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How the fight against Stomach Cancer can be won: Decline in Incidence of Gastric Cancer in Europe: A Review of Epidemiologic Trends, Contributing Factors and Recent Treatment Standards

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Abstract

Gastric cancer (GC) incidence and mortality rates have notably declined across Europe, indicating that GC may become a rarer disease in the future. Between 1988 and 2012, GC incidence rates decreased by 33.2% in Europe overall, with significant declines observed in Central Europe (48.38%), Western Europe (49.28%), and Southern Europe (39.5%). Similarly, age-standardized rates of GC incidence and mortality have decreased by up to 48% and 54.4%, respectively, from 1990 to 2019 in various European regions. This decline is attributed to multifactorial causes including improvements in GC treatment, notably perioperative chemotherapy and chemoradiotherapy, and increased H. pylori eradication rates due to better sanitation and socioeconomic conditions. Additionally, dietary changes, reductions in salt intake, and effective tobacco control policies have contributed to the lower GC rates. Europe's progress in food production and preservation, along with these health policy efforts, combined with widely standardized and guideline-based H. pylori elimination strategies, reflects a comprehensive approach to mitigating GC risk.

Keywords: Gastric cancer; Incidence decline; Europe; Risk factors; Treatment.

Introduction

When looking at the map of prevalence and incidence of malignant tumors of the gastrointestinal tract it is noticeable that the incidence of some entities is increasing in absolute and relative terms, such as for pancreatic adenocarcinomas [1, 2], or that initial diagnoses are shifting to younger age groups, as is the case with colorectal malignancies [3]. The simultaneous decrease in the incidence of gastric cancer in many countries, as a contrary trend to rising life standards, better socio-economic conditions, food hygiene and enhanced health care is still a subject of intense discussion and speculation [4, 5]. The present paper attempts to explain this phenomenon and to provide an outlook on how GC could be marginalized through the interaction of prevention and therapeutic advances in a sensible manner. The authors are aware that the recommended measures and strategies are primarily aimed at countries with optimal conditions and a seamless pattern starting with effective prevention measures and leading to a timely application of effective therapies. Gastric cancer, ranking as the fifth most malignant cancer with approximately 1.1 million new cases annually worldwide and being the fourth leading cause of cancer deaths claiming around 800.000 lives according to GLOBOCAN 2020, poses as a significant health challenge in Europe and globally [6].

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Being a multifactorially caused disease associated with both environmental and genetic risk factors [7]. it is often diagnosed in advanced stages of the disease and its prevalence is more common in lower socioeconomic classes [8, 9]. With certain risk factors being non modifiable such as age, ethnicity, sex and genetics (4,5,8,10), other risk factors such as Helicobacter pylori infection, obesity, poor dietary choices, lifestyle, smoking and alcohol consumption [10-13] are accessible to external control measures and can influence GC pathogenesis and incidence [14]. Despite still having high probability of development in regions like Central and South America, Eastern Europe and East Asia [15], there has been steady decline in gastric cancer incidence and mortality rates since the middle of the 20th century in developed nations [16]. Due to advancements in prevention, screening and therapeutic strategies declining incidence rates can be seen in USA, as well as northern, middle and western Europe [6, 17]. The present review describes the epidemiology of gastric cancer in Europe, summarizes risk factors, prognostic factors and therapeutic strategies and focuses on contributing factors for the remarkable decline in incidence for gastric cancer in many, but by far not all European countries.

Epidemiology

Examining global trends in incidence and mortality of gastric cancer a large global variability in rates can be seen comparing regions [18]. The age-standardized incidence rate of gastric cancer ranges from 1- to 4-fold globally [19]. High numbers of gastric cancer diagnoses can be observed in nations with a high human development index [18] such as Central and South America, Eastern Europe and East Asia (China and Japan) [15]. The highest rates are found in East Asia, with an age-standardized incidence rate of 14.3/100.000 (19, 20). Taking a closer look at incidence and mortality in Europe, Eastern and Central European countries have the second highest gastric cancer rates after East Asia with an ASIR of 13.5/100,000 and age-standardized mortality rate of 10.9/100,000 respectively [21]. According to GLOBOCAN 2020 ASIR by sex was 17.4/100.000 in males and 7.1/100.000 in females for Central-Eastern Europe. In Southern Europe ASIR was 10.2/100.000 for men, as well as 5.0/100.000 for women respectively [6, 22]. The five European countries with the highest ASIR standardized to European Standard Population in 2013 according to European Cancer Information System were Albania (30.5/100.000), Estonia (29.8/100.000), Portugal (29.5/100.000), Latvia (25.9/100.000) and Lithuania (25.3/100.000). Age-standardized mortality rate was also highest in those countries with 23.4/100.000, 20.8/100.000, 20.3/100.000 and 20.0/100.000 respectively [23]. Western Europe and Northern Europe show intermediate to low rates of gastric cancer incidence with an ASIR of 6.2 and 8.2/100.000 for men and 3.2 and 3.8/100.000 for women respectively [6, 24]. According to the European Cancer Information System (ECIS) the five countries with the lowest ASIR in Europe were Sweden (8.2 /100.000), United Kingdom (8.9 /100.000), Finland and Iceland (9.4/100.000) and Montenegro (9.5/100.00). The five countries with the lowest ASMR were Iceland (4.8/100.000), Sweden (5.1/100.000), Belgium (6.1/100.000), United Kingdom (6.2/100.00) and Finland (6.3/100.000) [23].

