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Review Article

Gastric Cancer in Iran: An Overview of Risk Factors and Preventive Measures

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Abstract

Despite all recent treatment advances and the worldwide decline in the incidence rate, gastric cancer (GC) remains an ongoing global health challenge and one of the major leading causes of cancer-specific deaths, particularly in high-incidence regions including Iran. Since GC is often diagnosed in advanced stages, the best action may be to enable early diagnosis of the disease or even prevent it in the first place through identification and control of the underlying risk factors. Endoscopy, as the gold standard method, is both expensive and invasive, making it an unfavorable device in this regard. Therefore, it is crucial to implement a reliable region-specific screening and surveillance program to identify high-risk individuals with more efficient screening modalities. Here, in addition to a review of current GC knowledge, we presented the data of newly-established Population-based Cancer Registries (PBCRs) in Iran. Our assessment confirmed earlier reports of a very high GC incidence rate in the northwestern and northern provinces of Iran, most notably Ardabil. Along with the important role of conventional risk factors such as *Helicobacter pylori* (HP) infection and high dietary intake of salt, of more interest, we highlighted new region-specific risk factors, namely hookah, and opium. In conclusion, it seems the best results in reducing GC incidence and mortality rates on larger scales arise from modifying behavioral and environmental risk factors and advancing genetic and molecular biomarkers in order to supersede endoscopy. Regular endoscopic screening and antibiotic chemoprophylaxis against HP are still more appropriate in high-risk groups with specified criteria.

Keywords: Epidemiology, Iran, Risk factor, Screening, Stomach cancer

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Introduction

Gastric cancer (GC) is the fifth most frequently diagnosed cancer and the third leading cause of cancer-specific mortality worldwide.[1] Currently, 18.08 million new cases of cancer are reported globally each year; of these, about 1.03 million (5.7%) are GC. Also, GC is responsible for about 783 000 (8.2%) out of 9.56 million cancer-related deaths across the world every year.[2] However, there exists a remarkable diversity in the geographical distribution of GC incidence and mortality rates across populations (Figure 1).[2] With 75% of all new cases and deaths of GC, Asia is considered a high-incidence area. Despite the downward trend in the incidence and mortality rates of GC over the past decades (Figure 2),[3-8] not only is it still among the top leading causes of cancer-related deaths, but will also maintain its position in the coming years.[9]

Since GC is either asymptomatic or may present with mild non-specific gastrointestinal symptoms in its early stages, it is often diagnosed in advanced stages and consequently, no therapeutic or survival benefit is acquired from conventional surgery or chemo/radiotherapy.[10] Unfortunately, this leads to a poor prognosis for this disease.[11] For example, numerous studies have shown that more than 80% of Iranian GC patients have been diagnosed in advanced stages of disease (predominantly stage IV) and their 5-year survival rates remain no better than 29.7% (ranging from 0.8% to 29.7%),[12-14] even those treated with surgery.[15,16] Therefore, it is essential to implement an efficient screening and surveillance program to detect GC in its early stages or even to prevent it from happening at the very beginning through identification and control of modifiable risk factors.[17,18] PBCRs are powerful tools to provide the required data in this context.

In this review, we focus on the current epidemiological aspects of GC in Iran, the attributed region-specific risk factors, as well as screening modalities and preventive measures.

Development of Population-Based Cancer Registries in Iran

Over the past few decades, the tremendous socioeconomic transition in developing countries has resulted in a large epidemiological data gap. In order to achieve reliable nationwide epidemiological data, establishing cancer registries is the first essential step to take.[19,20]

In 1955, Tehran University of Medical Sciences (TUMS)

