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

Parisa Karimi[1], **Farhad Islami**[2,3], **Sharmila Anandasabapathy**[4], **Neal D. Freedman**[5], and **Farin Kamangar**[3,6]

[1]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, United States

[2]Institute for Transitional Epidemiology, Mount Sinai School of Medicine, New York, NY, United States

[3]Digestive Oncology Research Center, Digestive Disease Research Institute, Tehran University of Medical Sciences, Tehran, Iran

[4]Division of Gastroenterology, Department of Medicine, Mount Sinai Medical Center, New York, NY, United States

[5]Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, MD, United States

[6]Department of Public Health Analysis, School of Community Health and Policy, Morgan State University, Baltimore, MD, United States

Abstract

Less than a century ago, gastric cancer (GC) was the most common cancer in the United States and perhaps throughout the world. Despite its worldwide decline in incidence over the past century, GC 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 GC, including its incidence, survival, and mortality, including trends over time. Next, we characterize the risk factors for gastric cancer, both environmental and genetic. Serological markers and histological precursor lesions of GC and early detection of GC of using these markers is reviewed. Finally, we discuss prevention strategies and provide suggestions for further research.

Keywords

gastric cancer; epidemiology; risk factors; screening; prevention

Correspondence to: Farin Kamangar, MD, PhD, Professor and Chairman, Department of Public Health Analysis, School of Community Health and Policy, Morgan State University, 4530 Portage Avenue, Room 302, Baltimore, MD 2123, farin.kamangar@morgan.edu.

Conflict of Interest: None.

Introduction

Less than a century ago, gastric cancer (GC) was the most common cancer in the United States and perhaps throughout the world. Although it is no longer the most common cancer worldwide, GC 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 GC, reviewing both classic studies and the new findings that have been added to the literature over the past few years.

1. 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 (GC) mainly pertains to adenocarcinomas. There are, however, other types of cancer arising from the stomach, including mucosa-associated lymphoid tissue (MALT) 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 GC adenocarcinomas into two major histological 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, histological differences, or both. Most relevant to this paper is the distinction between adenocarcinomas arising from the cardia (cardia GC) and other parts of the stomach (noncardia GC), as they have different epidemiologic patterns and causes.

2. Incidence, mortality, and burden

Each year approximately 990,000 people are diagnosed with GC worldwide, of whom about 738,000 die from this disease (4), making GC the 4th most common incident cancer and the 2nd most common cause of cancer death (5). GC also causes one of the highest cancer burdens, as measured by disability-adjusted life years lost (6).

GC 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, while the lowest rates are observed in North America and most parts of Africa (7). For example, the annual age-standardized GC incidence rates per 100,000 in men are 65.9 in Korea versus 3.3 in 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 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 Zeland, suffer from high rates of GC (9).

3. Trends

GC 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 GC rates have remained stable or increased (13, 14), at least in Western countries. Such contrasting trends for cardia and noncardia GC may result from distinct etiologies. Unlike for noncardia GC, *H. pylori* does not seem to be a risk factor for cardia GC in Western countries (15), so its decline in prevalence would not be expected to affect cardia GC rates. In contrast, obesity and gastroesophageal reflux seem to be risk factors for cardia but not non-cardia GC. Obesity has been increasing in prevalence in Western countries (16), which may contribute to the rates of cardia GC. 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 GC 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.

4. Survival

Since the 1970s, there have been notable improvements in the relative 5-year survival rates for GC; 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 GC 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, i.e. 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 GC tumors that harbor Ebstein-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).

5. Demographic and Environmental Risk Factors

GC 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 GC include older age, male sex, tobacco smoking, radiation, and family history. Intake of aspirin and statins

may prevent against both of these cancers. While race is a risk factor for each, the direction differs by site. In the United States, Whites are more likely to acquire cardia GC, whereas Hispanics are more likely to be diagnosed with noncardia GC. Factors associated with cardia GC, but not noncardia GC, include obesity and gastroesophageal reflux disease. On the other hand, risk factors that are exclusive for noncardia GC include *H. pylori* infection (at least in Western countries), low socioeconomic status (22), and perhaps dietary factors such as low consumption of fruits and vegetables and high intake of salty and smoked food.

5.1. Age

The incidence rate of GC 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 and 34 years, whereas 29% occurred between 75 and 84 years (25). During this period, the median age at diagnosis of GC was 70 years (25).

5.2. Male Sex

Compared to females, males have a higher risk of both cardia (5-fold) noncardia GC (2-fold) (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 appear to persist even in countries where men and women have similar smoking patterns (27). Alternatively, sex differences may reflect physiological differences. Estrogens may protect against the development of GC. In women, delayed menopause and increased fertility may lower the risk of GC, whereas anti-estrogen drugs, e.g., tamoxifen may increase the rates of GC (28, 29). These hormones may provide protection against GC during the fertile years of women but their effect is diminished after menopause, such that females develop GC in a manner similar to males, albeit with a 10 to 15 year lag after their male counterparts (30, 31).

5.3. 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 (IARC) concluded that there was 'sufficient' evidence of causality between smoking and GC (32). The reason for such delay is in part that the association between smoking and GC has not been consistent across studies, and that the association is not strong. A meta-analysis of cohort studies showed that the risk of GC is increased by only 60% (RR:1.6) in male smokers and 20% (RR:1.2) in female smokers compared to never smokers, and the associations are even weaker in former smokers (33). While studies vary, overall the accumulated data suggest that smoking is a risk factor for both cardia and noncardia GC (33-35). Other forms of tobacco use, such as hookah use, have also been associated with higher risk of GC (36), although these associations have not been found in other studies (37) and need further confirmation.

5.4. Race

Comparing Whites to other racial groups, cardia GC is approximately twice as common (26) whereas noncardia GC is approximately half as common (38). The risk of noncardia GC 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 GC seems to be mediated mostly via environmental effects, rather than genetic variations. Japan has one of the highest rates of GC 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).

5.5. Helicobacter Pylori (H. 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 GC (41), with relative risks of approximately 6 for noncardia GC (42). Certain *H. pylori* types, particularly those positive for the virulence factor cytotoxin-associated gene A (CagA), are more likely to cause GC (43-45). *H. pylori* is estimated to cause 65% to 80% of all GC cases, or 660,000 new cases annually (42, 46). These numbers may be underestimates, 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 GC but not for cardia GC (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 GC. It is not entirely clear how *H. pylori* causes GC. 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 GC development (50).

5.6. 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 (22) is associated with higher risk of total and cause-specific mortality, including mortality from most cancers (53, 54). GC and its precursor lesions have been associated with markers of low SES, 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 SES and higher risk of GC (58). The prevalence of *H. pylori*, particularly CagA-postive strains, is substantially higher in low-income African-Americans (59) and may contribute to higher risks in this group.

5.7. 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 [GC]" (60). A 1965 study showed a strong correlation between mortality from stroke and GC across

geographic areas and over time, which suggested salt as a risk factor for both (61). Epidemiological 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 GC by 22% (62). Also, large cohort studies in Korea have shown that people who tend to prefer salty food have higher risk of GC (63). Salt may increase the risk of GC 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 GC 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 GC rates (67).

In addition, certain cooking practices may be associated with increased risk of GC. 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 (NNC) (68).

5.8. Low consumption of fruits and vegetables

The World Cancer Research Fund/American institute for Cancer Research (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 GC, 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 GC 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. While 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 GC. In a high-risk Chinese population, a randomized trial of 7.3 years of supplementation with garlic extract and oil resulted in a statistically non-significant reduction in gastric cancer incidence or mortality (74).

5.9. Antioxidant use

While 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 GC or to promote overall health (75, 76). However, dietary

supplementation may play a preventive role in populations with high rates of GC and low intake of micronutrients (74, 77).

5.10. Other dietary factors

Several other dietary factors or patterns have been studied in relation to GC. 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 GC risk. Conversely, diets that have a Western pattern (79) may increase GC risk. However, these findings need to be confirmed in future studies.