Recent data researching global trends of GC incidence and mortality showed declining rates in most countries during the past several decades [14, 25-27]. All over Europe a reduction of incidence of 50.17% was observed, with declining incidence rates of 2.0 between 1988 and 2012 [28]. In Eastern Europe a decline in rates of 33.2%, in Central Europe 48.38%, in Western Europe 49.28% and in Southern Europe 39.5% was observed for both sexes over the entire period [28]. Data showed that the annual decrease in incidence was most pronounced in Italy (3.0%), the Netherlands (2.9%), Finland and the UK (both 2.8%) in men and in the Czech Republic (2.8%), Finland and Italy (both 2.7%), as well as Estonia (2.5%) among women [29]. Comparing incidence rates, incidence decreased from 26.7 per 100 000 in 1993 to 11.0 in 2007 for men and from 9.7 to 6.6 for women in Austria (Tyrol and Vorarlberg), from 16.1 in 1993 to 11.0 in 2007 for men and from 10.0 to 6.6 for women in Germany (Saarland), from 20.3 in 1993 to 12.1 in 2006 for men and from 7.3 to 6.4 for women in Poland (Kraków) and from 38.7 in 1994 to 27.1 in 2007 for men and from 17.9 to 12.9 for women in Russia (St Petersburg) [29]. Comparing cancer incidence and mortality trends from 2007 to 2016 on 41 128 patients diagnosed with gastric cancer from national registers of Belgium, the Netherlands and Northern Portugal, data showed a decrease in ASIR of 8.6 %, 4.5 %, and 46.8 % and a decrease in ASMR of 22.0 %, 30.9 %, and 50.0 %, respectively [30]. Data reflecting global, national and regional burden of stomach cancer from 1990 to 2019 showed a percentage change of -43% (49.3 to 36.2%) in GC incidence with a percentage change of -48.4% (-54.1 to -42.1%) in ASR per 100.000 for GC deaths for Central Europe, a percentage change of -48% (-52.9 to 42.4%) in GC incidence with a percentage change of -54.4% (− 58.6 to − 49.7) in ASR per 100.000 for GC deaths in Eastern Europe and a percentage change of − 41.5% (− 48.5 to − 34.2%) in GC incidence with a percentage change of − 52.9 % (− 54.7 to − 51.1%) for GC deaths in Western Europe.(31). Looking at DALYs (disability adjusted life years), a percentage change in ASRs per 100.000 of − 49.4% (− 55.6 to − 43.2%) in Eastern Europe, − 56.2% (− 60.6 to − 51.6%) in Western Europe and -54.3 % (− 56 to − 52.7%) in Western Europe could be observed [31]. Trends for European countries, where the GC incidence rates are historically low like Austria, Bulgaria, Croatia, Cyprus, the Czech Republic, Denmark, Estonia, France, Germany, Iceland, and Ireland, predict a maintaining incidence rate of <10 per 10.000 for 2030 [28].

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Prognosis

Tumor related prognostic factors

Using predictive tools for long-term prognosis in GC patients, the latest 8th edition of the TNM/UICC staging system is the current standard for solid tumor staging [32]. Studies have proved a decreased overall survival rate associated with a higher tumor stage, with 5-year survival rate being 50.8% and 59.3% for stage IIA, 35.3–46.4% for stage IIB and 20.5–30.5% for stage IIIA, 13.5-20.5% for stage IIIB, 5.3- 8.3 for stage IIIC and 5.9% for stage IV respectively [33, 34]. Based on the Lauren classification [35], gastric cancer is categorized into intestinal and diffuse types, with diffuse gastric cancer typically associated with a worse prognosis in comparison to the intestinal-type gastric cancer type with a five-year survival of 3-10% in several studies [36-38]. Data shows improvement in prognosis for patients with diffuse type gastric cancer only through a complete surgical resection. If peritoneal carcinomatosis or a positive lavage cytology is detected, a radical resection does not provide any survival advantage [39]. Due to conflicting data, the prognostic role of signet cell carcinomas, which are defined as carcinomas consisting of more than 90% poorly cohesive cells [40], is not fully clarified [41]. Although some authors suggest a correlation between SRC and unfavorable prognosis due to infiltrating tumors along with a potentially higher affinity for lymphatic tissue, which may lead to higher rates of peritoneal carcinomatosis [42]. A more recent meta-analysis has shown that prognostic significance varies according to the stage of the disease, showing a favorable impact in early stages but an adverse one in advanced tumor stages [40, 43-45].