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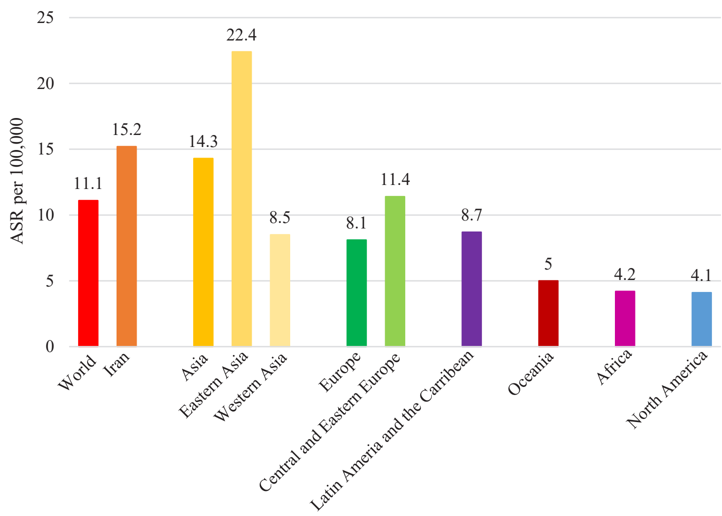

Figure 1. Worldwide Geographical Variation in The Age-Standardized Incidence Rate (ASR) of Gastric Cancer, Reproduced from the International Agency for Research on Cancer (IARC).

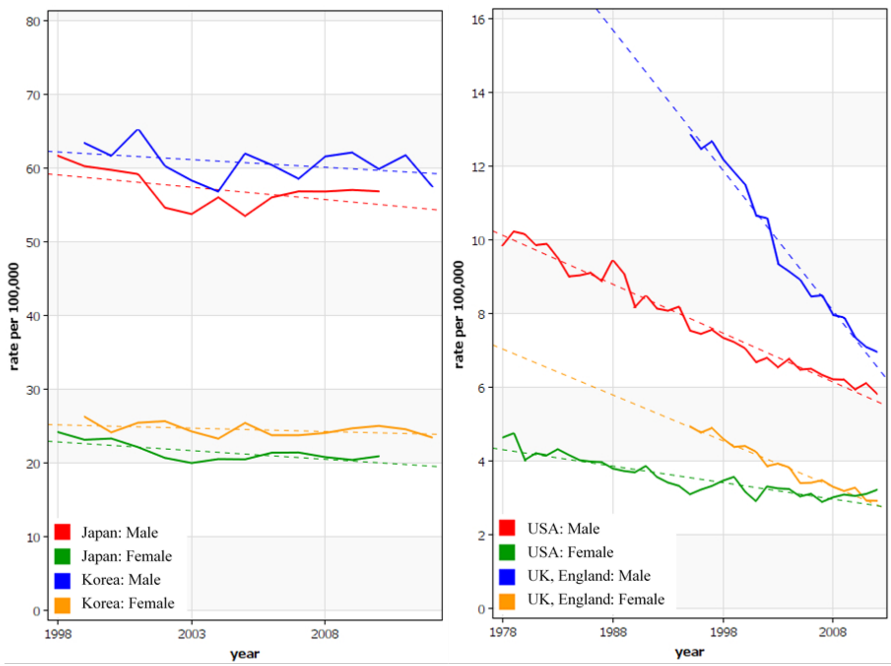

Figure 2. Time Trend of the Age-Standardized Incidence Rate of Gastric Cancer in (a) High- (South Korea and Japan) Versus (b) Low- (USA and UK) Incidence Selected Countries. Reproduced from the International Agency for Research on Cancer (IARC). As seen, high-incidence regions have experienced a slower decline.

made the first attempts to organize cancer reporting by the establishment of Cancer Institute.[21] Then in 1986, a pathology-based cancer registry was officially established in Iran with the joint collaboration of TUMS, the Iranian Ministry of Health and Medical Education and International Agency for Research on Cancer (IARC).[21] In the beginning, the program was launched in a few high- and low-incidence regions and was then expanded to cover more populations. At maximum, only 81% of all estimated new cancer cases were covered in the latest series of pathology-based statistics published in 2005.[22] In order to attain a thorough GC epidemiological map, the Digestive Disease Research Institute (DDRI) of TUMS initiated a large population-based study named "Gastric and Esophageal Malignancies in Northern Iran" (GEMINI) for the first time in selected provinces during the early 2000s.[23-25] Since Population-based Cancer Registry (PBCR) seeks data from any source in which cancer cases may be diagnosed or treated (such as hospital records in practice, cytopathological reports in diagnostic departments, or even death certificates when possible),[26] it was more comprehensive than former pathology-based cancer registries in providing data for a better understanding of diseases and contributing to cancer prevention plans. These encouraged us to shift from pathology-based to PBCR nationwide. Therefore, in the early 2010s, the Iranian national PBCR was developed and today, it covers about 100% of the Iranian population.[23] Comparing the Iranian national PBCR data quality indicators with those from other high-quality cancer registries (microscopic verification of 68.28%, death certification only of 12.99% and unknown primary site of 5.62%), our quality indices are within acceptable ranges.