5.11. Non-steroidal anti-inflammatory drugs

Current evidence suggests that intake of non-steroidal anti-inflammatory drugs (NSAIDs) may have an inverse association with GC risk. Two meta-analyses of observational studies have shown an inverse association between aspirin or any other NSAIDs and cardia and noncardia GC (82, 83), while another one reported an inverse association of aspirin use with noncardia GC but not with cardia GC (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 GC (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 sub-sites of GC. 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 GC in the aspirin taking group was not lower than in the control group: the hazard ratio (95% CI) was 1.85 (0.81-4.23) for 0-5 years of follow-up and 3.09 (0.64-14.9). These estimates were, however, based on 36 GC deaths only (87).

5.12. Statins

Two recent meta-analyses (88, 89) suggested that statin intake was associated with an approximately 30% reduced risk of GC. 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 have 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 morality, particularly in randomized trials (92). As such, the reduced risk of GC associated with statin use needs to be further investigated.

5.13. Obesity

Obesity is a growing problem in modern societies and has been associated with a range of diseases, including the cardia GC. Compared to a individuals with BMI of < 25, individuals with BMIs of 30 to 35 have a two-fold, and those with a BMI of > 40 have a three-fold risk of cancers of the esophagogastric junctional, including the cardia GC (93). In contrast, obesity is not a risk factor for noncardia GC (94). Several mechanisms have been proposed. Abdominal fat may directly cause GERD, a risk factor for esophageal cancer and cardia GC. 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 pro-growth changes in the cell cycle, decreased cell death, and pro-neoplastic cellular changes (95, 96).

5.14. Physical activity

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

5.15. Gastro-esophageal reflux disease (GERD)

GERD is strongly associated with risk of esophageal adenocarcinoma, with approximately 5-7 fold increase in the risk (98). Several studies have also reported statistically significant associations between GERD and cardia GC (99-103), with increased risks of 2-4 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 GC: one similar to esophageal adenocarcinoma and associated with GERD and one similar to noncardia GC 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 GC 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 GC (100, 101, 104, 106, 110). This may be explained, at least partly, by the association between atrophic gastritis and noncardia GC. Severe atrophic gastritis may be associated with decreased secretion of gastric acid and lower risk of GERD (106).

5.16. Radiation

Long-term follow-up of survivors of Hiroshima and Nagasaki established radiation as a risk factor for GC (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 GC (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 GC.

5.17. Other potential risk factors

A number of other risk factors have been investigated in relation to GC 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 Ebstein-Barr virus (118, 119), and eating pickled vegetables (120).

6. Familial Aggregation

A positive family history (having a first-degree relative with GC) is a risk factor for GC (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, e.g., 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 GC 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 post-migration; 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 GC risk than current place of residence (126, 127). These findings show the importance of childhood exposure in the etiology of GC, 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 *H. pylori* infection usually happens before the age of 10 (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).

7. Genetic Risk Factors

Only 1-3% of GC cases arise as a result of inherited syndromes (130), which are briefly discussed in Section 7.1. The rest are sporadic GC cases, for whom no major high-penetrance genes have been discovered. Investigation of genetic risk factors for sporadic cases is discussed in Section 6.2.

7.1. 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 GC, 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 age 80, and the median age at diagnosis of 38.

FAP is an autosomal-dominant colorectal cancer syndrome, caused by a mutation in the adenomatous polyposis coli (25) gene (133). FAP patients carry a 100% risk of colorectal cancer by the age of 35–40, as well as a high risk of other malignancies, including GC.

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.

7.2. Single nucleotide polymorphisms (SNPs)

Prior to 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 GC. 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 *IL-1B* polymorphisms, were not replicated in future studies (135), including in genome wide association studies.

In contrast to candidate studies, results from very large genome-wide association studies (GWAS) appear to be reproducible (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 SNPs located in the *prostate stem cell antigen* (*PSCA*) gene and GC 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 GC than with the intestinal type (Table 2). In one of the Chinese studies, a SNP in *PSCA* was associatied with noncardia GC but not with cardia GC (138). The other Chinese study that reported a positive association included noncardia GC cases only (137).

Significant associations between SNPs at 1q22, located in *Mucin 1*, cell surface associated (*MUC1*) gene, and GC 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 GC risk (140). These SNPs had stronger associations with diffuse type than with intestinal type of GC. 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 GC 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 GC risk (138, 139). One of these GWAS did not include noncardia GC cases (139). The other one did not find any association between SNPs in *PLCE1* region and noncardia GC (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) (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.

8. Screening

Screening to detect GC 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 GC remains controversial (141), it has been provided in some countries with high incidence of GC, such as Japan, Venezuela, and Chile. By contrast, in countries with low incidence of GC, such as the United States, this strategy is costly and unwarranted. In low risk regions, only people with certain conditions may benefit from GC screening, including older individuals with chronic gastric atrophy or pernicious anemia, and patients who have had gastric polyps, partial gastrectomy, familial adenomatous polyposis, and hereditary nonpolyposis colon cancer (142).

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

8.1. Photofluorography

Barium studies, including photofluorography, have been used for GC 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 GC, 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.

8.2. Serum pepsinogens

Pelayo Correa has suggested a progression model for intestinal type of GC (146). In this model, intestinal type GC 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) (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 GC. Some studies suggest that

PGI/II ratio can be used as a continuous marker, meaning that the lower PGI/II ratio, the higher the risk of GC (148, 149). Lower PGI/II ratio predicts higher risk of both noncardia and cardia GC.

Combining *H. pylori* serology and serum pepsinogen concentrations may aid in better prediction of GC 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 *H. pylori* populations in the stomach.

8.3. 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 GC. 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 GC associated with lower concentrations of ghrelin (152, 153). In these studies, serum ghrelin was a predictor of GC independent of serum PGI or PGI/II ratio.

8.4. 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 GC 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, then G-17 levels may be normal or low. Therefore, atrophy of the stomach, a precursor lesion of the GC, 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 GC (141), the value of G-17 for screening GC is unclear.

8.5. Antigastric parietal cell antibodies (APCA)

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, APCA may play a role in gastric carcinogenesis via causing atrophy, and it may be used a complement to other markers, such as *H. pylori* and pepsinogens. However, this needs to be tested in prospective cohort studies.

8.6. Endoscopy

Upper gastrointestinal endoscopy is the gold standard for the diagnosis of GC. This technique is widely used for GC screening in Japan, Korea, Venezuela and other high-risk areas because of its high detection rate. While 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 familial adenomatous polyposis, hereditary non polyposis 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.

9. Prevention

Prevention of GC may be achieved using primary prevention, i.e., by reducing GC incidence, or using secondary prevention, i.e., 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 GC, and their benefits and harms, have been discussed below.

9.1. Smoking cessation

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

9.2. Reducing salt intake

Salt intake restriction may not only be useful for reducing the incidence of GC (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). While 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).

9.3. Increasing fruit and vegetable intake

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

9.4. Other healthy behaviors

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

9.5. H. Pylori eradication

A meta-analysis of seven randomized studies has demonstrated that treatment of *H. pylori* can reduce GC 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 GC patients in addition to endoscopic and histological surveillance (67). The Asian Pacific Gastric Cancer Consensus has recommended population-based screening and treatment of *H. pylori* infection in regions with an annual GC incidence more than 20/100,000 (167). Screening and treatment for *H. pylori* is perhaps most effective in younger ages (168), at least 10 to 20 years prior to the age of rapid increase in GC incidence (e.g., between 30 to 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 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).

9.6. Other medications

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

9.7. 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 population, targeting high-risk populations for aggressive screening and prevention may decrease GC mortality. However, neither the American Cancer Society (175) nor the National Cancer Institute currently recommends GC screening in the United States.

10. Summary and suggestions for further research

GC remains a common cancer and a substantial focus of clinical, epidemiological, 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 GC. 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 GC 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 GC 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 GC; whole genome sequencing of tumors to identify common mutations and rearrangements and to determine whether these alterations are associated with particular etiological risk factors and with particular treatments and improving early detection of these deadly tumors.