Patient related prognostic factors

Among patient-related prognostic factors, ethnicity plays a significant role in long-term GC prognosis [46]. Cohort studies comparing overall survival between Western and Eastern countries in patients with resectable GC have found significant survival differences [47-49]. A paper by Yamada et al. comparing survival difference between patients from UK and Japan using weighted propensity score analysis based on patients' characteristics like age, gender, tumor location, extent of surgery, TNM-staging etc. detected a significant difference in overall survival between the two countries. In Japan, the 5-year overall survival stood at 69%, significantly higher than OS (52.2%) observed in the UK. Similarly, the 5-year survival rates specifically related to cancer were notably higher in Japan, with a rate of 75.3%, compared to 64.9% in the UK. In the Japanese study group, individuals aged over 65 years and those with stage pT4 and pN2-3 were found to have an independent association with long-term mortality. Conversely, within the UK cohort, factors such as tumor localization throughout the entire stomach, simultaneous pancreatectomy, R1 resection, and the collection of fewer than 15 lymph nodes collected during dissections were identified as additional predictors of a poor prognosis [46, 50]. Wang et al compared survival between Asian and Caucasian patients treated in the United States, showing a 12% higher 5-year survival of the Asian patients in comparison to Caucasian patients with a median survival time that was 37, 72, and 13 months longer for IB, IIA, and IIB disease [51]. The prognostic impact of age in gastric cancer has sparked a global debate. While some studies downplay age as a prognostic factor [52], other argue, that older patients tend to have a worse prognosis than younger patients, due to being diagnosed at more advanced stages of the disease and having a lower likelihood of undergoing curative resection [53, 54]. However, despite recent regional data indicating a decrease in gastric cancer deaths across all age groups since 2013, the number of people dying at age 80 and older is still increasing. The mortality rate from gastric cancer among individuals in their 80s was twice as high as that of those in their 70s and four times higher than that of those in their 60s [55]. A number of studies have revealed noticeable differences in different treatment options and their associated side effects between male and female patients with gastric and esophagogastric cancer undergoing curative treatment [56]. Kalff et al. proved that female patients had better postoperative outcomes, but a significantly lower 5-year relative survival compared to males for unknown reasons. (49% vs 56%) [57].

Therapy Options

Surgical Treatment

Being the only procedure that completely eradicates GC [58, 59], resection offers the best opportunity for extended survival among individuals with localized disease [60, 61]. Surgical strategies include subtotal and total gastrectomy depending on tumor localization and tumor depth [62]. For proximal gastric cancer total gastrectomy continues to be the preferred treatment option, although proximal gastrectomy may be appropriate for certain patients and provide nutritional benefits [63]. Data comparing both approaches showed proximal subtotal gastrectomy has similar five-year survival (61 vs. 64%) but more recurrences (39 vs 24%), as well as a higher percentage of surgery related complications including anastomotic stenosis (27 vs. 7%) and reflux esophagitis (20 vs. 2%). For gastric cancer of the middle or lower third of the stomach the choice of optimal resection extent is still up for debate [64]. While some studies advocate for total gastrectomy as the preferred procedure due to potential long-term survival benefits and reduced risk of gastric remnant cancer [65, 66], others suggest that distal gastrectomy may offer superior outcomes in terms of intraoperative results, short-term recovery, and quality of life considerations [67, 68]. A meta-analysis by Li et al. published in 2018 showed no significant differences between the two approaches in rates of recurrence and cancer–related death, with the distal

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gastrectomy group having a slightly better 5-year overall survival without significant differences in stage-specific analysis respectfully [64]. Regional European guidelines state that for distal tumors, preservation of the proximal stomach can be achieved without compromising prognosis, with a sufficient resection margin of 5cm for intestinal type and 8cm for diffuse type GC according to Lauren classification [69].