In the following, we will present our latest knowledge about GC in Iran greatly obtained from the Iranian national PBCR.

Epidemiology of Gastric Cancer in Iran

Like many other Asian countries, Iran has high incidence and mortality rates of GC. In a recent study by Roshandel et al, GC ranked the first most common cancer in males (age-standardized incidence rate [ASR] = 21.2) and the third in females (ASR = 9.4).[23] More importantly, it is the first cause of cancer-related deaths overall.[2] In line with the global diversity in GC distribution, Iran itself has a wide variation in the incidence and mortality rates across different provinces (Figure 3).[27,28] Most northern and northwestern regions of Iran are hotspots for GC. The risk gradient falls towards the southern regions of the country.[29] For instance, while in Ardabil (a northwestern province) the ASR value was 48.4 in men and 20.6 in women, the corresponding figures were 7.1 and 5.3 in Hormozgan (a southern province), respectively.[23] The same pattern is also seen in the west Asian population, so that northern countries like Iran and Turkey suffer more from upper gastrointestinal malignancies.[30] These discrepancies may be justified by the heterogeneous geographical distribution of GC attributed risk factors, which are discussed further. Contrary to the recent global decline, Iran has experienced a slight increase in the incidence rate of GC.[27,31] However, we speculate that this observation may be due to prior misclassification of gastric cardia cancers as esophageal cancers.[8,32] With advances in diagnostic strategies, today the diagnosis of GC has improved.[33]

Risk Factors of Gastric Cancer in Iran

The pattern of GC distribution demonstrates its robust association with environmental, racial and geographical factors. The prevalence of GC risk factors and their contributing attributable risks differs across high- and low-incidence populations.[34] Given that South Korea has the highest (ASR = 39.6) and the UK one of the lowest (ASR = 3.9) rates of incidence in the world,[1] stating some of their statistics outlines this fact appropriately. A systematic review has reported very different *Helicobacter pylori* (HP) prevalence in two countries; 54.8% in South Korea, and 27% in the UK, revealing a two-fold difference.[35] Again, it has been estimated that the prevalence of smoking and its population attributable fraction for GC in males were 65.1% and 28.8% in South Korea and 27% and 14.3% in the UK, respectively.[36]

