplasia, colonic metaplasia, mild, moderate, and severe dysplasia. Development of atrophic gastritis leads to reduced production of several proteins secreted from the normal stomach, including pepsinogen I, which could be used for screening. There are two immunologically distinct types of pepsinogens: serum pepsinogen I (PGI) and serum pepsinogen II (PGII; ref. 147). With the development of atrophic gastritis, serum PGI concentration declines, whereas levels of PGII remain relatively constant. Therefore, serum PGI/II ratio may be used as a marker future development of gastric cancer. Some studies suggest that PGI/II ratio can be used as a continuous marker, meaning that the lower the PGI/II ratio, the higher the risk of gastric cancer (148, 149). Lower PGI/II ratio predicts higher risk of both noncardia and cardia gastric cancer.

Combining *H. pylori* serology and serum pepsinogen concentrations may aid in better prediction of gastric cancer development. It has been suggested that a combination of low PGI (or PGI/II ratio) with negative *H. pylori*

antibodies suggests the highest risk (150), as it may indicate that atrophy is so severe that it has led to the decline of *H. pylori* populations in the stomach.

### Serum ghrelin

Ghrelin, a hormone secreted by the gastric mucosa, has a key role in maintaining energy balance (151). Chronic inflammation and atrophic gastritis due to *H. pylori* infection may reduce production of ghrelin, thus low serum ghrelin may indicate higher risk of gastric cancer. This theory has so far been supported by a case-control and a cohort study, showing a substantial and statistically significant increased risk of both cardia and noncardia gastric cancer associated with lower concentrations of ghrelin (152, 153). In these studies, serum ghrelin was a predictor of gastric cancer independent of serum PGI or PGI/II ratio.

### Gastrin-17

Gastrin-17 (G-17), a peptide hormone synthesized in the G cells of the gastric antral region, stimulates the secretion of gastric acid. Therefore, its levels are determined by the health and function of the antrum of the stomach, as well as by the acid produced from the gastric parietal cells. As such, the interpretation of G-17 levels in relation to gastric cancer is not straightforward. When atrophy is predominantly in the corpus, but the antrum is relatively intact, lower acid levels produced in the corpus increase the levels of G-17. However, when atrophy is seen in both the antrum and the corpus, G-17 levels may be normal or low. Therefore, atrophy of the stomach, a precursor lesion of the gastric cancer, may result in lower, normal, or higher levels of G-17. Given that there are very few epidemiologic studies of G-17 in relation to gastric cancer (141), the value of G-17 for screening gastric cancer is unclear.

### Antigastric parietal cell antibodies

These antibodies, which target parietal cells of the stomach, have been recently associated with a substantially higher risk of atrophic gastritis (154). The association was much stronger in *H. pylori*-negative (OR = 11.3) than in *H. pylori*-positive (OR = 2.6) individuals. Therefore, antigastric parietal cell antibody (APCA) may play a role in gastric carcinogenesis via causing atrophy, and it may be used as a complement to other markers, such as *H. pylori* and pepsinogens. However, this needs to be tested in prospective cohort studies.

### Endoscopy

Upper gastrointestinal endoscopy is the gold standard for the diagnosis of gastric cancer. This technique is widely used for gastric cancer screening in Japan, Korea, Venezuela, and other high-risk areas because of its high detection rate. Although the recent literature suggests that endoscopic screening is cost-effective in high-incidence areas, further studies are needed to determine the overall effectiveness of this approach (155). In average-risk



populations, there is no evidence that endoscopic screening is effective or cost-effective (156). Moreover, endoscopy is an invasive procedure, with a small risk of hemorrhage and perforation, and reported mortality of 0.0008% and a morbidity of 0.43% (157).

Consensus guidelines developed in a recent meeting of several European gastroenterology societies (158) suggest that patients with extensive atrophy and/or intestinal metaplasia should be offered surveillance endoscopy every 3 years. In addition, the guidelines recommend surveillance for patients with other high-risk conditions, including FAP and hereditary nonpolyposis colorectal cancer. The success of endoscopic evaluation is highly dependent on the skills of the endoscopist and the ability to detect highly subtle mucosal changes (159). Several recent studies suggest that advanced endoscopic imaging modalities have greater accuracy for the diagnosis of gastric neoplasia than standard, "white light" endoscopy. For example, chromoendoscopy, using mucosal dyes and stains (typically indigo carmine or methylene blue) is frequently used in Japan and Korea to highlight subtle mucosal irregularities and delineate areas for endoscopic removal (160). Narrow band imaging, a filter-based enhancement technology, has been shown to increase the diagnostic yield and accuracy for the detection of gastric neoplasia (161). Additional, digital-based enhancement technologies have been developed; however, none have been evaluated rigorously in randomized trials. The limitation of these advanced imaging technologies is lack of widespread availability and issues relating to training in the interpretation of these "enhanced" images. Further studies are needed to determine the optimal modality, or more likely, combination of modalities needed for the detection of gastric neoplasia.