Due to its superior 5-year-survival rate D2 lymph node dissection is the recommended surgical procedure as compared to D1 dissection [70]. Guidelines published by the National Comprehensive Cancer Network advise that surgical resection of GC should include regional lymph nodes, comprising perigastric nodes (D1) along with those situated around the left gastric artery, common hepatic artery, celiac artery, splenic hilum, and splenic artery (D2 lymph nodes), with the objective of evaluating at least 15 lymph nodes in total [71].

Chemotherapy

Due to most patients presenting with advanced stages at diagnosis, such as clinical T2N0 or higher a multimodal therapy concept including perioperative chemotherapy improves survival of operable GC patients [72]. Due to survival benefits over upfront surgery, neoadjuvant chemotherapy is recommended in current therapy guidelines [73]. The advantage in outcome for this regimen has been shown in several trials comparing surgery alone or together with perioperative chemotherapy, with the largest being the MAGIC trial [74-76]. The trial including 503 patients with potentially resectable gastric, distal esophageal and esophagogastric cancer showed significantly higher overall survival rates (HR for death 0.75, five-years survival 36 vs 23%) with perioperative chemotherapy compared to surgery alone [76]. A metanalysis by Cheng et al. showed that patients with advanced gastric cancer receiving perioperative chemotherapy had significantly improved OS (OR 1.32), progression free survival (OR 1.85), tumor down-staging rates (OR 1.71) and R0 resection rate (OR 1.38) [77]. Several trials have shown additional efficiency for including chemotherapy after surgical resection [76, 78-80], with variability in chemotherapy regimens regionally. The PRODIGY trial, consisting of 266 patients receiving neoadjuvant DOS (Docetaxel, Oxaliplatin) and S-1, which contains tegafur and two types of enzyme inhibitor 5-chloro-2,4-dihydroxypyridine and potassium oxonate in ratio of 1: 0.4:1 [81], before D2 surgery (CSC) and 264 patients receiving D2 surgery followed by adjuvant S-1 (SC), found higher PFS (HR 0.7) for CSC patients demonstrating the superiority of neoadjuvant versus adjuvant chemotherapy for resectable gastric cancer [82].

When comparing neoadjuvant triple chemotherapy options, reports confirmed survival benefits for docetaxel-based triplet like FLOT (docetaxel, oxaliplatin, leucovorin and short-term FU) over epirubicin-containing regimens such as ECF (epirubicin, cisplatin, FU) and ECX (epirubicin, cisplatin capecitabine) as used in the MAGIC trial [83]. Despite data showing significantly higher median overall survival [83, 84], patients receiving FLOT, also reached significantly higher portions of pathological complete regression in comparison to ECF/ECX [85]. For patients not receiving perioperative chemotherapy, the optimal adjuvant chemotherapy regimen is not yet established. The CLASSIC study, comparing adjuvant capecitabine and oxaliplatin (CAPOX) versus surgery alone after D2 gastrectomy showed significant higher 3-year DFS (74 vs. 59%) in the CAPOX group, making it a considerable treatment option for patients with resectable gastric cancer [86]. A randomized controlled trial comparing leucovorin, 5-fluorouracil either alone or with oxaliplatin (FOLFOX4 vs LV5Fu2) showed significantly better 3-year recurrence free survival rates and 3-year OS rates in FOLFOX4 group compared to the control group (median, 30.0 months vs. 16.0 months, 36.0 months vs. 28.0 months) offering effective treatment outcomes and a favorable safety profile for patients diagnosed with advanced gastric adenocarcinoma [87].

Chemoradiotherapy

Due to a lack of randomized controlled trials the use of neoadjuvant chemoradiotherapy for resectable non-cardia gastric cancer is less validated [88]. Data from mostly uncontrolled studies showed NCHRT mediated R0 resection rates and pathologic complete response rates of 70-80% and 20-25%, respectively [89-91]. A recent randomized controlled trial found that patients receiving neoadjuvant chemoradiotherapy with postoperative adjuvant XELOX (capecitabine, oxaliplatin) chemotherapy had higher R0 resection rates (84.6 vs 56.7%) and lower loco-regional recurrence rates (36.7 vs. 11.5%) with prolonged PFS in comparison to patients receiving adjuvant XELOX Chemotherapy alone. However, 1-year, 2-year and 3-year PFS and OS did not differ between the subgroups [92]. Another study by Martin-Romano et al. also showed that chemoradiotherapy led to locoregional benefits, with NCHRT patients with initial lymph node metastasis showing a higher likelihood for a better local response (Becker Ia-b response, 58 vs. 32%), together with a higher percentage of grade D nodal regression (30 vs 6%) and a favorable pathological response (23% vs. 3%). Still, there was no difference in survival between the subgroups [93]. Two large RCTs directly comparing preoperative chemotherapy alone with chemoradiotherapy (TOPGEAR and CRITICS-II) are currently ongoing [94].