Acknowledgments

References

1. Bray F, Ren JS, Masuyer E, Ferlay J. Global estimates of cancer prevalence for 27 sites in the adult population in 2008. Int J Cancer. 2013; 132:1133–45. [PubMed: 22752881]

2. Lauren P. The Two Histological Main Types of Gastric Carcinoma: Diffuse and So-Called Intestinal-Type Carcinoma. An Attempt at a Histo-Clinical Classification. Acta Pathol Microbiol Scand. 1965; 64:31–49. [PubMed: 14320675]

3. Henson DE, Dittus C, Younes M, Nguyen H, Albores-Saavedra J. Differential trends in the intestinal and diffuse types of gastric carcinoma in the United States, 1973-2000: increase in the signet ring cell type. Arch Pathol Lab Med. 2004; 128:765–70. [PubMed: 15214826]

4. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer. 2010; 127:2893–917. [PubMed: 21351269]

5. Jemal A, Center MM, DeSantis C, Ward EM. Global patterns of cancer incidence and mortality rates and trends. Cancer Epidemiol Biomarkers Prev. 2010; 19:1893–907. [PubMed: 20647400]

6. Soerjomataram I, Lortet-Tieulent J, Parkin DM, Ferlay J, Mathers C, Forman D, et al. Global burden of cancer in 2008: a systematic analysis of disability-adjusted life-years in 12 world regions. Lancet. 2012; 380:1840–50. [PubMed: 23079588]

7. Forman D, Burley V. Gastric cancer: global pattern of the disease and an overview of environmental risk factors. Best Pract Res Clin Gastroenterol. 2006; 20:633–49. [PubMed: 16997150]

8. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin. 2014; 64:9–29. [PubMed: 24399786]

9. Arnold M, Moore SP, Hassler S, Ellison-Loschmann L, Forman D, Bray F. The burden of stomach cancer in indigenous populations: a systematic review and global assessment. Gut. 2014; 63:64–71. [PubMed: 24153248]

10. Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. J Clin Oncol. 2006; 24:2137–50. [PubMed: 16682732]

11. Bosetti C, Bertuccio P, Malvezzi M, Levi F, Chatenoud L, Negri E, et al. Cancer mortality in Europe, 2005-2009, and an overview of trends since 1980. Ann Oncol. 2013; 24:2657–71. [PubMed: 23921790]

12. Edwards BK, Noone AM, Mariotto AB, Simard EP, Boscoe FP, Henley SJ, et al. Annual Report to the Nation on the status of cancer, 1975-2010, featuring prevalence of comorbidity and impact on survival among persons with lung, colorectal, breast, or prostate cancer. Cancer. 2013; 16:28509.

13. Devesa SS, Blot WJ, Fraumeni JF Jr. Changing patterns in the incidence of esophageal and gastric carcinoma in the United States. Cancer. 1998; 83:2049–53. [PubMed: 9827707]

14. Powell J, McConkey CC. Increasing incidence of adenocarcinoma of the gastric cardia and adjacent sites. Br J Cancer. 1990; 62:440–3. [PubMed: 2206952]

15. Cavaleiro-Pinto M, Peleteiro B, Lunet N, Barros H. Helicobacter pylori infection and gastric cardia cancer: systematic review and meta-analysis. Cancer Causes Control. 2011; 22:375–87. [PubMed: 21184266]

16. Shields, M.; Carroll, MD.; Ogden, LO. Adult Obesity Prevalence in Canada and the United States. National Center for Health Statistics; Hyattsville, MD: 2011. NCHS data brief, no 56

17. Corley DA, Kubo A. Influence of site classification on cancer incidence rates: an analysis of gastric cardia carcinomas. J Natl Cancer Inst. 2004; 96:1383–7. [PubMed: 15367571]

18. Anderson WF, Camargo MC, Fraumeni JF Jr, Correa P, Rosenberg PS, Rabkin CS. Age-specific trends in incidence of noncardia gastric cancer in US adults. JAMA. 2010; 303:1723–8. [PubMed: 20442388]

19. Cunningham SC, Kamangar F, Kim MP, Hammoud S, Haque R, Maitra A, et al. Survival after gastric adenocarcinoma resection: eighteen-year experience at a single institution. J Gastrointest Surg. 2005; 9:718–25. [PubMed: 15862270]

20. Isobe Y, Nashimoto A, Akazawa K, Oda I, Hayashi K, Miyashiro I, et al. Gastric cancer treatment in Japan: 2008 annual report of the JGCA nationwide registry. Gastric Cancer. 2011; 14:301–16. [PubMed: 21894577]

21. Bollschweiler E, Boettcher K, Hoelscher AH, Siewert JR, Sasako M, Kinoshita T, et al. Is the prognosis for Japanese and German patients with gastric cancer really different? Cancer. 2006; 71:2918–25. [PubMed: 8490819]

22. Camargo MC, Kim WH, Chiaravalli AM, Kim KM, Corvalan AH, Matsuo K, et al. Improved survival of gastric cancer with tumour Epstein-Barr virus positivity: an international pooled analysis. Gut. 2014; 63:236–43. [PubMed: 23580779]

23. Tabuchi T, Ito Y, Ioka A, Nakayama T, Miyashiro I, Tsukuma H. Tobacco smoking and the risk of subsequent primary cancer among cancer survivors: a retrospective cohort study. Ann Oncol. 2013; 24:2699–704. [PubMed: 23894040]

24. Tao L, Wang R, Gao Y-T, Yuan J-M. Impact of Postdiagnosis Smoking on Long-term Survival of Cancer Patients: The Shanghai Cohort Study. Cancer Epidemiol Biomarkers Prev. 2013; 22:2404–11. [PubMed: 24319070]

25. Howlader, N.; Noone, A.; Krapcho, M.; Neyman, N.; Aminou, R.; Waldron, W., et al. SEER cancer statistics review, 1975-2008. National Cancer Institute; Bethesda, MD: 2011. p. 19

26. Brown LM, Devesa SS. Epidemiologic trends in esophageal and gastric cancer in the United States. Surg Oncol Clin N Am. 2002; 11:235–56. [PubMed: 12424848]

27. Freedman N, Derakhshan M, Abnet C, Schatzkin A, Hollenbeck A, McColl K. Male predominance of upper gastrointestinal adenocarcinoma cannot be explained by differences in tobacco smoking in men versus women. Eur J Cancer. 2010; 46:2473–8. [PubMed: 20605442]

28. Sheh A, Ge Z, Parry NMA, Muthupalani S, Rager JE, Raczynski AR, et al. 17β-Estradiol and Tamoxifen Prevent Gastric Cancer by Modulating Leukocyte Recruitment and Oncogenic Pathways in Helicobacter Pylori-Infected INS-GAS Male Mice. Cancer Prev Res. 2011; 4:1426–35.

29. Derakhshan MH, Liptrot S, Paul J, Brown IL, Morrison D, McColl KE. Oesophageal and gastric intestinal-type adenocarcinomas show the same male predominance due to a 17 year delayed development in females. Gut. 2009; 58:16–23. [PubMed: 18838486]

30. Sipponen P, Correa P. Delayed rise in incidence of gastric cancer in females results in unique sex ratio (M/F) pattern: etiologic hypothesis. Gastric Cancer. 2002; 5:213–9. [PubMed: 12491079]

31. Camargo MC, Goto Y, Zabaleta J, Morgan DR, Correa P, Rabkin CS. Sex hormones, hormonal interventions, and gastric cancer risk: a meta-analysis. Cancer Epidemiol Biomarkers Prev. 2012; 21:20–38. [PubMed: 22028402]

32. IARC monographs on the evaluation of carcinogenic risks to humans. Ingested nitrate and nitrite, and cyanobacterial peptide toxins. IARC Monogr Eval Carcinog Risks Hum. 2010; 94:1–412.