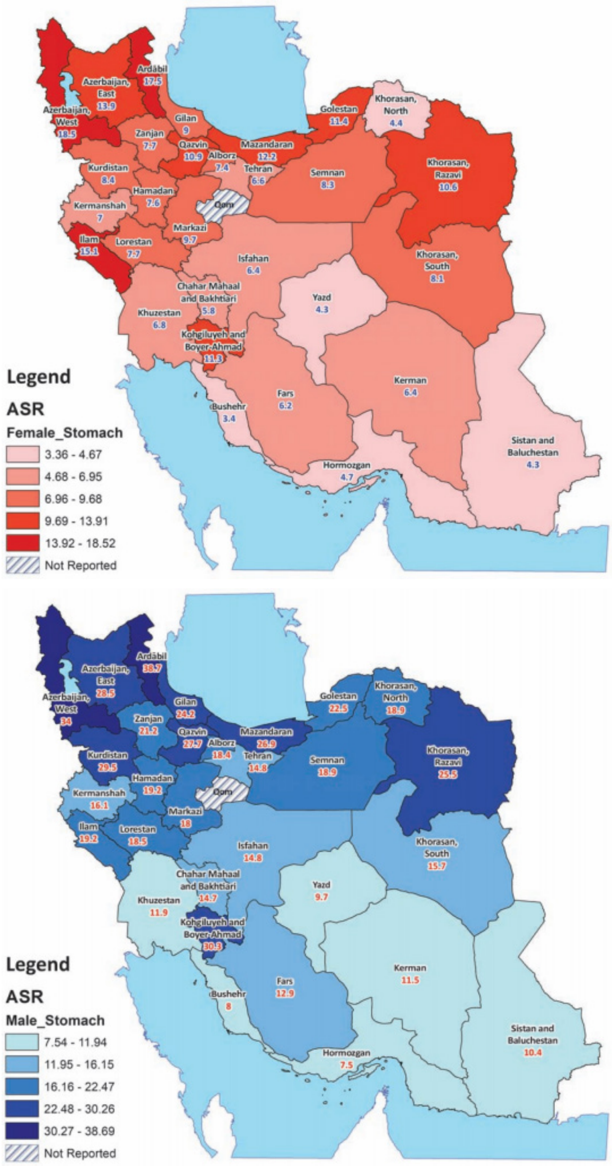

Figure 3. The Estimated Age-Standardized Incidence Rate of Gastric Cancer in Different Provinces of Iran, Retrieved from Iran's Latest Population-Based Cancer Registry Study.

Another excellent example in this regard is the average amount of dietary salt intake, which is 13 g/d in South Korea versus 9 g/d in the UK.[37] Furthermore, it was estimated that a relatively high proportion of GCs would be prevented by increasing the consumption of fruits and vegetables up to the theoretical minimum-risk exposure levels (300 and 400 g/d, respectively), defined by the Global Burden of Disease.[38]

Thus, in order to establish an efficient, cost-effective strategy against GC, identifying and incorporating these risk factors in the plan is pivotal. Correspondingly, we have also addressed a few of our national and local challenges in the following.

Helicobacter pylori

It has been well-established that the current or past history of HP infection is associated with an increased risk of GC.[39]

In the largest retrospective cohort study, Bae et al observed that the risk of developing GC in the non-eradication group was significantly higher than HP-negative individuals (hazard ratio [HR] = 4.12) and eradication groups (HR = 2.73) in a time frame of 6.4 years.[40] Similar to other high-incidence areas, the prevalence of HP among the Iranian population, both adults and children, is very high.[41-43] For example, in a population-based study in the Ardabil province, about 89% of adults aged 40 or older had positive HP test.[25] Nouraie et al declared that these high figures are correlated to the family education, low socioeconomic status and poor sanitary conditions.[43] Additionally, the acquisition age of HP infection is very low in Iran. In a study in Shiraz, in southern Iran, 82% of 9-month-old infants and 98% of children aged 2 years were infected with HP.[44]

Special virulence factors of HP infection, namely cytotoxin-associated gene A (CagA) and vacuolating-cytotoxin A (VacA), are more commonly found in the stomach of patients with GC.[45] In Iran, CagA positive strains are the most common strains among HP-infected subjects. The prevalence varies between 66% and 91% in different populations.[46-49] The contribution of CagA positive HP to an excess cancer risk is yet to be studied. VacA i1-type strains, on the other hand, were shown to have a stronger association with gastric adenocarcinoma than, and independently of, CagA status.[50]

Despite the high prevalence of HP infection in Iran, there is still uncertainty about its contribution to excess risk of GC. Comparing the prevalence of HP infection in three distinct areas of Iran with low to high GC prevalence, we found no significant difference between the rates of HP across these regions.[10] This means that not all of the HP-infected subjects develop GC, which highlights the necessity of the concurrent presence of both environmental and host-related factors. As a confirmation, our study on immigrants from high-(Iran) to low-(Canada) incidence regions indicated a downtrend in GC incidence among them, notably in the second and third generations.[51]

In addition to HP, infection with Epstein-Barr virus (EBV) is thought to be associated with 10% of all GCs.[52] Nevertheless, no significant difference was seen between the outcomes of the infected and non-infected patients; it was even shown that the presence of EBV has a favorable impact on GC patients' survival.[53,54] Considering the very high infection rate among the general population and many unidentified confounding factors, the real image of EBV-related GC remains to be clarified by well-controlled studies.