Targeted Therapies

Molecular targeted therapies using specific molecules to block cancer growth, progression and metastasis, have shown remarkable clinical success in the treatment of various

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cancer types. Better understanding of molecular mechanisms in the emergence and progression of gastric cancer has allowed some considerable advances in patient care over the years [46, 95]. For cancer entities showing overexpression or amplification of HER-2 in 7-34% of tumors [96, 97], an anti-HER2 targeting strategy with the monoclonal antibody trastuzumab was proposed as a therapy option. The ToGA trial showed that patients with HER-2 overexpression who underwent therapy with trastuzumab plus chemotherapy resulted in higher OS (13.8 vs 11 months) in that treatment group compared to patients receiving chemotherapy alone. Although the absolute survival change appeared clinically minor, it is important to note, that this cohort consisted of metastatic patients with limited treatment options [46].

Recent data show good results and prolonged survival for using immunotherapy for patients with advanced GC [98-100]. A post-hoc analysis of three randomized controlled trials showed a remarkable 2-year OS rate of 24% when standard chemotherapy was combined with anti PD-1 agent pembrolizumab with an increase of 65% in patients with microsatellite instable tumors. Next to immune checkpoint inhibitors other immunotherapeutic options for GC, like cellular immunotherapy [101-103] and cancer vaccines [104, 105] could be promising therapy options in the future, although the patient groups that will benefit from these therapies must first be identified and defined.

Reasons for the Decline in Incidence of Gastric Cancer in Europe

Based on the factors so far that are responsible for carcinogenesis of GC the following prevention strategies emerge:

Decline of Helicobacter pylori- Infection

Being classified as a group 1 carcinogen by the IARC [106], helicobacter pylori is a confirmed major risk factor for gastric cancer development and may be related to approximately 90% of non-cardia GC cases [14, 107, 108]. H. pylori is a gram-negative microaerophilic bacterium that infects the epithelial cells of the stomach lining [109,110]. The mechanism involves damage to epithelial cell DNA combined with downregulation of repair processes, mitochondrial DNA mutations and the simultanous emerge of a transient mutator phenotype [111], impairing gastric cancer microenvironment, promoting epithelial-mesenchymal transition and therefore further GC progression [112, 113]. Reducing the prevalence of H. pylori is crucial for the prevention of gastric cancer [22, 114]. In populations with high infection rates, stomach cancer remains a major public health issue, even with other interventions in place [25, 115, 116]. Recent epidemiological reviews indicate a steady reduction of the prevalence of H. pylori [114, 117-120], correlating with the recent decrease of incidence of stomach cancer [121]. A meta-analysis by Chen et al from 2024 comparing prevalence of Helicobacter pylori infection and incidence of GC between 1980 and 2022 from 111 countries showed global prevalence of H. pylori has reduced from 52.6% before 1990 to 43.9% in adults during 2015 to 2022. It also showed global prevalence of H. pylori has declined by 15.9% in the last three decades in adults, with a significantly reduction of prevalence in European regions of 14% [122]. A systematic review by Venneman et al in 2018 found Northern Europe had the lowest infection rates, whereas Eastern and Southern Europe had the highest, with prevalence reaching up to 84% in Portugal and Poland [123].

Reasons for significant reduction rates of the prevalence of H. pylori infection can be explained by a higher index-ranking, due to the fact, that infections rates are higher in regions with lower Human Development Index ranking than with very high standards [122]. Furthermore, since the 1950s, better sanitation has significantly decreased the transmission of the bacterium within families among younger generations in high-income and upper-middle-income countries [108]. Reports show that almost every household in the EU owns basic sanitary facilities in 2020, and most countries reported less than 1% of their population were still living in households without a bath, shower or flushing toilette. Therefore, connection to secondary wastewater treatment has increased up to 80.9% in the EU in 2021 in comparison to 72.6% in 2006. The biochemical oxygen demand, measurement for organic water pollution, declined from 3.1 mg/L in 2006 to 2.8 mg/L in 2021 [124]. Eradication of H. pylori is proven in numerous trials to lower the likelyhood of developing gastric cancer, especially in patients at risk [125-127]. A metanalysis by Lee et al showed patients after eradication of H. pylori had a lower incidence of GC compared to those without eradication therapy (pooled incidence rate ratio 0.53). The reduction applied especially for patients in the intermediate and higher tertile of GC incidence [128]. Another RCT by Yan et al in 2022 showed that patients receiving H. pylori treatment had a lower incidence of GC in comparison to patients in the placebo arm (HR 0,57), including a greater risk reduction among patients without premalignant gastric lesions or dyspepsia symptoms at baseline (HR 0.46) [129]. Data from the European registry on H. pylori management indicate that the use of triple therapy declined from over 50% of prescriptions between 2013 and 2015 to less than 32% between 2017 and 2018. Meanwhile, the use of quadruple therapy increased from 2013 to 2018. Despite this shift, standard triple therapy remained the most popular first-line treatment. The study also reported an improvement in first-line H. pylori eradication success rates, rising from 74% to 88%. Overall, the eradication rate of H. pylori in Europe increased from 83.9% to 87.8% during this period [130, 131].