33. Ladeiras-Lopes R, Pereira AK, Nogueira A, Pinheiro-Torres T, Pinto I, Santos-Pereira R, et al. Smoking and gastric cancer: systematic review and meta-analysis of cohort studies. Cancer Causes Control. 2008; 19:689–701. [PubMed: 18293090]

34. Cook MB, Kamangar F, Whiteman DC, Freedman ND, Gammon MD, Bernstein L, et al. Cigarette smoking and adenocarcinomas of the esophagus and esophagogastric junction: a pooled analysis from the international BEACON consortium. J Natl Cancer Inst. 2010; 102:1344–53. [PubMed: 20716718]

35. Freedman ND, Abnet CC, Leitzmann MF, Mouw T, Subar AF, Hollenbeck AR, et al. A prospective study of tobacco, alcohol, and the risk of esophageal and gastric cancer subtypes. Am J Epidemiol. 2007; 165:1424–33. [PubMed: 17420181]

36. Sadjadi A, Derakhshan MH, Yazdanbod A, Boreiri M, Parsaeian M, Babaei M, et al. Neglected role of hookah and opium in gastric carcinogenesis: A cohort study on risk factors and attributable fractions. Int J Cancer. 2014; 134:181–8. [PubMed: 23797606]

37. Shakeri R, Malekzadeh R, Etemadi A, Nasrollahzadeh D, Abedi-Ardekani B, Khoshnia M, et al. Association of tooth loss and oral hygiene with risk of gastric adenocarcinoma. Cancer Prev Res. 2013; 6:477–82.

38. El-Serag H, Mason A, Petersen N, Key C. Epidemiological differences between adenocarcinoma of the oesophagus and adenocarcinoma of the gastric cardia in the USA. Gut. 2002; 50:368–72. [PubMed: 11839716]

39. Maskarinec G, Noh JJ. The effect of migration on cancer incidence among Japanese in Hawaii. Ethn Dis. 2004; 14:431–9. [PubMed: 15328946]

40. Unidentified curved bacilli on gastric epithelium in active chronic gastritis. Lancet. 1983; 1(8336): 1273–5. [PubMed: 6134060]

41. Kamangar F, Sheikhattari P, Mohebtash M. Helicobacter pylori and its effects on human health and disease. Arch Iran Med. 2011; 14:192–9. [PubMed: 21529109]

42. Gastric cancer and Helicobacter pylori: a combined analysis of 12 case control studies nested within prospective cohorts. Gut. 2001; 49:347–53. [PubMed: 11511555]

43. Huang JQ, Zheng GF, Sumanac K, Irvine EJ, Hunt RH. Meta-analysis of the relationship between cagA seropositivity and gastric cancer. Gastroenterology. 2003; 125:1636–44. [PubMed: 14724815]

44. Yoshida T, Kato J, Inoue I, Yoshimura N, Deguchi H, Mukoubayashi C, et al. Cancer development based on chronic active gastritis and resulting gastric atrophy as assessed by serum levels of pepsinogen and Helicobacter pylori antibody titer. Int J Cancer. 2014; 134:1445–57. [PubMed: 24009139]

45. Shiota S, Suzuki R, Yamaoka Y. The significance of virulence factors in Helicobacter pylori. J Dig Dis. 2013; 14:341–9. [PubMed: 23452293]

46. de Martel C, Ferlay J, Franceschi S, Vignat J, Bray F, Forman D, et al. Global burden of cancers attributable to infections in 2008: a review and synthetic analysis. Lancet Oncol. 2012; 13:607–15. [PubMed: 22575588]

47. González C, Megraud F, Buissonniere A, Barroso LL, Agudo A, Duell E, et al. Helicobacter pylori infection assessed by ELISA and by immunoblot and noncardia gastric cancer risk in a prospective study: the Eurgast-EPIC project. Ann Oncol. 2012; 23:1320–4. [PubMed: 21917738]

48. Chen Y, Blaser MJ. Helicobacter pylori colonization is inversely associated with childhood asthma. J Infect Dis. 2008; 198:553–60. [PubMed: 18598192]

49. Blaser MJ, Falkow S. What are the consequences of the disappearing human microbiota? Nat Rev Microbiol. 2009; 7:887–94. [PubMed: 19898491]

50. Chiba T, Marusawa H, Seno H, Watanabe N. Mechanism for gastric cancer development by Helicobacter pylori infection. J Gastroenterol Hepatol. 2008; 23:1175–81. [PubMed: 18637055]

51. Julia C, Valleron A-J, Louis-René Villermé. (1782-1863), a pioneer in social epidemiology: re-analysis of his data on comparative mortality in Paris in the early 19th century. J Epidemiol Community Health. 2011; 65:666–70. [PubMed: 19767321]

52. Hanley J. Edwin Chadwick and the poverty of statistics. Med Hist. 2002; 46:21. [PubMed: 11877982]

53. Kamangar F. Socio-economic health inequalities: ever-lasting facts or amenable to change? Int J Prev Med. 2013; 4:621–3. [PubMed: 23930178]

54. Adler NE, Ostrove JM. Socioeconomic status and health: what we know and what we don't. Ann N Y Acad Sci. 2006; 896:3–15. [PubMed: 10681884]

55. Mendoza D, Herrera P, Gilman RH, Lanfranco J, Tapia M, Bussalleu A, et al. Variation in the prevalence of gastric cancer in Peru. Int J Cancer. 2008; 123:414–20. [PubMed: 18449884]

56. Hansson LE, Baron J, Nyren O, Bergstrom R, Wolk A, Lindgren A, et al. Early-life risk indicators of gastric cancer. A population-based case-control study in Sweden. Int J Cancer. 1994; 57:32–7. [PubMed: 8150538]

57. Uthman OA, Jadidi E, Moradi T. Socioeconomic position and incidence of gastric cancer: a systematic review and meta-analysis. J Epidemiol Community Health. 2013; 67:854–60. [PubMed: 23929615]

58. Kelley JR, Duggan JM. Gastric cancer epidemiology and risk factors. J Clin Epidemiol. 2003; 56:1–9. [PubMed: 12589864]

59. Epplein M, Signorello LB, Zheng W, Peek RM Jr. Michel A, Williams SM, et al. Race, African ancestry, and Helicobacter pylori infection in a low-income United States population. Cancer Epidemiol Biomarkers Prev. 2011; 20:826–34. [PubMed: 21357376]

60. Wiseman M. The second World Cancer Research Fund/American Institute for Cancer Research expert report. Food, nutrition, physical activity, and the prevention of cancer: a global perspective. Proc Nutr Soc. 2008; 67:253–6. [PubMed: 18452640]

61. Joossens JV, Hill MJ, Elliott P, Stamler R, Lesaffre E, Dyer A, et al. European Cancer Prevention (ECP); INTERSALT Cooperative Research Group. Dietary salt, nitrate and stomach cancer mortality in 24 countries. Int J Epidemiol. 1996; 25:494–504. [PubMed: 8671549]

62. Ge S, Feng X, Shen L, Wei Z, Zhu Q, Sun J. Association between Habitual Dietary Salt Intake and Risk of Gastric Cancer: A Systematic Review of Observational Studies. Gastroenterol Res Pract. 2012; 808120:22.

63. Kim J, Park S, Nam BH. Gastric cancer and salt preference: a population-based cohort study in Korea. Am J Clin Nutr. 2010; 91:1289–93. [PubMed: 20219954]

64. Tsugane S, Sasazuki S, Kobayashi M, Sasaki S. Salt and salted food intake and subsequent risk of gastric cancer among middle-aged Japanese men and women. Br J Cancer. 2004; 90:128–34. [PubMed: 14710219]

65. Dungal N. The special problem of stomach cancer in Iceland with particular reference to dietary factors. JAMA. 1961; 178:789–98. [PubMed: 13888467]

66. Dungal N, Sigurjónsson J. Gastric cancer and diet. A pilot study on dietary habits in two districts differing markedly in respect of mortality from gastric cancer. Br J Cancer. 1967; 21:270–6. [PubMed: 6028080]

67. Nagini S. Carcinoma of the stomach: A review of epidemiology, pathogenesis, molecular genetics and chemoprevention. World J Gastroint Oncol. 2012; 4:156–69.

