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Screening and Preventive Strategies in Esophagogastric Cancer

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INTRODUCTION

Gastric and esophageal cancers are among the most common tumors that cause significant mortality worldwide, although their incidence is much higher in specific geographic locations. Unfortunately, although new treatment protocols have improved the outcome of most major malignancies, prognosis in gastric and esophageal cancer remains poor. Screening and prevention programs offer the hope of reducing morbidity and mortality from these diseases.

GASTRIC CANCER

Gastric cancer is among the most common cancers in the world with more than 900,000 cases in 2012, making it the fifth most common cancer in the world.^{1, 2} The incidence of gastric cancer, however, is much higher in the developing world, particularly in East Asia where more than 50% of cases occur.³ Although screening programs have been developed in Asian countries, particularly Japan and Korea, significantly improving outcomes through early detection,^{4–6} mortality rates in the West have remained high.^{7, 8}

Risk Factors

There are numerous risk factors for developing gastric cancer. These risks can be broken down into modifiable and nonmodifiable (Table 1).

Nonmodifiable risk factors—Race and ethnicity are nonmodifiable risk factors for gastric cancer. Although environmental factors likely play a role, they alone cannot explain the high incidence of disease in East Asia; particularly because this increased incidence persists in immigrants and their offspring from East Asia to the West.^{9, 10} Age is also

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important, with more than 90% of cases occurring after the age of 45 years.⁸ Family history also contributes to risk, with studies from both the West and East showing a first-degree relative with gastric cancer increases a person's risk 2- to 4-fold.^{11–13} Gender also plays a role, with men having a 2- to 5-fold increased risk of gastric cancer.¹⁴ Higher estrogen levels seem to protect women from the disease. Increased rates of gastric cancer in women on estrogen-blocking therapies (tamoxifen) and after menopause demonstrate this effect.^{15, 16} In fact, women seem to develop gastric cancer at a similar rate to men but with a 10 to 15 year lag.¹⁷

Although gastric cancer is usually sporadic, about 10% of cases seem linked to genetic syndromes.¹⁸ The most common syndrome is hereditary diffuse gastric cancer (HDGC), recently defined by the International Gastric Cancer Linkage Consortium.¹⁹ HDGC is characterized by autosomal dominant inheritance, with about a 60% to 80% increase in the risk of gastric cancer and a 40% to 50% increase in breast cancer. About 40% of HDGC is due to mutations in E-cadherin (CDH1). Mutations in CTNNA1 have also recently been found in a subset of patients with the condition.¹⁸ Other cancer syndromes have been associated with increased risk of gastric cancer, including Lynch syndrome (DNA mismatch repair gene mutation), familial adenomatous polyposis (APC gene mutation), Peutz-Jeghers syndrome (STK11 gene mutation), juvenile-polyposis syndrome (SMAD4 or BMPR1A mutation), hereditary breast and ovarian cancer syndrome (BRCA 1 or BRCA 2 mutation), and Li-Fraumeni syndrome (p53 mutation). However, gastric cancer still remains very uncommon in these syndromes, with rates of occurrence less than 5%.²⁰

Modifiable risk factors—The most clear modifiable risk factor for gastric cancer is *Helicobacter pylori* infection. Although gastric cancer develops in only about 1% of infected humans, more than 90% of those with gastric cancer have been infected with *H pylori*.⁸ Other modifiable risk factors are less influential. Cigarette use seems to increase the risk of both cardia and noncardia cancer.²¹ Obesity (body mass index [BMI] >30) seems to increase the risk of noncardia cancer.²² A high salt diet also seems to increase the risk, whereas diets high in fruit and vegetables seem to be protective.^{23, 24}

Precursor Lesions

Chronic gastritis seems to lead to atrophic gastritis, which leads to intestinal metaplasia, which can develop into dysplasia and, ultimately, cancer.²⁵ Within 5 years of diagnosis, the annual incidence of gastric cancer was 0.1% for patients with atrophic gastritis, 0.25% for intestinal metaplasia, 0.6% for mild-to-moderate dysplasia, and 6% for severe dysplasia.²⁶ The progression from intestinal metaplasia to gastric cancer also greatly depends on the histologic subtype of intestinal metaplasia. Complete intestinal metaplasia (characterized by normal-appearing goblet cells and crypts) is much less likely to progress to gastric cancer than incomplete intestinal metaplasia (characterized by tortuous crypts and elongated columnar cells).⁸

Screening Techniques for Gastric Cancer

Serology screening—*H pylori* serology is the least invasive test for gastric cancer but is limited by a very low sensitivity and an inability to detect premalignant lesions.²⁷

Furthermore, the test may become negative as gastric atrophy progresses, causing false-negative results in those most at risk for the condition.⁸