Dietary Factors

1. Salt Intake

The topmost influential and well-recognized dietary risk factor of GC is excessive salt intake, which not only causes atrophic gastritis, but also facilitates HP colonization.[55,56] In a population-based study conducted in Ardabil, it was shown that people with a preference for higher salt intake and some traditionally preserved salted foods, especially meats and pickles, were at about 3 times greater risk of GC.[57] Based on our study in the same region, 70.6% of GC cases were attributable to excess salt intake (>6 g/d).[56] In a large systematic analysis of 24 hours urinary sodium excretion and dietary surveys, the age-standardized estimate of "sodium" intake in Iran was 4.02 g/d in 2012, which is equivalent to ~10 g/d "salt" intake as multiplied by 2.5. This figure is much higher than the 5 g/d limit of "salt" intake recommended by the WHO.[58]

2. Low Levels of Fresh Fruits and Vegetables

A diet with an insufficient level of antioxidants is a common risk factor of GC.[59] Accordingly, diets containing vitamin C, E, A, and carotenoids have an inverse relationship with GC development.[60,61] That is why lower levels of fresh fruits and vegetable intake, which are rich in antioxidants and fibers, increase the risk of GC.[38,62] Citrus fruits and white vegetables are the most renowned in this category.[38,63]

In Iran, Vitamin E was shown to have a strong protective effect only on the cardia subgroup of GC. On the other hand, an inverse association was observed for vitamin C in all GC subtypes.[64] In a population-based case-control study in Ardabil, Pourfarzi et al highlighted the importance of consuming citrus fruits (OR = 0.31) for GC prevention.[57] Later in the same region, the diet-GC association was assessed using a food frequency questionnaire.[64] It was shown that fruits and vegetables consumption (OR = 0.72), particularly raw vegetables (OR = 0.12), was protective against GC. Both studies emphasized especially the protective effect of allium vegetables (garlic and onion) against GC and this was consistent with the results of a review by Guercio et al[65] We also found that 31.5% of GC cases were attributable to a low intake of fruits and vegetables (<400 g/d) in Ardabil.[56]

3. Preserved Food

Consumption of any kind of preserved food, including salted, smoked, pickled, cured, or processed, could be responsible for GC.[57] This is probably due to the loss of vitamins and antioxidants as well as increased nitrite concentrations found in these products.[66] New methods of food storage such as refrigeration could indirectly decrease the risk of GC through reducing the intake of preserved food. This reduction could reach 30%, according to a meta-analysis of 12 observational studies.[67] Iranians also used to traditionally preserve meat and vegetables, namely *ghorme* and pickles, from years ago. Pakseresht et al from Ardabil also observed an estimated risk reduction of 25% for every 10 years of refrigerator use.[64]

4. Meat

Diets rich in red meat seem to be connected with high-incidence rates of GC.[68] In contrast, the increase in white meat consumption, especially fish meat, may reduce the risk of GC.[68] We have also observed this fact in several studies conducted in high-risk regions in Iran. With red meat consumption, one might be 2 to 3 times more likely to develop GC, while with regular fish meat intake, the risk of GC could be reduced by one-third to one-fifth.[57,69]

5. Other Dietary Components

Several other risk and protective nutrients are introduced in the literature, as well. Overall, prudent healthy diets, like the Mediterranean diet, which are "rich" in fruits and vegetables, cereals, beans, "moderate" in fish, white meat, eggs, and alcohol and "low" in salt, dairy products, red and processed meat, sugar, and fat can prevent GC incidence in the long term.[70]

Interestingly, in a population-based case-control study in Ardabil, Pourfarzi et al reported that GC development was attributed to an increase in the frequency of dairy products intake (OR = 2.28).[57] Besides, different types of dairy products were discussed in detail in a study by Somi *et al*., which indicated that high-fat milk, yogurt and special types of cheeses (*khiki* and *koze*) increased the risk of GC.[71] However, the cause is unknown; the association may be confounded by other environmental risk factors, particularly in rural areas where dairy consumption is higher than the urban population.