68. Wogan GN, Hecht SS, Felton JS, Conney AH, Loeb LA. Environmental and chemical carcinogenesis. Semin Cancer Biol. 2004; 14:473–86. [PubMed: 15489140]

69. Zhou Y, Zhuang W, Hu W, Liu GJ, Wu TX, Wu XT. Consumption of Large Amounts of Allium Vegetables Reduces Risk for Gastric Cancer in a Meta-analysis. Gastroenterology. 2011; 141:80–9. [PubMed: 21473867]

70. Key TJ. Fruit and vegetables and cancer risk. Br J Cancer. 2011; 104:6–11. [PubMed: 21119663]

71. Kamangar F, Karimi P. The state of nutritional epidemiology: why we are still unsure of what we should eat? Arch Iran Med. 2013; 16:483–6. [PubMed: 23906255]

72. Freedman ND, Subar AF, Hollenbeck AR, Leitzmann MF, Schatzkin A, Abnet CC. Fruit and vegetable intake and gastric cancer risk in a large United States prospective cohort study. Cancer Causes Control. 2008; 19:459–67. [PubMed: 18166992]

73. Gonzalez CA, Lujan-Barroso L, Bueno-de-Mesquita HB, Jenab M, Duell EJ, Agudo A, et al. Fruit and vegetable intake and the risk of gastric adenocarcinoma: a reanalysis of the European Prospective Investigation into Cancer and Nutrition (EPIC-EURGAST) study after a longer follow-up. Int J Cancer. 2012; 131:2910–9. [PubMed: 22473701]

74. Ma J-L, Zhang L, Brown LM, Li J-Y, Shen L, Pan K-F, et al. Fifteen-year effects of Helicobacter pylori, garlic, and vitamin treatments on gastric cancer incidence and mortality. J Natl Cancer Inst. 2012; 104:488–92. [PubMed: 22271764]

75. Kamangar F, Emadi A. Vitamin and mineral supplements: do we really need them? Int J Prev Med. 2012; 3:221–6. [PubMed: 22448315]

76. Taylor PR, Greenwald P. Nutritional interventions in cancer prevention. J Clin Oncol. 2005; 23:333–45. [PubMed: 15637396]

77. Qiao Y-L, Dawsey SM, Kamangar F, Fan J-H, Abnet CC, Sun X-D, et al. Total and cancer mortality after supplementation with vitamins and minerals: follow-up of the Linxian General Population Nutrition Intervention Trial. J Natl Cancer Inst. 2009; 101:507–18. [PubMed: 19318634]

78. Praud D, Bertuccio P, Bosetti C, Turati F, Ferraroni M, La Vecchia C. Adherence to the Mediterranean diet and gastric cancer risk in Italy. Int J Cancer. 2013 Epub ahead of print. doi: 10.1002/ijc.28620.

79. Bertuccio P, Rosato V, Andreano A, Ferraroni M, Decarli A, Edefonti V, et al. Dietary patterns and gastric cancer risk: a systematic review and meta-analysis. Ann Oncol. 2013; 24:1450–8. [PubMed: 23524862]

80. Serafini M, Jakszyn P, Lujan-Barroso L, Agudo A, Bas Bueno-de-Mesquita H, van Duijnhoven FJ, et al. Dietary total antioxidant capacity and gastric cancer risk in the European prospective investigation into cancer and nutrition study. Int J Cancer. 2012; 131:E544–54. [PubMed: 22072493]

81. Zhang Z, Xu G, Ma M, Yang J, Liu X. Dietary fiber intake reduces risk for gastric cancer: a meta-analysis. Gastroenterology. 2013; 145:113–20. [PubMed: 23567349]

82. Abnet C, Freedman N, Kamangar F, Leitzmann M, Hollenbeck A, Schatzkin A. Non-steroidal anti-inflammatory drugs and risk of gastric and oesophageal adenocarcinomas: results from a cohort study and a meta-analysis. Br J Cancer. 2009; 100:551–7. [PubMed: 19156150]

83. Tian W, Zhao Y, Liu S, Li X. Meta-analysis on the relationship between nonsteroidal anti-inflammatory drug use and gastric cancer. Eur J of Cancer Prev. 2010; 19:288–98. [PubMed: 20386312]

84. Yang P, Zhou Y, Chen B, Wan H-W, Jia G-Q, Bai H-L, et al. Aspirin use and the risk of gastric cancer: a meta-analysis. Dig Dis Sci. 2010; 55:1533–9. [PubMed: 19672710]

85. Algra AM, Rothwell PM. Effects of regular aspirin on long-term cancer incidence and metastasis: a systematic comparison of evidence from observational studies versus randomised trials. Lancet Oncol. 2012; 13:518–27. [PubMed: 22440112]

86. Bosetti C, Rosato V, Gallus S, Cuzick J, La Vecchia C. Aspirin and cancer risk: a quantitative review to 2011. Ann Oncol. 2012; 23:1403–15. [PubMed: 22517822]

87. Rothwell PM, Fowkes FGR, Belch JF, Ogawa H, Warlow CP, Meade TW. Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomised trials. Lancet. 2011; 377:31–41. [PubMed: 21144578]

88. Singh PP, Singh S. Statins are associated with reduced risk of gastric cancer: a systematic review and meta-analysis. Ann Oncol. 2013; 24:1721–30. [PubMed: 23599253]

89. Wu XD, Zeng K, Xue FQ, Chen JH, Chen YQ. Statins are associated with reduced risk of gastric cancer: a meta-analysis. Eur J Clin Pharmacol. 2013; 69:1855–60. [PubMed: 23748751]

90. Beales IL, Hensley A, Loke Y. Reduced esophageal cancer incidence in statin users, particularly with cyclo-oxygenase inhibition. World J Gastrointest Pharmacol Ther. 2013; 4:69–79. [PubMed: 23919219]

91. Vallianou NG, Kostantinou A, Kougias M, Kazazis C. Statins and Cancer. Anticancer Agents Med Chem. 2013; 28:28.

92. Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet. 2010; 376:1670–81. [PubMed: 21067804]

93. Hoyo C, Cook MB, Kamangar F, Freedman ND, Whiteman DC, Bernstein L, et al. Body mass index in relation to oesophageal and oesophagogastric junction adenocarcinomas: a pooled

analysis from the International BEACON Consortium. Int J Epidemiol. 2012; 41:1706–18. [PubMed: 23148106]

94. Chen Y, Liu L, Wang X, Wang J, Yan Z, Cheng J, et al. Body mass index and risk of gastric cancer: a meta-analysis of a population with more than ten million from 24 prospective studies. Cancer Epidemiol Biomarkers Prev. 2013; 22:1395–408. [PubMed: 23697611]

95. Corley DA, Kubo A, Zhao W. Abdominal obesity and the risk of esophageal and gastric cardia carcinomas. Cancer Epidemiol Biomarkers Prev. 2008; 17:352–8. [PubMed: 18268119]

96. Aleman JO, Eusebi LH, Ricciardiello L, Patidar K, Sanyal AJ, Holt PR. Mechanisms of obesity-induced gastrointestinal neoplasia. Gastroenterology. 2014; 146:357–73. [PubMed: 24315827]

97. Singh S, Varayil JE, Devanna S, Murad MH, Iyer PG. Physical Activity Is Associated with Reduced Risk of Gastric Cancer: A Systematic Review and Meta-analysis. Cancer Prev Res. 2014; 7:12–22.