## Prevention

Prevention of gastric cancer may be achieved using primary prevention, that is, by reducing gastric cancer incidence, or using secondary prevention, that is, by detecting and treating the disease at its early stages. Any prevention strategy should consider all benefits and harms (162). Some methods of primary and secondary prevention of gastric cancer, and their benefits and harms, have been discussed below.

### Smoking cessation

Because smoking has been recognized as a cause of gastric cancer, avoiding smoking would likely reduce gastric cancer incidence as well as provide many other health benefits.

### Reducing salt intake

Salt intake restriction may not only be useful for reducing the incidence of gastric cancer (142), but also for lowering the risk of other major diseases, including stroke and myocardial infarction (163). World Health Organization has made it a goal to reduce salt intake globally to less

than 5 g/day by the year 2025 (164). Although salt restriction is a topic that most agree on, there seems to be a delicate balance; too restrictive intake of salt, below individual's needs, may not be recommended either (165).

### Increasing fruit and vegetable intake

The causal association between higher intake of fruit and vegetables with gastric cancer remains unclear. However, it may still be advisable to increase fruit and vegetable intake, as this is an overall healthy behavior.

### Other healthy behaviors

Studies thus far suggest that Mediterranean diet, higher intake of fibers, and physical activity are associated with lower risk of gastric cancer. Similar to what was discussed for fruit and vegetable intake, the causality with respect to gastric cancer is unclear but they can be advised because of their other health benefits.

### H. Pylori eradication

A meta-analysis of seven randomized studies has demonstrated that treatment of *H. pylori* can reduce gastric cancer risk by 35% (166). American and European guidelines recommend *H. pylori* eradication for all patients with atrophy and/or intestinal metaplasia and for all first-degree relatives of gastric cancer patients in addition to endoscopic and histologic surveillance (67). The Asian Pacific Gastric Cancer Consensus has recommended population-based screening and treatment of *H. pylori* infection in regions with an annual gastric cancer incidence more than 20 of 100,000 (167). Screening and treatment for *H. pylori* are perhaps most effective in younger ages (168), at least 10 to 20 years before the age of rapid increase in gastric cancer incidence (e.g., between 30–40 years of age), as treatment is less helpful when dysplasia has occurred (142, 169). Nevertheless, treatment has some effect even after cancer has occurred; treating *H. pylori* after cancer diagnosis reduces the risk of metachronous cancer to almost half (170). Despite these findings and guidelines, some have argued that the presence of *H. pylori* in the stomach may have some benefits (41), and that a decision to mass eradicate it may be premature (171).

### Other medications

Observational studies suggest that intake of NSAIDs and statins may reduce gastric cancer risk. If truly causal, a byproduct of the recent recommendations to expand the use of statins (172, 173) may be a reduction of gastric cancer incidence too.

### Secondary prevention

In high-risk populations, such as Japan, annual screening with a double-contrast barium technique and endoscopy is recommended for persons over the age of 40 years (174). In other populations, targeting high-risk people for aggressive screening and prevention may decrease gastric cancer mortality. However, neither the American Cancer Society (175) nor the National Cancer Institute

currently recommends gastric cancer screening in the United States.

### Summary and Suggestions for Further Research

Gastric cancer remains a common cancer and a substantial focus of clinical, epidemiologic, and translational research. Previous research has identified several environmental and genetic risk factors and also some predisposing conditions. However, there are still many gaps in our knowledge of causes and early detection of gastric cancer. Some areas of potential interest for future research include monitoring the incidence trends (18), further evaluation of suggested but unconfirmed risk factors such as opium, further assessment of radiation and chemotherapy as risk factors for gastric cancer in cancer survivors, conducting GWAS in Caucasian and African populations, identifying the mechanisms of identified SNPs, assessing the role of ghrelin, other gastrointestinal tract hormones, and APCA in gastric cancer risk, understanding why

incidence rates are higher in men than women, further well-conducted trials on the role of aspirin, other NSAIDs, and statins in the prevention of gastric cancer, whole-genome sequencing of tumors to identify common mutations and rearrangements, and to determine whether these alterations are associated with particular etiologic risk factors and with particular treatments and improving early detection of these deadly tumors.

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No potential conflicts of interest were disclosed.

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