Another potent contributor to GC is suspected to be the habit of drinking strong and hot tea in northwestern and northern parts of Iran, similar to esophageal cancer (OR = ~2.5).[57] Food groups containing fat and sugar and mixed nuts have also displayed a clear association with non-cardia GC.[64]

Low doses of capsaicin (in hot red chili pepper), flavonoid (in leafy vegetables and onion), zinc, iron, selenium, and folate are some of the examples of this sort.[64,72-75] The proportion of the population with selenium deficiency was 71% in Ardabil, which may partially explain the high rates of GC.[73]

Smoking, Opium, and Hookah

Tobacco smoking (both cigarette and hookah) and opium abuse are further risk factors (OR = 1.8-2.5) having a direct relationship with GC development.[56,76-78] Hookah is a traditional instrument for tobacco smoking in western Asia. Considering the global rise in hookah smoking due to misconceptions about its safety compared to cigarettes as well as the increase in opium abuse, it is essential to perform studies to evaluate their nature and mechanism of action in GC pathogenesis, and so to notify the public at the primary prevention level.[78] In a recent study, we demonstrated hookah as a neglected risk factor (OR = 2.4) not only for GC, but also for precancerous lesions, which may eventually progress to GC.[56] Comparable results were also found for opium abuse.[56,77] With an attributable fraction of 62%, tobacco smoking was the second most preventable risk factor of GC after HP infection. Opium was also strongly associated with GC (OR = 3.2), but its lower prevalence made it responsible for 8.3% of cases.[56]

Family History and Hereditary Factors

GC appears to be clustered in certain families.[79] A meta-analysis of 15 case-control studies affirms this relationship with 1.5-3.5-fold risk ratios for familial GC.[80] A study by Setia et al showed that 10% of all GCs have familial clustering and only 1-3% of cases are promoted by hereditary factors.[81] It is worth mentioning that exceptionally, patients with a specific type of GC, hereditary diffuse type, are independent of HP infection status and also show an unclear relationship with other environmental risk factors. In Iran, gastric precancerous lesions, like atrophy and dysplasia, were more prevalent in first-degree relatives of patients with known GC.[82] Furthermore, the risk of developing GC was estimated to be increased by over 2-folds for these groups.[83]

Precancerous Lesions

Unlike most risk factors that are mainly applicable to classic non-cardia cancer, both severe gastric atrophy (OR = 3.92) and frequent gastroesophageal reflux disease symptoms (OR = 10.08) have been significantly associated with increased risk of cardia GC in Ardabil.[84] Other well-documented pathological stages are gastric ulcer, gastric atrophy, intestinal metaplasia and dysplasia, and gastric polyps.

Suggested Screening and Surveillance Interventions

The insidious nature of GC and all mentioned regional differences leave us no choice but to pursue an efficient region-specific screening and surveillance strategy to identify high-risk individuals and enable early cancer detection.

Endoscopy

Endoscopy has been shown to be the gold standard screening-diagnostic method in different studies. Nationwide GC screening programs with regularly targeted endoscopy have been conducted in two high-incidence eastern Asian countries, Japan and South Korea, and led to a marked decrease in the burden of the disease.[85] In Japan, both endoscopic and photofluorographic screenings are recommended over the age of 50 every 2–3 years.[86] The Japanese screening program has identified 25% of all GCs; of these, about 60% of cases are diagnosed in early stages with much better response to therapy.[87] In South Korea, biennial screening through endoscopy or upper gastrointestinography is done for individuals at the age of 40 and older.[88] Similar to Japan, this program has also resulted in the identification of about 46% to 67% of GCs in the early stages with favorable outcomes.[89]

On the other hand, the widespread use of endoscopy as a screening modality has been found as an unpleasant, expensive, hard-to-reach, and invasive approach.[85,90] So, the question persists regarding those who are the most appropriate candidates for multiple short-interval regular endoscopic exams. For example, it has been demonstrated in various studies that the precancerous lesions of intestinal metaplasia (IM) are associated with an increased risk of GC, which suggests regular endoscopy for IM patients' surveillance in order to reduce GC incidence[56,91-93] However, these results are based on a limited number of subjects, which may yield negligible positive predictive value, and also there is no evidence from randomized studies to support surveillance of IM.[94] So, endoscopic screening of younger patients with IM, even in high-incidence areas, might not be efficient or cost-effective. Altogether, based on the current GC screening programs and our point of view, we tend to suggest that definite high-risk individuals of 50 years of age and above, particularly from a high-risk region, might benefit more from frequent endoscopy surveillance every 2–3 years.