98. Rubenstein JH, Taylor JB. Meta-analysis: the association of oesophageal adenocarcinoma with symptoms of gastro-oesophageal reflux. Aliment Pharmacol Ther. 2010; 32:1222–7. [PubMed: 20955441]

99. Lagergren J, Bergstrom R, Lindgren A, Nyren O. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. N Engl J Med. 1999; 340:825–31. [PubMed: 10080844]

100. Ye W, Chow WH, Lagergren J, Yin L, Nyren O. Risk of adenocarcinomas of the esophagus and gastric cardia in patients with gastroesophageal reflux diseases and after antireflux surgery. Gastroenterology. 2001; 121:1286–93. [PubMed: 11729107]

101. Wu AH, Tseng CC, Bernstein L. Hiatal hernia, reflux symptoms, body size, and risk of esophageal and gastric adenocarcinoma. Cancer. 2003; 98:940–8. [PubMed: 12942560]

102. Whiteman DC, Sadeghi S, Pandeya N, Smithers BM, Gotley DC, Bain CJ, et al. Combined effects of obesity, acid reflux and smoking on the risk of adenocarcinomas of the oesophagus. Gut. 2008; 57:173–80. [PubMed: 17932103]

103. Derakhshan MH, Malekzadeh R, Watabe H, Yazdanbod A, Fyfe V, Kazemi A, et al. Combination of gastric atrophy, reflux symptoms and histological subtype indicates two distinct aetiologies of gastric cardia cancer. Gut. 2008; 57:298–305. [PubMed: 17965056]

104. Farrow DC, Vaughan TL, Sweeney C, Gammon MD, Chow WH, Risch HA, et al. Gastroesophageal reflux disease, use of H2 receptor antagonists, and risk of esophageal and gastric cancer. Cancer Causes Control. 2000; 11:231–8. [PubMed: 10782657]

105. Engel LS, Chow WH, Vaughan TL, Gammon MD, Risch HA, Stanford JL, et al. Population attributable risks of esophageal and gastric cancers. J Natl Cancer Inst. 2003; 95:1404–13. [PubMed: 13130116]

106. Figueroa JD, Terry MB, Gammon MD, Vaughan TL, Risch HA, Zhang FF, et al. Cigarette smoking, body mass index, gastro-esophageal reflux disease, and non-steroidal anti-inflammatory drug use and risk of subtypes of esophageal and gastric cancers by P53 overexpression. Cancer Causes Control. 2009; 20:361–8. [PubMed: 18989634]

107. Hansen S, Vollset SE, Derakhshan MH, Fyfe V, Melby KK, Aase S, et al. Two distinct aetiologies of cardia cancer; evidence from premorbid serological markers of gastric atrophy and Helicobacter pylori status. Gut. 2007; 56:918–25. [PubMed: 17317788]

108. Horii T, Koike T, Abe Y, Kikuchi R, Unakami H, Iijima K, et al. Two distinct types of cancer of different origin may be mixed in gastroesophageal junction adenocarcinomas in Japan: evidence from direct evaluation of gastric acid secretion. Scand J Gastroenterol. 2011; 46:710–9. [PubMed: 21446884]

109. Solaymani-Dodaran M, Logan RF, West J, Card T, Coupland C. Risk of oesophageal cancer in Barrett's oesophagus and gastro-oesophageal reflux. Gut. 2004; 53:1070–4. [PubMed: 15247170]

110. Derakhshan MH, McColl KE. Gender, hiatus hernia and Barrett's oesophagus. Gut. 2009; 58:1025. author reply 1025-6. [PubMed: 19520893]

111. Preston DL, Ron E, Tokuoka S, Funamoto S, Nishi N, Soda M, et al. Solid cancer incidence in atomic bomb survivors: 1958-1998. Radiat Res. 2007; 168:1–64. [PubMed: 17722996]

112. Morton LM, Dores GM, Curtis RE, Lynch CF, Stovall M, Hall P, et al. Stomach cancer risk after treatment for hodgkin lymphoma. J Clin Oncol. 2013; 31:3369–77. [PubMed: 23980092]

113. Abnet CC, Kamangar F, Dawsey SM, Stolzenberg-Solomon RZ, Albanes D, Pietinen P, et al. Tooth loss is associated with increased risk of gastric non-cardia adenocarcinoma in a cohort of Finnish smokers. Scand J Gastroenterol. 2005; 40:681–7. [PubMed: 16036528]

114. Abnet CC, Qiao YL, Mark SD, Dong ZW, Taylor PR, Dawsey SM. Prospective study of tooth loss and incident esophageal and gastric cancers in China. Cancer Causes Control. 2001; 12:847–54. [PubMed: 11714113]

115. Malekzadeh MM, Khademi H, Pourshams A, Etemadi A, Poustchi H, Bagheri M, et al. Opium Use and Risk of Mortality from Digestive Diseases: A Prospective Cohort Study. Am J Gastroenterol. 2013; 108:1757–65. [PubMed: 24145676]

116. Shakeri R, Malekzadeh R, Etemadi A, Nasrollahzadeh D, Aghcheli K, Sotoudeh M, et al. Opium: an emerging risk factor for gastric adenocarcinoma. Int J Cancer. 2013; 133:455–61. [PubMed: 23319416]

117. Kamangar F, Shakeri R, Malekzadeh R, Islami F. Opium use: an emerging risk factor for cancer? Lancet Oncol. 2014; 15:70550–3.

118. Koshiol J, Qiao YL, Mark SD, Dawsey SM, Abnet CC, Kamangar F, et al. Epstein-Barr virus serology and gastric cancer incidence and survival. Br J Cancer. 2007; 97:1567–9. [PubMed: 17987041]

119. Levine PH, Stemmermann G, Lennette ET, Hildesheim A, Shibata D, Nomura A. Elevated antibody titers to Epstein-Barr virus prior to the diagnosis of Epstein-Barr-virus-associated gastric adenocarcinoma. Int J Cancer. 1995; 60:642–4. [PubMed: 7860138]

120. Ren JS, Kamangar F, Forman D, Islami F. Pickled food and risk of gastric cancer--a systematic review and meta-analysis of English and Chinese literature. Cancer Epidemiol Biomarkers Prev. 2012; 21:905–15. [PubMed: 22499775]

121. Bernini M, Barbi S, Roviello F, Scarpa A, Moore P, Pedrazzani C, et al. Family history of gastric cancer: a correlation between epidemiologic findings and clinical data. Gastric Cancer. 2006; 9:9–13. [PubMed: 16557430]

122. La Vecchia C, Negri E, Gentile A, Franceschi S. Family history and the risk of stomach and colorectal cancer. Cancer. 2006; 70:50–5. [PubMed: 1606546]

123. Yaghoobi M, Bijarchi R, Narod S. Family history and the risk of gastric cancer. Br J Cancer. 2009; 102:237–42. [PubMed: 19888225]

124. Kolonel, LN.; Hankin, JH.; Nomura, AM. Multiethnic studies of diet, nutrition, and cancer in Hawaii; Princess Takamatsu Symp; 1985; p. 29-40.

125. McMichael AJ, McCall MG, Hartshorne JM, Woodings TL. Patterns of gastrointestinal cancer in European migrants to Australia: the role of dietary change. Int J Cancer. 1980; 25:431–7. [PubMed: 7372370]

126. Fascioli S, Capocaccia R, Mariotti S. Cancer mortality in migrant populations within Italy. Int J Epidemiol. 1995; 24:8–18. [PubMed: 7797360]

127. Coggon D, Osmond C, Barker DJ. Stomach cancer and migration within England and Wales. Br J Cancer. 1990; 61:573–4. [PubMed: 2331443]

128. Malaty HM, El-Kasabany A, Graham DY, Miller CC, Reddy SG, Srinivasan SR, et al. Age at acquisition of Helicobacter pylori infection: a follow-up study from infancy to adulthood. Lancet. 2002; 359:931–5. [PubMed: 11918912]

129. Falush D, Wirth T, Linz B, Pritchard JK, Stephens M, Kidd M, et al. Traces of human migrations in Helicobacter pylori populations. Science. 2003; 299:1582–5. [PubMed: 12624269]

130. Lynch HT, Grady W, Suriano G, Huntsman D. Gastric cancer: new genetic developments. J Surg Oncol. 2005; 90:114–33. [PubMed: 15895459]

131. Kaurah P, MacMillan A, Boyd N, Senz J, De Luca A, Chun N, et al. Founder and recurrent CDH1 mutations in families with hereditary diffuse gastric cancer. JAMA. 2007; 297:2360–72. [PubMed: 17545690]

