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Giovanni de Manzoni
Franco Roviello *Editors*

Gastric Cancer: the 25-year R-Evolution

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Gastric Cancer: the 25-year R-Evolution

Springer

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Foreword

During the last 25 years, gastric cancer surgery has undergone a number of technical evolutions, concept progressions, and outcome improvements. This has resulted not only from better patient stratification, more efficient multidisciplinary management, and, no doubt, the revolution and evolution of minimally invasive surgery, but also from refinements in surgical approach and the experiences of dedicated centers.

All these aspects and much more have been deeply examined and magisterially illustrated in the present volume that I have the privilege to introduce. It has been for both the Editors an invaluable opportunity to share with the surgical community their extraordinary experience and ideas in the field, combining a long-standing tradition of prestigious surgical schools with a far-sighted view of the future developments.

The structure of the book reflects the lengthy experience of the Editors and Authors and their deep knowledge of the topic, giving us the opportunity to be brought up to date on the results and evidence acquired while sharing the most important trends and innovations in the field.

As the President of Italian Surgeons, I wish to express my deep gratitude to the Authors for this fantastic feat so that, looking at the final results of this scientific endeavor, the words that easily come to my mind are that, without any doubt, the esteemed Colleagues Professor de Manzoni and Professor Roviello have truly honored the Italian academic tradition through the very high scientific quality of this monograph.

Catania, Italy
September 2021

Francesco Basile
President
Italian Society of Surgery

Preface

Gastric cancer is undoubtedly among the most heterogeneous gastrointestinal neoplasias both from the clinical and morphological-molecular points of view.

The drafting of this book has not only involved the experience of Italian surgeons who have been dealing with gastric cancer for years but also integrated the knowledge of other national experts such as oncologists, molecular biologists, pathologists, endoscopists, and radiologists, who dedicate a large part of their working life to the study of gastric cancer.

The content of this work embodies the philosophy of the holistic approach to gastric cancer. Indeed, nowadays, the surgeon who treats this disease cannot ignore the essential knowledge dispensed within the present volume, when selecting the most appropriate multimodal treatment in gastric cancer for each patient based on the latest evidence available in the literature.

The entire volume culminates in the chapter *Gastric Cancer: Synopsis of Treatment Indications*, which offers practical guidance for the clinical challenges of everyday practice, leaving the reader the opportunity to explore the various topics covered more in detail in the dedicated chapters.

It was a pleasure and an honor to coordinate the experience of the Italian Research Group for Gastric Cancer (GIRCG), which matured over the past twenty years, also in drafting this book. A special thanks goes to the Society of Surgery that allowed us to bring this work to life.

Verona, Italy
Siena, Italy
September 2021

Giovanni de Manzoni
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Part III Treatment

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Part I

Epidemiology, Pathology, and Diagnosis

Epidemiology and Risk Stratification in Gastric Cancer

1

Lorena Torroni, Roberta Vesentini, Emanuele Crocetti, and Giuseppe Verlato

1.1 Incidence and Mortality of Gastric Cancer

Gastric cancer (GC) ranks fifth for incidence and third for mortality among cancers worldwide. With over one million new cases (n = 1,033,701) and 782,685 deaths in 2018, GC accounts for 5.7% of all cancer incidence and 8.2% of total cancer mortality [1]. Considering that death occurs in about 75% of new cases, it can be inferred that the case fatality rate is high.

GC affects more men than women: in 2018, a total of 683,754 new cases and 513,555 deaths were recorded among men, and 349,947 new cases and 269,130 deaths among women. Accordingly, the age-standardized incidence and mortality rates are more than double in men (15.7 new cases and 11.7 deaths per 100,000 person-years) compared to women (7.0 new cases and 5.2 deaths per 100,000 person-years) [2].

The incidence of GC dramatically increases with age, from 0.58 per 100,000 person-years under 40 years to 98.5 over 70 years in 2020. It is more common among women below 40 years, and in men thereafter. The trend is similar when considering only the European region (Table 1.1) [3].