Dietary related factors

With diet being a potentially modifiable risk factor for GC, the World Cancer Research Fund and the American

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Institute for Cancer Research stated, that broiled and charbroiled animal meats, salt-preserved foods and smoked foods probably enhance GC progression [132]. Processed smoked and salted meat is classified as a general carcinogen, and the consumption of red meat is linked to the development of non-cardia gastric cancer [133]. Data shows significantly increased risk of GC with an OR of 1.24 for red meat, 1.23 for processed meat and 1.3 for total meat, which is attributed to its carcinogen compounds such as heme- iron and N-nitroso compounds, which promote the development of DNA adducts being risks factors for carcinogenesis [134]. Furthermore, high dietary salt is also an important risk factor for GC development with studies suggesting a significant increase in gastric cancer incidence with greater than 10 g of salt intake per day [135]. Cohort studies strongly support a correlation between increased dietary intake of high-salt foods, such as miso soup, pickled vegetables, dried fish, and salted fish, and a higher incidence of gastric cancer [136].

Despite H. pylori eradication is recognized and proven to be a major factor for decline of gastric cancer incidence in Europe among other, environmental factors, environmental conditions, diet related factors (beyond meat and salt consumption) play also an important role for recent changes [137]. Reduction in incidence and prevalence is mainly associated to preferred regions, where diets rich in fruits, vegetables, fish and whole grains is preferred over processed meats, refined grains and high fat products [138]. Throughout the nineteenth and early twentieth centuries, Europe saw substantial improvements in how food was produced, processed, preserved, and transported. These advancements led to a notable decline in H. pylori infections by the latter half of the twentieth century, along with the year-round availability of fresh fruits and vegetables [137]. This was illustrated in a study by Jarosz et al showing that vitamin C intake grew from approximately 100mg per day in 1960 to 124 mg per day in 2006 in Poland. In accordance, a negative correlation was found between vegetables (-0.7), fruit (-0.65) and vitamin C consumption with stomach cancer incidence rates [139]. Other important diet related factors include improvements in food preservation switching from smoking and salting to refrigerators [136, 140]. Refrigerators symbolize the shift in food preservation methods, encouraging the consumption of fresher, more diverse diets with less salt. They promote eating seasonal vegetables and fruits by at the same minimizing microbial and fungal contamination, reducing the reliance on salted, pickled, and smoked foods. Additionally, refrigeration helps maintain higher levels of vitamins and antioxidants, which protect against exposure to nitrosamin compounds and other carcinogens [141-144]. Several studies show nitrosamine compounds like N-nitrosodimethylamine consumption to be a major risk factor for gastric cancer (145-147). A systematic review by Jakszyn et al analyzed the relationship between diets consisting of nitrosamine and nitrite (meat and processed meat, preserved vegetables and fish, smoked foods and beer drinking) and gastric cancer risk and found a significant positive association [145].

Relationship between salt intake and virulence of H. pylori

As already stated, high dietary salt is an important risk factor for GC development with studies suggesting a significant increase in gastric cancer incidence associated with a greater than 10 g salt intake per day. (135) Cohort studies have also supported a correlation between increased dietary intake of high-salt foods, such as miso soup, pickled vegetables, dried and salted fish and a higher incidence of gastric cancer [136]. It is theorized that glandular mucus contains glycans that inhibit the production of glycolipids in the cell wall of H. pylori. A diet rich in salt is believed to boost the production of mucus from superficial mucus cells and reduce the mucus from glandular mucus cells [148, 149]. Despite RCT lacking in that area, there is data indicating significant association between salt intake and higher mortality rates for GC [150, 151], as well as a modulating effect on the virulence potential of H. pylori, making its infection more likely and more severe [152-154]. The World Health Organization aims to decrease daily salt intake for a variety of medical reasons to under 5 grams (2000 mg of sodium) per person by 2025 [155]. A systematic review by Kwong et al in 2022 showed mean population salt intake in the WHO European Region is well above the recommended level in fifty-two out of fifty-three member states, with forty-six countries having an average population intake of 7.5g/d exceeding the recommended level by 50% and twenty-three countries having a population intake of 10g/d, which is two times as high as the recommended level [156]. According to a 2017 report by the WHO Regional Office for Europe, 47% of European countries have fully implemented national salt reduction policies, including measures such as taxes on high-salt foods (Hungary), mandatory high-salt content labels (Finland, Israel), and targets for food reformulation and monitoring (Spain, UK). Evaluations show that these strategies can significantly reduce salt intake. For example, the UK's comprehensive strategy led to a 15% reduction in salt intake from 2003 to 2011, and Finland saw a 25-30% reduction from 1979 to 2007 [157].