132. Oliveira C, Senz J, Kaurah P, Pinheiro H, Sanges R, Haegert A, et al. Germline CDH1 deletions in hereditary diffuse gastric cancer families. Hum Mol Genet. 2009; 18:1545–55. [PubMed: 19168852]

133. Galiatsatos P, Foulkes WD. Familial adenomatous polyposis. Am J Gastroenterol. 2006; 101:385–98. [PubMed: 16454848]

134. Takahashi M, Sakayori M, Takahashi S, Kato T, Kaji M, Kawahara M, et al. A novel germline mutation of the LKB1 gene in a patient with Peutz-Jeghers syndrome with early-onset gastric cancer. J Gastroenterol. 2004; 39:1210–4. [PubMed: 15622488]

135. Kamangar F, Cheng C, Abnet CC, Rabkin CS. Interleukin-1B polymorphisms and gastric cancer risk--a meta-analysis. Cancer Epidemiol Biomarkers Prev. 2006; 15:1920–8. [PubMed: 17035400]

136. Sakamoto H, Yoshimura K, Saeki N, Katai H, Shimoda T, Matsuno Y, et al. Genetic variation in PSCA is associated with susceptibility to diffuse-type gastric cancer. Nat Genet. 2008; 40:730–40. [PubMed: 18488030]

137. Shi Y, Hu Z, Wu C, Dai J, Li H, Dong J, et al. A genome-wide association study identifies new susceptibility loci for non-cardia gastric cancer at 3q13.31 and 5p13.1. Nat Genet. 2011; 43:1215–8. [PubMed: 22037551]

138. Abnet CC, Freedman ND, Hu N, Wang Z, Yu K, Shu XO, et al. A shared susceptibility locus in PLCE1 at 10q23 for gastric adenocarcinoma and esophageal squamous cell carcinoma. Nat Genet. 2010; 42:764–7. [PubMed: 20729852]

139. Wang LD, Zhou FY, Li XM, Sun LD, Song X, Jin Y, et al. Genome-wide association study of esophageal squamous cell carcinoma in Chinese subjects identifies susceptibility loci at PLCE1 and C20orf54. Nat Genet. 2010; 42:759–63. [PubMed: 20729853]

140. Saeki N, Saito A, Choi IJ, Matsuo K, Ohnami S, Totsuka H, et al. A functional single nucleotide polymorphism in mucin 1, at chromosome 1q22, determines susceptibility to diffuse-type gastric cancer. Gastroenterology. 2011; 140:892–902. [PubMed: 21070779]

141. Leung WK, Wu M, Kakugawa Y, Kim JJ, Yeoh K, Goh KL, et al. Screening for gastric cancer in Asia: current evidence and practice. Lancet Oncol. 2008; 9:279–87. [PubMed: 18308253]

142. Fock KM, Talley N, Moayyedi P, Hunt R, Azuma T, Sugano K, et al. Asia-Pacific consensus guidelines on gastric cancer prevention. J Gastroenterol Hepatol. 2008; 23:351–65. [PubMed: 18318820]

143. Hamashima C, Shibuya D, Yamazaki H, Inoue K, Fukao A, Saito H, et al. The Japanese guidelines for gastric cancer screening. Jpn J Clin Oncol. 2008; 38:259–67. [PubMed: 18344316]

144. Croswell JM, Ransohoff DF, Kramer BS. Principles of cancer screening: lessons from history and study design issues. Semin Oncol. 2010; 37:202–15. [PubMed: 20709205]

145. Suzuki KJ, Nakaji S, Tokunaga S, Shimoyama T, Umeda T, Sugawara K. Confounding by dietary factors in case-control studies on the efficacy of cancer screening in Japan. Eur J Epidemiol. 2005; 20:73–8. [PubMed: 15756907]

146. Correa P. Human gastric carcinogenesis: a multistep and multifactorial process--First American Cancer Society Award Lecture on Cancer Epidemiology and Prevention. Cancer Res. 1992; 52:6735–40. [PubMed: 1458460]

147. Samloff IM, Taggart RT. Pepsinogens, pepsins, and peptic ulcer. Clin Invest Med. 1987; 10:215–21. [PubMed: 3113799]

148. Ren JS, Kamangar F, Qiao YL, Taylor PR, Liang H, Dawsey SM, et al. Serum pepsinogens and risk of gastric and oesophageal cancers in the General Population Nutrition Intervention Trial cohort. Gut. 2009; 58:636–42. [PubMed: 19136509]

149. Abnet CC, Zheng W, Ye W, Kamangar F, Ji BT, Persson C, et al. Plasma pepsinogens, antibodies against Helicobacter pylori, and risk of gastric cancer in the Shanghai Women's Health Study Cohort. Br J Cancer. 2011; 104:1511–6. [PubMed: 21407214]

150. Watabe H, Mitsushima T, Yamaji Y, Okamoto M, Wada R, Kokubo T, et al. Predicting the development of gastric cancer from combining Helicobacter pylori antibodies and serum pepsinogen status: a prospective endoscopic cohort study. Gut. 2005; 54:764–8. [PubMed: 15888780]

151. Dong CX, Brubaker PL. Ghrelin, the proglucagon-derived peptides and peptide YY in nutrient homeostasis. Nat Rev Gastroenterol Hepatol. 2012; 9:705–15. [PubMed: 23026903]

152. Murphy G, Kamangar F, Dawsey SM, Stanczyk FZ, Weinstein SJ, Taylor PR, et al. The relationship between serum ghrelin and the risk of gastric and esophagogastric junctional adenocarcinomas. J Natl Cancer Inst. 2011; 103:1123–9. [PubMed: 21693726]

153. Sadjadi A, Yazdanbod A, Lee YY, Boreiri M, Samadi F, Alizadeh BZ, et al. Serum ghrelin; a new surrogate marker of gastric mucosal alterations in upper gastrointestinal carcinogenesis. PLoS One. 2013; 8:0074440.

154. Zhang Y, Weck MN, Schottker B, Rothenbacher D, Brenner H. Gastric parietal cell antibodies, Helicobacter pylori infection, and chronic atrophic gastritis: evidence from a large population-based study in Germany. Cancer Epidemiol Biomarkers Prev. 2013; 22:821–6. [PubMed: 23456556]

155. Areia M, Carvalho R, Cadime AT, Rocha Goncalves F, Dinis-Ribeiro M. Screening for gastric cancer and surveillance of premalignant lesions: a systematic review of cost-effectiveness studies. Helicobacter. 2013; 18:325–37. [PubMed: 23566268]

156. Choi KS, Kwak MS, Lee HY, Jun JK, Hahm MI, Park EC. Screening for gastric cancer in Korea: population-based preferences for endoscopy versus upper gastrointestinal series. Cancer Epidemiol Biomarkers Prev. 2009; 18:1390–8. [PubMed: 19383892]

157. Ricci C, Holton J, Vaira D. Diagnosis of Helicobacter pylori: invasive and non-invasive tests. Best Pract Res Clin Gastroenterol. 2007; 21:299–313. [PubMed: 17382278]

158. Dinis-Ribeiro M, Areia M, de Vries AC, Marcos-Pinto R, Monteiro-Soares M, O'Connor A, et al. Management of precancerous conditions and lesions in the stomach (MAPS): guideline from the European Society of Gastrointestinal Endoscopy (ESGE), European Helicobacter Study Group (EHSG), European Society of Pathology (ESP), and the Sociedade Portuguesa de Endoscopia Digestiva (SPED). Endoscopy. 2012; 44:74–94. [PubMed: 22198778]

159. Aida K, Yoshikawa H, Mochizuki C, Mori A, Muto S, Fukuda T, et al. Clinicopathological features of gastric cancer detected by endoscopy as part of annual health checkup. J Gastroenterol Hepatol. 2008; 23:632–7. [PubMed: 18397489]

160. Lee BE, Kim GH, Park do Y, Kim DH, Jeon TY, Park SB, et al. Acetic acid-indigo carmine chromoendoscopy for delineating early gastric cancers: its usefulness according to histological type. BMC Gastroenterol. 2010; 10:97. [PubMed: 20731830]

161. Yao K, Iwashita A, Tanabe H, Nishimata N, Nagahama T, Maki S, et al. White opaque substance within superficial elevated gastric neoplasia as visualized by magnification endoscopy with narrow-band imaging: a new optical sign for differentiating between adenoma and carcinoma. Gastrointest Endosc. 2008; 68:574–80. [PubMed: 18656862]

162. Byers T. Physical Activity and Gastric Cancer: So What? An Epidemiologist's Confession. Cancer Prev Res. 2014; 7:9–11.