In the world, the age-standardized incidence rates of GC vary considerably, with maximum levels in Eastern Asia (Japan, South Korea, China, with 22.6 new cases among males per 100,000 person-years), Central/Eastern Europe (22.7) and South/Central America (12.1), especially along the Pacific coast, and minimum levels in

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Table 1.1 Incidence of gastric cancer in the WHO European region in 2020, according to Globocan [3]

	Total cases		Crude incidence rate per 100,000 person-years	
Age	Men	Women	Men	Women
0–39 years	1167	1544	0.5	0.7
40–54 years	11,123	6199	11.9	6.5
55–69 years	41,574	19,520	53.6	21.8
>70 years	45,825	34,472	106.9	52.5
Total	99,689	61,735	22.0	12.8

Australia/New Zealand (10.5), North America/Northern Europe (10.3) and Africa (2.6) [4]. According to the World Health Organization "GLOBOCAN" monitoring system (2018), 74.5% of new diagnoses of GC and 74.7% of deaths from the disease worldwide have occurred in Asia; in particular, China alone contributes to more than half of cases. The different incidence, as well as the different clinical-pathological presentation between the Asian and Western populations, are suggestive of different pathogenesis and different underlying biological, environmental, and nutritional risk factors [1].

Thanks to survival improvement, nowadays it is possible to describe not only the cancer's incidence and mortality, but also its prevalence. In 2018, a total of 1,589,752 individuals (1,025,232 men and 564,520 women) had been diagnosed with GC at least 5 years earlier, yielding a worldwide prevalence of 20.8 per 100,000 (26.6 in men and 14.9 in women).

1.2 Risk Assessment and Stratification in Gastric Cancer

Most GC cases (about 90%) are sporadic, while only 10% show a familial aggregation, and 1–3% arise from inherited cancer syndromes [5]. Hence most GC cases arise from the interplay of genetic and environmental factors, whose weight increases with aging. An important contribution to GC decline has been given by identifying relevant risk factors, which can be classified into two general groups: environmental and host-related factors.

The majority of GC cases are related to chronic infection with *Helicobacter pylori*, which is the strongest known environmental risk factor for GC, accounting for 89% of cases worldwide [6]. Indeed, de Martel et al. estimated that, in 2018, 760,000 cases of non-cardia cancer could be attributed to *H. pylori* infection, as well as 36,000 cases of cardia cancer and 16,000 of gastric non-Hodgkin lymphoma [7]. *H. pylori* was classified by the World Health Organization (WHO) as a class I carcinogen in the early 1990s, and this recently confirmed by the International Agency for Research on Cancer (IARC) [8, 9]. The cytotoxin-associated gene A (cagA) increases the virulence of *H. pylori*: compared with non-infected individuals, the odds ratio (OR) of GC is 2.31 (95% CI 1.58–3.39) in people with *H. pylori*