Tobacco smoking and drinking

Smoking and alcohol consumption are also proven to be major risk factors contributing to GC development [158-160]. Studies show a risk of developing gastric cancer correlating with cigarette use of less than 30 years, 30–39, and greater than 40 years with a hazard ratio of 1.31, 1.58 and 2.36, respectively [161]. Data also show tobacco use is associated with 43% increase in disease recurrence and death from gastric cancer [162]. According to Eurostat 2020 the percentage of daily smokers in the European Union is 19.3%

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for both sexes, with the highest total amounts in Bulgaria (29.1%), Greece and Hungary (24.9%), Germany (22.9%) and Latvia (22.6%). Countries with the lowest percentages are Sweden (7.4%), Finland (10.7%), Luxembourg (11.4%) and Denmark (12.9%) [163]. Taking a look at the prevalence of smoking among people aged 15 and older it decreased from 29% in 2010 to 22.5% in 2020 [163-165]. An ecological study by Feliu et al in 2019 showed prevalence of smokers in 27 EU member states decreased by 13.9% from 2006 to 2014 with a quit ratio of 44.2% [166]. The recent decrease in smoking rates in Europe is primarily due to the aggressive tobacco control policies enforced throughout the continent [166, 167]. Those policies include implementing the WHO 'Framework Convention' on Tobacco Control highlighting essential evidence-based policies to combat the tobacco epidemic [168], as well as mandating additional control measures like warning labels on cigarette products, as suggested by the EU Tobacco Products Directive [169]. The WHO states that most countries in the European region perform well in tracking tobacco use, prohibiting tobacco advertising, enforcing health warnings about tobacco dangers, taxing tobacco products, and providing support for smoking cessation. This makes Europe the region with the highest adherence to the 'WHO's MPOWER' guidelines [167, 170]. In 2006 Jossens and Raw developed the Tobacco Control Scale to monitor the implementation of tobacco control policies in Europe [171]. Comparing scores in 2007, Austria had the lowest score while the UK had the highest among all member states. Data showed a moderate inverse association between TCS and the prevalence of smokers in 2014, with a direct moderate association between TCS scores and the relative change in prevalence in 27 EU member states from 2006 to 2014 [166].

Summary

Incidence and mortality rates of GC have shown a downward trend in Europe, which suggests that GC will be a rare disease in the future and will provide steady declines. Reduction in gastric cancer rates across all stages of the disease has seen a decline of incidence of 50.17% in Europe, with a decline in incidence of 33.2% in Eastern Europe, 48.38% in Central Europe, 49.28% in Western Europe and 39.5% in Southern Europe for both sexes between 1988 and 2012. Furthermore, data showed declines in GC incidence in ASR per 100.000 of 43% in Central Europe, 48% in Eastern Europe and 41.1% in Western Europe, as well as declines in GC deaths in ASR per 100.000 of 48.4% in Central Europe, 54.4% in Eastern Europe and 52.9% in Western Europe between 1990 and 2019. Reasons for the reduction in both incidence and mortality rates are multifactorial. Reasons for decline in mortality are mostly attributed to improvements in GC therapy, with RCTs showing benefit in survival including perioperative chemotherapy and chemoradiotherapy, while the claim to even more effective therapy regimes is still a matter of ongoing research. Decline in incidence can be attributed to reduction of prevalence in Helicobacter pylori infections, linked to improvements in socioeconomic conditions and sanitation, as well as improved eradication rates especially in high-risk populations and more successful treatment strategies. In addition, changes in public health issues also contributed to the declining numbers of gastric cancer incidence, like dietary related factors, limitation of salt intake and tobacco consumption. Europe has seen significant improvements in production, processing, preservation and transport of food, leading to more versatile diets containing fruits, vegetables, fish and whole grains. Improvements in food preservation, such as the shift from smoking and salting to refrigeration, have led to reducing reliance on preserved foods and to lowering exposure to carcinogens like nitrosamines. Studies show that nitrosamines, found in processed meats and preserved foods, are linked to an increased risk of gastric cancer. Although randomized controlled trials are lacking, evidence links high salt intake to higher gastric cancer mortality and increased H. pylori virulence. The WHO aims to reduce daily salt intake to below 5 grams per person by 2025, but many European countries still exceed this limit. On the other hand, successful strategies implemented by the EU through national salt reduction policies in countries like the UK and Finland led to significant reductions in salt consumption. The recent decline in smoking rates across Europe is largely attributed to strict tobacco control policies, including the WHO Framework Convention on Tobacco Control and EU directives on warning labels. Europe excels in adhering to these guidelines, with the Tobacco Control Scale showing varying effectiveness among countries, indicating a moderate link between higher tobacco control scores and lower smoking prevalence. Taxes resulting in higher prices and the offer of replacement products free from smoke ingredients contribute to this first success.