Non-invasive Biomarkers

Currently, there is an increasing interest in using reliable, convenient, non-invasive tools to detect precancerous lesions or early stages of GC of individuals at-risk. The use of biomarkers seems to fulfill this goal.[95] So far, many of the recognized tumor markers such as carcinoembryonic antigen and carbohydrate antigen 19-9 (CA19-9), which are neither highly sensitive nor specific, are just useful for monitoring tumor progression and recurrence.[96,97] In the following, some of the promising biomarkers for screening are reviewed:

Pepsinogen: In a cascade, HP infection changes gastric mucosa to precancerous pathological stages, from atrophic gastritis and IM, ultimately to dysplasia and neoplasia. Accordingly, serum pepsinogen I (PGI), produced mainly by chief cells in gastric body mucosa will decrease significantly. Another pepsinogen, PGII, which is produced by gastric mucosa along with other sources, may decrease to a smaller extent or remain unchanged. These alterations make serum PGI and PGI/II ratios reliable surrogate biomarkers for precancerous lesions.[98-100] As a marker of gastric atrophy, serum pepsinogen has certain drawbacks: limited to intestinal types of GC, small positive predictive value because of low GC incidence rates in most countries, uncertain sensitivity and specificity due to diversity of cut-off points in various studies, and being affected by both age and HP infection which disrupts its interpretation, are a few of these issues to name.[101-103] In Iran, the results from studies investigating the role of PGI, PGII, and PGI/II ratios in the identification of atrophic gastritis are contradictory. In a study exploring these biomarkers in high (Ardabil) and low (Kerman and Yazd) risk populations for GC, the mean serum levels of both PGI and PGII, as well as their ratio (≤3), did not differ significantly between these regions.[101] It was therefore concluded that these biomarkers are probably not sensitive predictors of atrophic gastritis. However, it was indicated in another study from Northeastern Iran that the PG I/II ratio with a threshold level of <5 can be a relatively good marker of fundic atrophy, particularly among those with nonatrophic pangastritis.[103] Additionally, PGII had potential sensitivity to detect the extension of nonatrophic gastritis to the corpus. Future studies will better delineate the utility and limitations of these biomarkers.

Ghrelin: Our study, together with those by others, introduced serum ghrelin as a new screening biomarker having an inverse correlation with GC and its precancerous lesions, e.g. atrophic gastritis.[104-106] In Ardabil, we observed that individuals with the lowest quintile of serum ghrelin were 8.71- and 6.58-folds more likely to have cardia and non-cardia GC, respectively, compared to the highest quintile.[104] Ghrelin is a peptide produced by P/D1 cells in oxyntic glands of the stomach with potential therapeutic effect; so, it can potentially detect any histological changes leading to GC.[107]

DNA methylation: Disruption of epigenetic processes can lead to malignant cellular transformation. DNA methylation, which is the most common and important phenomenon of epigenetics in GC, can be targeted for early GC detection and predicting its prognosis.[108] To monitor the progression of gastric precancerous lesions, DNA methylation of AMPH, PCDH10, RSPO2, SORCS3, and ZNF610 may be helpful.[109]

Other biomarkers: Another candidate for the GC screening might be gastrin-17, which is also used to develop anti-gastrin vaccines for GC prevention.[110] Other convincing biomarkers of either atrophic or inflammatory conditions of the gastric mucosa are anti-CagA antibody, anti-parietal cells antibody, Trefoil factor family protein, and IgG anti-HP antibody.[111,112]

Further well-powered, long-term studies are required to ascertain an optimal serum marker and its cut-off points with sufficient sensitivity, specificity, and predictive values for routine use in GC screening.