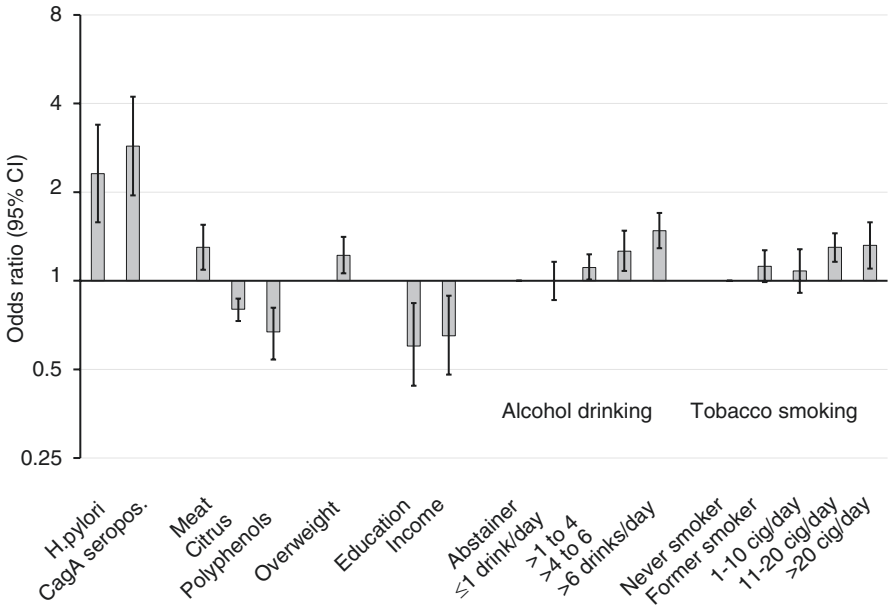

Fig. 1.1 Main risk factors for gastric cancer. Sources of risk estimates: *H. pylori* infection and CagA seropositivity [10]; highest vs. lowest tertile of meat [13] and citrus [14] consumption; highest vs. lowest quartile of polyphenol intake [18]; overweight/obesity vs. normal weight [19]; highest vs. lowest level of education [20]; highest vs. lowest household income [20]; alcohol drinking [22]; tobacco smoking [25]

infection, and increases to 2.87 (1.95–4.22) in people with cagA seropositivity [10]. Generally, the natural history of *H. pylori*–related GC includes a latency period, followed by a preclinical stage, where the risk increases exponentially [11]. Although *H. pylori* eradication involves healing from gastric mucosa inflammation, eradication alone cannot immediately reverse the "peak" risk, but it does place the individual on a more favorable trajectory [12].

Substantial evidence suggests that diet has an important role in the onset of GC (Fig. 1.1). In detail, the risk is increased by a high intake of meat [13] and salty or smoked food, and decreased by a diet rich in fresh fruit and vegetables [14]. Salt can directly damage the stomach mucosa [15] and increase the persistency of *H. pylor*i infection in animal models [16]. The protective effect of fresh fruit and vegetables can be attributed to the high content of antioxidants, such as ascorbic acid, carotenoids and polyphenols [17, 18].

Excess body weight is associated with a slight increase in the risk of GC: according to a meta-analysis of cohort studies, the OR of GC is 1.22 (95% CI 1.06–1.41) in overweight/obese compared with normal weight subjects [19]. Of note, the association was stronger for cardia (OR = 1.55, 1.31–1.84) than for non-cardia (OR = 1.18, 0.96–1.45) GC.

GC risk is inversely related to socioeconomic status, e.g., education level and household income. In a recent meta-analysis, the pooled OR for the highest compared to the lowest level of education was 0.60 (95% CI 0.44–0.84). The negative association was recorded both for non-cardia (OR 0.39, 95% CI 0.22–0.70) and cardia (OR 0.47, 95% CI 0.22–0.99) GC [20].

Alcohol drinking is a major risk factor for esophageal cancer, but plays a minor role also in gastric oncogenesis. In a nationwide South Korean cohort study [21], the hazard ratio (HR) showed a risk for esophageal cancer three times higher in people drinking ≥30 g alcohol/day than non-drinkers (HR = 3.13, 95% CI 2.95–3.32), while the risk for GC was increased by only one-fourth (HR = 1.24, 1.21–1.26). A similar result was found by a cohort study from the Stomach cancer Pooling (StoP) project [22], where the pooled OR for GC, compared to abstainers, was 1.26 (95% CI 1.08–1.48) in people consuming >4–6 drinks per day and 1.48 (1.29–1.70) in people consuming >6 drinks/day. It is still debated whether moderate alcohol consumption (<10 g/day) does not affect [22] or slightly increases [21] GC risk. The carcinogenic effect of alcohol seems to be higher for gastric cardia (OR for heavy drinkers = 1.61, 95% CI 1.11–2.34) than non-cardia (OR = 1.28, 95% CI 1.13–1.45) cancer [22].

Tobacco smoke is one of the most important risk factors for cancer. For instance, cigarette smokers are 15–30 times more likely to develop lung cancer than non-smokers [23]. Tobacco smoke has a significant, although lesser, effect also on the stomach mucosa [24]. According to the StoP project, compared to never smokers, the ORs of GC were 1.12 (95% CI 0.99–1.27) for former smokers, and 1.25 (95% CI 1.11–1.40) for current cigarette smokers. The ORs were slightly higher for cardia (1.58, 95% CI 1.11–2.24) than non-cardia (1.29, 95% CI 1.03–1.61) cancer [25].