Conclusion

This review examines the causes for regional disparities and trends in incidence and mortality of gastric cancer in Europe as well as for assessed risk factors and prognostic factors for gastric cancer and represents effective treatment options and most promising prevention strategies. Data showed significant declines in gastric cancer rates in the last decades. This encouraging development can be attributed to decline in H. pylori prevalence, correlating with improved sanitation, better socioeconomic conditions, and enhanced treatment regimens, including still increasing eradication rates. Overall, while H. pylori eradication has notably reduced gastric cancer risk, ongoing attention to both -infection control and public health issues like diet, salt intake and tobacco consumption- is essential for further progress. At the same time improved

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technology and wider availability of diagnostics, particularly gastroscopy with biopsies of all kinds of suspect lesions, can contribute to early detection of gastric cancer in curable stages. Epidemiological data support the practical recommendations that can be derived from the stated facts on origin, pathogenesis and risk factors for gastric cancer.

Nonetheless the crucial fact is that carcinomas of the stomach still have a high lethality rate in advanced stages. However, compared to a large number of solid tumors, the incidence of gastric cancer has been falling in almost the entire world in recent years. The reasons for this phenomenon are largely known and can become starting points for effective prevention strategies rolled out by local or national authorities and health care providers. Early detection of early cancers, together with the steadily increasing advances in surgery, oncological treatments using a classical chemotherapy backbone and combining it with targeted treatment tools, could take gastric cancer off the map of problematic oncological disease entities in the near future. Unfortunately, this vision only applies to countries with high standards in socio-economic terms, comprehensive medical facilities and well imbursed health care budgets. Despite the remarkable progress not all questions have been satisfactorily answered further trials are necessary to solve the unresolved problems in prevention and to bring the most suitable therapies into widespread use.

Before these goals are achieved the battle against stomach cancer- as long as curative options against metastatic disease stages are not available- can only be won through prevention.

Abbreventions

ASIR	age-standardized incidence rate
ASMR	age-standardized mortality rate
CAPOX	capecitabine, oxaliplatin
CLASSIC	apecitabine and oxaliplatin adjuvant study in stomach cancer
DALY	disability adjusted life years
DFS	disease free survival
DNA	deoxyribonucleic acid
DOS	Docetaxel, Oxaliplatin
ECF	epirubicin, cisplatin, FU
ECX	epirubicin, cisplatin capecitabine
EU	European Union
FLOT	docetaxel, oxaliplatin, leucovorin and short-term FU
FOLFOX	leucovorin, FU, oxaliplatin
FU	5-fluorouracil
GC	gastric cancer
GI-Tract	gastrointestinal tract
GLOBOCAN	Global Cancer Statistics
H. pylori	Helicobater pylori
HDI	Human Development Index
HDI	human development index
HER2	human epidermal growth factor
HR	hazard ratio
IARC	International Agency for Research on Cancer
LV5Fu2	aflibercep, FU, folinic acid
MAGIC	United Kingdom Medical Research Council Adjuvant Gastric Infusional Chemotherapy
NCHRT	neoadjuvant chemoradiotherapy
OR	odds ratio
OS	overall survival
p	pathological staging
PCR	pathological complete response
PD-1	programmed cell death protein 1
R	resection status
RCT	randomized controlled trial
SRC	signet cell carcinomas
TCS	Tobacco Control Scale
TNM	tumor, nodes, metastasis
ToGA	Trastuzumab for Gastric Cancer
UICC	Union for International Cancer Control
UK	United Kingdom
USA	United States of America
WHO	World Health organization
XELOX	capecitabine, oxaliplatin

Conflict of interest

There was no conflict of interest.

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