Preventive HP Eradication

As an essential risk factor for GC, HP is classified as a class I carcinogen by the IARC.[113] Hence, HP eradication seems one of the most reasonable preventive strategies against GC,[114] supported by the Maastricht V consensus.[115] The ideal way for HP eradication in high-risk regions appears to be an active prophylactic immunization of children; however, there is no commercial vaccine available yet.[116,117] Hence, massive therapeutic eradication of HP in children and young adults seems to be the method of choice at the moment. In this context, a protective relative risk of 0.65 for GC was estimated among treated patients in a meta-analysis of six studies.[118] However, the emerging data question this statement.[119] In another meta-analysis of limited, moderate-quality trials, no evidence of an effect on all-cause mortality was observed for HP eradication in healthy asymptomatic infected patients.[120] Therefore, the screen-and-treat strategy for HP infection "needs more experience from different geographical areas and faces several shortcomings".[121] Moreover, large-scale HP eradication in endemic populations like Iran is almost impractical for several reasons, including heavy expenses and the development of multi-drug resistant microorganisms.

Based on our results from the Ardabil cohort study, we tend to agree with Wang et al that the GC incidence could be delayed rather than prevented by HP eradication.[119] We also believe that the value of regular early endoscopic screening in preventing GC is much greater than anti-HP therapy. Just like endoscopy, anti-HP therapy may be appropriate as a preventive strategy in determined high-risk groups, not at provincial or national levels.

Chemoprophylaxis

In addition to antimicrobial agents used to treat HP infection, some other medications have been shown to be protective against GC, as well. Since inflammation plays an important role in GC development, anti-inflammatory drugs, such as aspirin, were among the first to be discussed in this setting.[122,123] However, controversies still exist.[124] We should be aware that prolonged aspirin use alone might damage the gastric mucosa, but its combination with proton pump inhibitors could potentially reduce injuries.[125] Statins are another category of this sort that reduce the incidence of GC by inhibiting HP CagA.[126] Although the literature has inconsistent evidence on the chemoprophylactic effect of statins on GC,[127] a recent meta-analysis supports this hypothesis.[128] Metformin use in diabetic patients has been also associated with reduced GC rates,[129] although it needs to be further elaborated.[130] Probiotics, hormone replacement therapy, and ursolic acid, are other examples of possible interventions.[131-133] Nonetheless, these chemopreventive strategies need to be evaluated and confirmed in larger trials.[134]

Minimizing Risk Factors

In addition to a targeted screening program with a focus on early GC detection, some joint efforts have been made to control and minimize the attributable risk factors of GC and therefore, to reduce its incidence and mortality.[135,136] To illustrate the results of these preventive strategies, the annual percent changes in GC mortality rates are about 3%-4% in the major European countries, 4.3% in South Korea, and 3.5% in Japan.[137]

Defining High-risk Individuals

In order to design an efficient preventive plan, the first step is to define the high-risk groups requiring preventive measures against GC. Currently, there is no consensus on an inclusive definition; nonetheless, individuals with the following characteristics might be cautiously considered at a higher risk for developing GC[138]: (*a*) Demographic features: male gender, age of 50 or more, positive family history of GC, low socioeconomic status, residence in a high-risk region. (*b*) Life Style: heavy smoking, chronic use of hookah, opium abuse, chronic heavy alcohol consumption, diets containing excessive salt intake, preserved food (smoked or salted), high amounts of meat, low amounts of antioxidants, fruits and vegetables. (*c*) Genetic factors: hereditary diffuse GC, familial adenomatous polyposis, hereditary non-polyposis colon cancer, blood group A, Li-Fraumeni syndrome. (d*)* Pathological features: positive HP infection, gastric precancerous lesions, and pernicious anemia.

Conclusion

To conclude, the best results in reducing GC incidence and mortality rates on larger scales appear to arise from modifying behavioral and environmental risk factors, with more attention to region-specific factors. It seems that regular endoscopic screening of GC and antibiotic chemoprophylaxis for HP eradication are more appropriate in high-risk groups with specified criteria, although not yet exactly defined. The future propensity should particularly include high-efficacy, non-invasive genetic and molecular biomarkers, which have shown promising values so far.

Ethical Statement

Not applicable.

Authors' Contributions

EA, AS: study conception and design. EA, AS: Data collection. EA, AS, MD, GR, MA: draft manuscript preparation. All authors reviewed the paper and approved the final version of the manuscript.

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