Infection with Epstein-Barr virus (EBV) is associated with GC especially in men and is characterized by DNA-methylation of specific regions of different cancer-associated genes.

As regards cancer site and histology, obesity and alcohol drinking have a larger impact on cardia than non-cardia cancer (Fig. 1.2), while alcohol drinking and tobacco smoke tend to have a larger effect on the onset of intestinal compared with diffuse histotypes (Fig. 1.3). Indeed, the latter histotype seems to be more affected by genetic factors and less affected by environmental factors compared with the intestinal histotype.

1.3 Prevention

There are two main strategies for preventing cancer: (1) primary prevention consists in removing cancer causes before cancer occurrence; (2) secondary prevention consists in early cancer detection through mass screening.

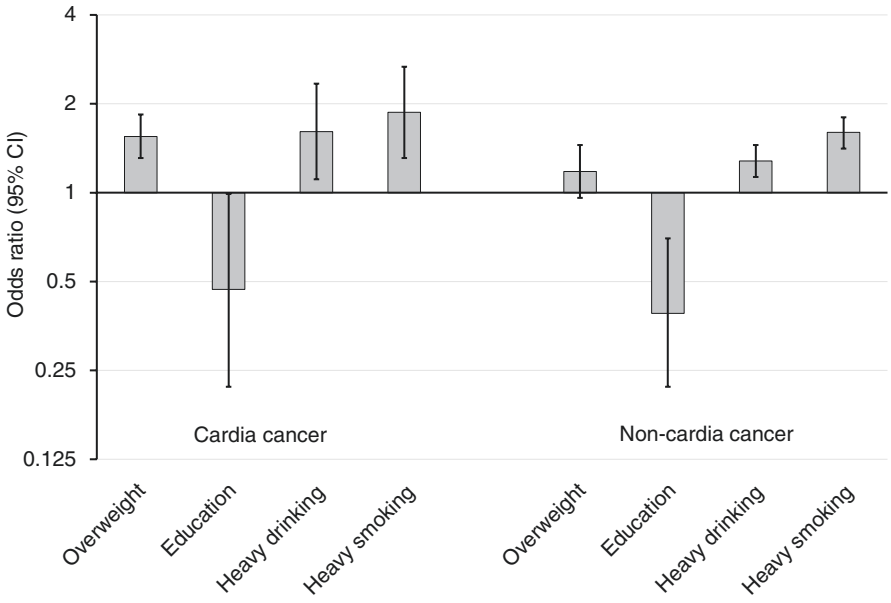

Fig. 1.2 Risk factors for gastric cancer as a function of tumor site (cardia vs. non-cardia cancer). Sources of risk estimates: overweight/obesity vs. normal weight [19]; highest vs. lowest level of education [20]; heavy alcohol drinking (4–6 drinks/day) vs. abstainer [22]; heavy tobacco smoking (>20 cigarettes/day) vs. never smoking [25]

1.3.1 Primary Prevention

As regards GC, primary prevention can be accomplished by avoidance of known carcinogens, changes in lifestyle, inhibiting cancer development through prescription of anti-carcinogenic drugs [26], and, above all, eradicating *H. pylori*.

Nonsteroidal anti-inflammatory drugs (NSAIDs), statins, and metformin seem to have a protective effect on GC [27]. Aspirin and NSAIDs inhibit cell proliferation and induce apoptosis in various cancer cell lines. The protective effect of aspirin (RR 0.70, 95% CI = 0.62–0.80) seems to be slightly higher than that of NSAIDs (RR 0.86, 95% CI = 0.80–0.94) [28]. Statins have been reported to reduce GC risk by 15–20% [29].