163. Bibbins-Domingo K, Chertow GM, Coxson PG, Moran A, Lightwood JM, Pletcher MJ, et al. Projected effect of dietary salt reductions on future cardiovascular disease. N Engl J Med. 2010; 362:590–9. [PubMed: 20089957]

164. Cappuccio FP, Capewell S, Lincoln P, McPherson K. Policy options to reduce population salt intake. BMJ. 2011:11.

165. Kotchen TA, Cowley AW Jr. Frohlich ED. Salt in health and disease--a delicate balance. N Engl J Med. 2013; 368:1229–37. [PubMed: 23534562]

166. Fuccio L, Zagari RM, Eusebi LH, Laterza L, Cennamo V, Ceroni L, et al. Meta-analysis: can Helicobacter pylori eradication treatment reduce the risk for gastric cancer? Ann Intern Med. 2009; 151:121–8. [PubMed: 19620164]

167. Fock KM, Katelaris P, Sugano K, Ang TL, Hunt R, Talley NJ, et al. Second Asia-Pacific consensus guidelines for helicobacter pylori infection. J Gastroenterol Hepatol. 2009; 24:1587–600. [PubMed: 19788600]

168. Asaka M. A new approach for elimination of gastric cancer deaths in Japan. Int J Cancer. 2013; 132:1272–6. [PubMed: 23180638]

169. Talley NJ, Fock KM, Moayyedi P. Gastric Cancer Consensus conference recommends Helicobacter pylori screening and treatment in asymptomatic persons from high-risk populations to prevent gastric cancer. Am J Gastroenterol. 2008; 103:510–4. [PubMed: 18341483]

170. Bae SE, Jung HY, Kang J, Park YS, Baek S, Jung JH, et al. Effect of Helicobacter pylori Eradication on Metachronous Recurrence After Endoscopic Resection of Gastric Neoplasm. Am J Gastroenterol. 2014; 109:60–7. [PubMed: 24343545]

171. Atherton JC, Blaser MJ. Coadaptation of Helicobacter pylori and humans: ancient history, modern implications. J Clin Invest. 2009; 119:2475–87. [PubMed: 19729845]

172. Goff DC Jr. Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB Sr. Gibbons R, et al. 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2013; 12:12.

173. Stone NJ, Robinson J, Lichtenstein AH, Merz CN, Blum CB, Eckel RH, et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2013; 12:12.

174. Ohata H, Oka M, Yanaoka K, Shimizu Y, Mukoubayashi C, Mugitani K, et al. Gastric cancer screening of a high risk population in Japan using serum pepsinogen and barium digital radiography. Cancer Sci. 2005; 96:713–20. [PubMed: 16232204]

175. Smith RA, Cokkinides V, Eyre HJ. American Cancer Society guidelines for the early detection of cancer, 2006. CA Cancer J Clin. 2006; 56:11–25. [PubMed: 16449183]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

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
Physical activity	Physical activity
Fiber intake	Fiber intake
Radiation	Radiation
--	*H. pylori*
--	Low socioeconomic status (22)
--	High intake of salty and smoked food
--	Low consumption of fruits and vegetables
Obesity	--
Gastro Esophageal Reflux Disease (GERD)	--

Table 2

Susceptibility loci associated with higher risk of gastric cancer identified in genome-wide association studies

SNPs by nearest gene (locus)	Study	Ethnicity	Subtype	Case/ control	Allele-specific OR (95% CI)	P-value
PSCA (8q24.3)						
rs2294008 (T>C)	Sakamoto et al. (136)	Japanese	–	749/750	1.58 (1.35–1.85)	6.3×10^{-9}
			Diffuse	925/1,396	1.67 (1.47–1.90)	2.2×10^{-15}
			Intestinal	599/1,396	1.29 (1.11–1.49)	6.0×10^{-4}
		Korean	Diffuse	454/390	1.91 (1.57–2.33)	6.3×10^{-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)	1.63×10^{-3}
	Shi et al. (137)	Chinese	Noncardia	4,294/ 5,882	1.36 (NR)	2.1×10^{-7}
rs2976392 (A>G)	Sakamoto et al. (136)	Japanese	_a	749/750	1.62 (1.38–1.89)	1.1×10^{-9}
			Diffuse	926/1,397	1.71 (1.50–1.94)	1.5×10^{-16}
			Intestinal	926/1,397	1.29 (1.12–1.49)	5.0×10^{-4}
		Korean	Diffuse	449/390	1.90 (1.56–2.33)	8.0×10^{-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)	3.7×10^{-7}
MUC1 (1q22)						
rs4072037 (A>G)	Abnet et al. (138)	Chinese	Cardia	1,213/3,302	0.75 (0.62–0.87)	9.5×10^{-5}
			Noncardia	917/3,302	0.72 (0.62–0.85)	5.7×10^{-5}
			Total	2,240/3,302	0.75 (0.67–0.84)	4.2×10^{-7}
	Shi et al. (137)	Chinese	Noncardia	4,294/ 5,882	0.73 (NR)	1.0×10^{-4}
rs4460629 (C>T)	Abnet et al. (138)	Chinese	Cardia	1,213/3,302	0.74 (0.64–0.86)	1.3×10^{-4}
			Noncardia	917/3,302	0.75 (0.64–0.88)	5.4×10^{-4}
			Total	2,240/3,302	0.75 (0.67–0.85)	2.3×10^{-6}
rs2070803 (A>G)	Sakamoto et al. (136) *	Japanese	_a	749/750	1.62 (1.33–1.98)	1.2×10^{-6}
rs2075570 (G>A)	Sakamoto et al. (136) *	Japanese	_a	749/750	1.65 (1.34–2.02)	9.2×10^{-7}
PLCE1 (10q23)						

SNPs by nearest gene (locus)	Study	Ethnicity	Subtype	Case/ control	Allele–specific OR (95% CI)	P-value
rs2274223 (A>G)	Wang et al. (139)	Chinese	Cardia	2,766/ 11,013	1.55 (1.45–1.66)	1.7×10^{-39}
	Abnet et al. (138)	Chinese	Cardia	1,213/3,302	1.57 (1.40–1.76)	4.2×10^{-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)	7.4×10^{-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)	1.1×10^{-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)	7.1×10^{-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)	8.0×10^{-12}
			Noncardia	917/3,302	1.19 (0.99–1.44)	0.16
C20orf54 (20p13)						
rs13042395 (C>T)	Shi et al. (137)	Chinese	Noncardia	4,294/ 5,882	0.80 (NR)	6.9×10^{-4}
	Wang et al. (139)	Chinese	Cardia	2,766/ 11,013	0.91 (0.85–0.97)	3.0×10^{-3}
PRKAA1, PTGER4 (5p13.1)						
rs13361707 (T>C)	Shi et al. (137)	Chinese	Noncardia	4,294/ 5,882	1.41 (1.32–1.49)	7.6×10^{-29}
ZBTB20 (3q13.31)						
rs9841504 (C>G)	Shi et al. (137)	Chinese	Noncardia	4,294/ 5,882	0.76 (0.69–0.83)	1.7×10^{-9}

NR, not reported; SNP, single nucleotide polymorphism.

*
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, 2.3×10^{-12}), and rs2070803 (OR= 1.71, 4.3×10^{-13}) and GC (140).

a
Only participants included in a part of the study (stage 2 of the screening study).