H. pylori eradication halves the incidence of GC both in healthy individuals (RR = 0.54, 95% CI 0.40–0.72, NNT = 72) and in survivors of previous GC (RR = 0.49, 95% CI 0.34–0.70, NNT = 21) and reduces, as a consequence of the lower incidence, also mortality from GC, although to a lower extent (RR = 0.61, 95% CI 0.40–0.92, NNT = 135) [30]. The Taipei Global Consensus, released by the Asian Pacific Alliance on Helicobacter and Microbiota, pointed out that "the

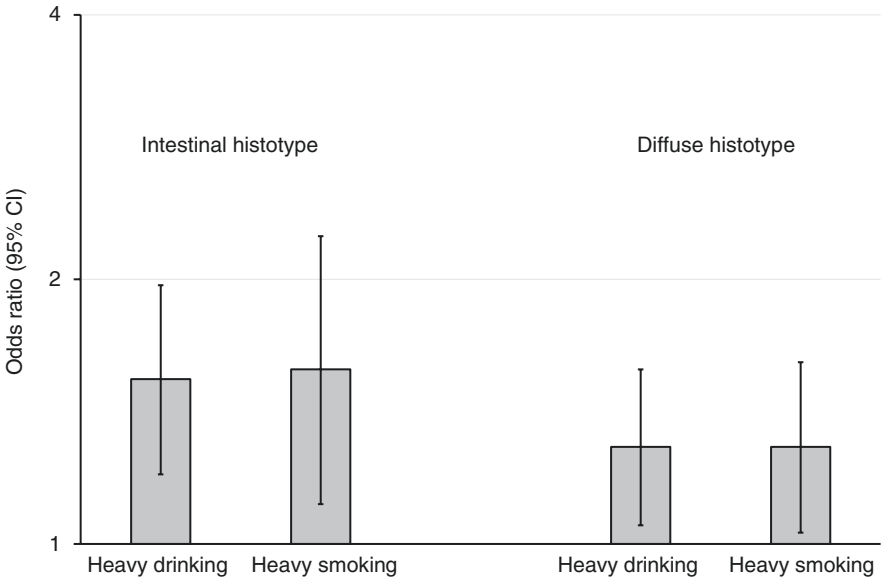

Fig. 1.3 Risk factors for gastric cancer as a function of Laurén histology (intestinal vs. diffuse histotype). Sources of risk estimates: heavy alcohol drinking (4–6 drinks/day) vs. abstainer [22]; heavy tobacco smoking (>20 cigarettes/day) vs. never smoking [25]

strategy of screen-and-treat for *H. pylori* infection is most cost-effective in young adults in regions with a high incidence of GC and is recommended preferably before the development of atrophic gastritis and intestinal metaplasia. However, such a strategy may still be effective in people aged over 50, and may be integrated or included into national healthcare priorities" [31].

1.3.2 Secondary Prevention (Screening)

Cancer diagnosis is often delayed as a substantial proportion of patients are either asymptomatic or, more commonly, have non-specific symptoms during the early stage of the disease. The purpose of cancer screening is to reduce cancer mortality and, for some cancers, also morbidity, by detecting early preclinical disease, which can be effectively treated unlike advanced cancer. In order to be advantageous, a screening program should be well-organized and ensure high coverage of the population at risk. To achieve these goals, a screening test should be accurate, feasible, culturally acceptable, safe, and low cost. To minimize the possible harms and increase the expected benefits of a screening program, diagnostic tests should be evidence-based, quality-assured, and equitably distributed [32].

Secondary prevention is currently ongoing in eastern Asia, which presents the highest incidence in the world [33]. In Japan, screening was introduced in the sixties, first restricted to the population older than 50 years and later extended to all

people aged 40 years and over, and it is based on double-contrast barium radiograph with photofluorography [34, 35]. At present, the Japanese guidelines recommend radiographic or endoscopic screening for people aged 50 years and over [34], while the Korean guidelines recommend endoscopy every 2 years for people aged >40 years [36].

On the other hand, no organized screening program can be found outside Japan and South Korea, although several screening approaches have been proposed. In the West, proposed GC screening programs are mainly focused on people with premalignant lesions, such as atrophy or *H. pylori* infection/inflammation, and employ upper endoscopy and double-contrast barium radiography with photofluorography or digital radiography. Among the two techniques, upper endoscopy is the most sensitive in diagnosing a variety of gastric lesions, but also the most expensive and the most invasive.

Non-invasive screening approaches have also been proposed which assess the blood concentration of specific markers, in particular pepsinogen and gastrin-17b. Pepsinogen levels decrease in atrophic gastritis, while gastrin-17b decreases in atrophic gastritis affecting the antrum or the whole stomach, while an opposite trend is recorded for atrophic gastritis in the body/fundus. However, the interpretation of these biomarkers is not straightforward, as pepsinogen levels increase during inflammation, while gastrin-17b levels decrease in gastroesophageal reflux disease and increase during treatment with proton-pump inhibitors. In Europe, a two-step screening has been proposed: first, subjects at high risk for GC are identified through a set of biomarkers, named Gastropanel (International Institute of Anticancer Research. Delinasios GJ) and comprising pepsinogen I, pepsinogen II, gastrin-17b and IgG to *H. pylori* [37]. In the second step, high-risk subjects are referred for gastroscopy. However, the implementation of this two-step strategy has been limited by the relatively high cost of biomarker assessment, which is amplified by its allocation in first-line screening.

It should be pointed out that a screen of the general European population is not feasible, unless a careful selection of at-risk categories is preliminarily performed. For instance, if the European population aged 55–69 years were screened every 2 years, the proportion of new cases would be 53.6/100,000 person-years × 2 years = 0.107% in men and 21.8/100,000 person-years × 2 years = 0.044% in women. Even assuming a fairly high sensitivity and specificity of 0.95, the positive predictive value would be 1.95% in men and 0.83% in women. In other words, only two men and less than one woman out of 100 individuals positive to the initial screen and referred for further examinations would be finally diagnosed with GC.

1.4 Discussion

Screening has been proved to be a lifesaving procedure in several tumors, including breast, endometrial and colorectal cancers. However, the risk-benefit balance is less favorable for other cancers, such as prostate or lung cancer.

To be cost-effective, a screening program should achieve an adequate positive predictive value (PPV). For instance, PPV is around 8% in breast cancer screening [38], and should not be lower than that to avoid increases in psychological and physical stress for the patients and costs for the health system. Screening programs, based on imaging or gastroscopy, have proved effective in anticipating GC diagnosis and reducing related mortality in South Korea and Japan, which have the highest incidence in the world [27]. However, at present a hypothetical screening on the European population aged 55–69 years would achieve a PPV <2% in men and <1% in women, due to the relatively low incidence of GC. To enhance PPV, a two-step approach should be adopted, where high-risk individuals should be detected in the first step through the use of simple tools, such as questionnaires or cheap non-invasive tests, and then referred for invasive procedures.

However, only weak risk factors emerged during the present review, as denoted by ORs comprised between 1 and 1.5, with the only exception of *H. pylori* infection, whose detection is rather expensive to be applied to the general population. Screening based on the blood concentration of specific biomarkers, such as the Gastropanel, is not feasible as a first-step screen for the same reason.

It should be remembered that even cost-effective approaches cannot be implemented in several regions due to resource constraints. Hence, an integrated and resource-sensitive approach should be developed for real-life practice [39].

1.5 Conclusion

In the West, there is no standard approach to GC screening. Endoscopic screening appears to be a viable option for high-risk areas, while serological screening can be used to identify high-risk individuals to be referred for endoscopic surveillance.

A strategy that combines adequate risk stratification with gastroscopy on pre-selected individuals could lead to an increase in early diagnosis and hopefully in patient survival and quality of life, as well as gastric pre-cancer surveillance. A future approach worth exploring would be to select high-risk individuals from healthcare utilization databases, routinely analyzed through innovative approaches, such as artificial intelligence [40].

References

1. Ferlay J, Colombet M, Soerjomataram I, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. Int J Cancer. 2019;144(8):1941–53.
2. The Global Cancer Observatory. Globocan 2018. Geneva: World Health Organization; 2019.
3. Ferlay J, Ervik M, Lam F, et al. Global Cancer Observatory: cancer today. Lyon, France: International Agency for Research on Cancer; 2021. https://gco.iarc.fr/today. Accessed 20 Feb 2021.
4. Verlato G, Di Leo A, Rossi GM, de Manzoni G. Epidemiology of gastric cancer and screening programs. In: de Manzoni G, Roviello F, Siquini W, editors. Surgery in the multimodal management of gastric cancer. New York: Springer-Verlag; 2012.

5. Setia N, Clark JW, Duda DG, et al. Familial gastric cancers. Oncologist. 2015;20(12):1365–77.
6. Plummer M, Franceschi S, Vignat J, et al. Global burden of gastric cancer attributable to Helicobacter pylori. Int J Cancer. 2015;136(2):487–90.
7. de Martel C, Georges D, Bray F, et al. Global burden of cancer attributable to infections in 2018: a worldwide incidence analysis. Lancet Glob Health. 2020;8(2):e180–90.
8. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Schistosomes, liver flukes and Helicobacter pylori. IARC Monogr Eval Carcinog Risks Hum. 1994;61:1–241.
9. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Biological agents. Volume 100 B. A review of human carcinogens. IARC Monogr Eval Carcinog Risks Hum. 2012;100(Pt B):1–441.
10. Park JY, Forman D, Waskito LA, et al. Epidemiology of Helicobacter pylori and CagA-positive infections and global variations in gastric cancer. Toxins (Basel). 2018;10(4):163. https://doi.org/10.3390/toxins10040163.
11. Kumar S, Metz DC, Ellenberg S, et al. Risk factors and incidence of gastric cancer after detection of Helicobacter pylori infection: a large cohort study. Gastroenterology. 2020;158(3):527–536.e7.
12. Tan MC, Graham DY. Gastric cancer risk stratification and surveillance after Helicobacter pylori eradication: 2020. Gastrointest Endosc. 2019;90(3):457–60.
13. Ferro A, Rosato V, Rota M, et al. Meat intake and risk of gastric cancer in the Stomach cancer Pooling (StoP) project. Int J Cancer. 2020;147(1):45–55.
14. Bertuccio P, Alicandro G, Rota M, et al. Citrus fruit intake and gastric cancer: the Stomach cancer Pooling (StoP) project consortium. Int J Cancer. 2019;144(12):2936–44.
15. Tatematsu M, Takahashi M, Fukushima S, et al. Effects in rats of sodium chloride on experimental gastric cancers induced by N-methyl-N-nitro-N-nitrosoguanidine or 4-nitroquinoline-1-oxide. J Natl Cancer Inst. 1975;55(1):101–6.
16. Fox JG, Dangler CA, Taylor NS, et al. High-salt diet induces gastric epithelial hyperplasia and parietal cell loss, and enhances Helicobacter pylori colonization in C57BL/6 mice. Cancer Res. 1999;59(19):4823–8.
17. Rousseau EJ, Davison AJ, Dunn B. Protection by beta-carotene and related compounds against oxygen-mediated cytotoxicity and genotoxicity: implications for carcinogenesis and anticarcinogenesis. Free Radic Biol Med. 1992;13(4):407–33.
18. Vitelli-Storelli F, Rossi M, Pelucchi C, et al. Polyphenol intake and gastric cancer risk: findings from the Stomach cancer Pooling project (StoP). Cancers (Basel). 2020;12(10):3064. https://doi.org/10.3390/cancers12103064.
19. Yang P, Zhou Y, Chen B, et al. Overweight, obesity and gastric cancer risk: results from a meta-analysis of cohort studies. Eur J Cancer. 2009;45(16):2867–73.
20. Rota M, Alicandro G, Pelucchi C, et al. Education and gastric cancer risk – an individual participant data meta-analysis in the StoP project consortium. Int J Cancer. 2020;146(3):671–81. Erratum in: Int J Cancer. 2020;146(11):E6.
21. Choi YJ, Lee DH, Han KD, et al. The relationship between drinking alcohol and esophageal, gastric or colorectal cancer: a nationwide population-based cohort study of South Korea. PLoS One. 2017;12(10):e0185778. https://doi.org/10.1371/journal.pone.0185778. Erratum in: PLoS One. 2018;13(5):e0197765.
22. Rota M, Pelucchi C, Bertuccio P, et al. Alcohol consumption and gastric cancer risk – a pooled analysis within the StoP project consortium. Int J Cancer. 2017;141(10):1950–62. Erratum in: Int J Cancer. 2018;143(8):E10.
23. Center for Disease Control and Prevention. Lung cancer. What are the risk factors? https://www.cdc.gov/cancer/lung/basic_info/risk_factors.htm. Accessed 20 Feb 2021.
24. Ladeiras-Lopes R, Pereira AK, Nogueira A, et al. Smoking and gastric cancer: systematic review and meta-analysis of cohort studies. Cancer Causes Control. 2008;19(7):689–701.
25. Praud D, Rota M, Pelucchi C, et al. Cigarette smoking and gastric cancer in the Stomach cancer Pooling (StoP) project. Eur J Cancer Prev. 2018;27(2):124–33.
26. Pasechnikov V, Chukov S, Fedorov E, et al. Gastric cancer: prevention, screening and early diagnosis. World J Gastroenterol. 2014;20(38):13842–62.

27. Eusebi LH, Telese A, Marasco G, et al. Gastric cancer prevention strategies: a global perspective. J Gastroenterol Hepatol. 2020;35(9):1495–502.
28. Huang XZ, Chen Y, Wu J, et al. Aspirin and non-steroidal anti-inflammatory drugs use reduce gastric cancer risk: a dose-response meta-analysis. Oncotarget. 2017;8(3):4781–95.
29. Singh PP, Singh S. Statins are associated with reduced risk of gastric cancer: a systematic review and meta-analysis. Ann Oncol. 2013;24(7):1721–30.
30. Ford AC, Yuan Y, Moayyedi P. Helicobacter pylori eradication therapy to prevent gastric cancer: systematic review and meta-analysis. Gut. 2020;69(12):2113–21.
31. Liou JM, Malfertheiner P, Lee YC, et al. Screening and eradication of Helicobacter pylori for gastric cancer prevention: the Taipei global consensus. Gut. 2020;69(12):2093–112.
32. Institute of Medicine (US) and National Research Council (US) National Cancer Policy Board. In: Curry SJ, Byers T, Hewitt M, editors. Fulfilling the potential of cancer prevention and early detection. Washington, DC: National Academies Press; 2003.
33. Kato M, Asaka M. Recent development of gastric cancer prevention. Jpn J Clin Oncol. 2012;42(11):987–94.
34. Hamashima C, Systematic Review Group and Guideline Development Group for Gastric Cancer Screening Guidelines. Update version of the Japanese guidelines for gastric cancer screening. Jpn J Clin Oncol. 2018;48(7):673–83.
35. Choi IJ. Endoscopic gastric cancer screening and surveillance in high-risk groups. Clin Endosc. 2014;47(6):497–503.
36. Guideline Committee of the Korean Gastric Cancer Association (KGCA), Development Working Group & Review Panel. Korean Practice Guideline for Gastric Cancer 2018: an evidence-based, multi-disciplinary approach. J Gastric Cancer. 2019;19(1):1–48. Erratum in: J Gastric Cancer. 2019;19(3):372–3.
37. Lomba-Viana R, Dinis-Ribeiro M, Fonseca F, et al. Serum pepsinogen test for early detection of gastric cancer in a European country. Eur J Gastroenterol Hepatol. 2012;24(1):37–41.
38. Giorgi D, Giordano L, Ventura L, et al. Mammography screening in Italy: 2003–2004 survey. Epidemiol Prev. 2006;30(1 Suppl 3):7–16.
39. Quach DT, Hiyama T, Gotoda T. Identifying high-risk individuals for gastric cancer surveillance from western and eastern perspectives: lessons to learn and possibility to develop an integrated approach for daily practice. World J Gastroenterol. 2019;25(27):3546–62.
40. Rajula HSR, Verlato G, Manchia M, et al. Comparison of conventional statistical methods with machine learning in medicine: diagnosis, drug development, and treatment. Medicina (Kaunas). 2020;56(9):455. https://doi.org/10.3390/medicina56090455.