Alternatively, pepsinogen testing has been studied as part of mass screening protocols. A precursor to pepsin, pepsinogen comes in subtypes I and II. Subtype I is secreted from the chief stomach cells. Subtype II is secreted from all gastric cells. Reductions in levels of subtype I and in the ratio of subtype I and II suggest increasing gastric atrophy. A subtype I cutoff of less than 70 ng/L and pepsinogen I to II ratio less than 3.0 were 77% sensitive and 73% specific for gastric cancer.²⁸ A case control study also demonstrated a reduction in odds ratio (OR) of death from gastric cancer at 1 and 2 years in subjects screened with pepsinogen levels.²⁹ However, the test was not found to be effective enough for it to be adopted into currently implemented mass screening programs.⁸

Gastric imaging—Although a barium upper gastrointestinal series only has a sensitivity of 60% to 80%,³⁰ 2 case control studies from Japan showed a 40% to 60% decline in gastric cancer mortality.^{31, 32} As such, barium imaging remains part of the mass screening programs of both Korea and Japan.

Endoscopy is the gold standard for gastric cancer screening because it has the highest detection rate (sensitivity of 78%–84%) and allows for biopsies to confirm the diagnosis.^{33, 34} In areas of high incidence, endoscopy is the mainstay of screening. In countries such as the United States, where gastric cancer is less prevalent and the cost of endoscopy is higher, endoscopic screening is unlikely to be cost-effective.⁸

Studies suggest that narrow-band imaging and digital-based image enhancement technologies, such as computed virtual chromoendoscopy, increase the diagnostic yield and accuracy of gastric neoplasia detection.⁸ However, imaging criteria are inconsistent and validation studies have yet to be performed.⁸ These techniques cannot be recommended currently.

Current Screening Guidelines

Countries with a high incidence of disease (eg, Japan and Korea) have implemented mass screening programs. Screening starts at age 40 to 50 years with upper gastrointestinal series or endoscopy every 2 to 3 years.⁸ Under these protocols, two-thirds of gastric cancers cases detected are in an early stage, leading to an increased 5-year survival rate.^{35, 36}

Mass screening programs are thought to be cost-ineffective in low-prevalence populations. However, a cost analysis of performing esophagogastroduodenoscopy at the time of screening colonoscopy in the United States found a cost-effectiveness ratio of \$95,559 per quality-adjusted life year saved, less than the \$100,000 cutoff for cost-effective screening.³⁷ Others have noted that a targeted approach to high-risk individuals would be even more cost-effective.⁸ Yeh and colleagues³⁸ recently suggested that serum pepsinogen screening in smokers had a cost-effectiveness ratio of \$76,000 per quality-adjusted life year saved.

The American Society of Gastrointestinal Endoscopy (ASGE) 2015 guideline suggests screening for those with known gastric intestinal metaplasia and an increased risk due to

ethnic background or family history. With minimal data on screening in the West, the ASGE guidelines offer no guidance on follow-up interval.³⁹ European guidelines suggest surveillance at 1 to 2 year intervals for all patients with intestinal metaplasia who have greater than 20% metaplasia, incomplete intestinal metaplasia, a first-degree relative with gastric cancer, or are actively smoking. Otherwise, a 3-year interval follow-up is recommended.⁴⁰ However, it is noteworthy that Eastern Europe, the Iberian Peninsula, and Italy have higher incidences of gastric cancer.⁴¹

Prevention

Currently, prevention requires adjusting modifiable risk factors. For instance, *H pylori* elimination in those with gastric atrophy can lead to normalization of stomach mucosa, significantly reducing risk.⁴² Improving lifestyle by reducing obesity, promoting smoking cessation, and increasing fruit and vegetable consumption may also decrease the incidence of gastric cancer, though the evidence for such prevention is less clear.

A recent large cohort study by Cao and colleagues⁴³ that looked at aspirin as a chemopreventive agent did show a preventative association between gastrointestinal cancer and aspirin use, with a relative risk of 0.85 after multivariate analysis. Although most of this reduction was due to colorectal cancer, in women a relative risk of 0.71 (CI 0.52–0.98) was noted between aspirin use and gastroesophageal cancer on multivariate analysis. Men, however, had a relative risk of 0.94 (CI 0.74–1.21). Whether this represents a true association between aspirin use and reduced gastroesophageal cancer in women requires further study. Furthermore, given the low rates of gastroesophageal cancer, it is unclear whether the benefit of using aspirin solely for cancer prevention would outweigh the risk of adverse events.

ESOPHAGEAL ADENOCARCINOMA

Esophageal adenocarcinoma is the dominant form of esophageal cancer in the developed world. Its incidence has increased 6-fold in the last 40 years but it continues to have a dismal prognosis with mortality rates that almost equal its incidence rates.⁴⁴ In fact, nearly half of patients diagnosed are unable to undergo treatment beyond palliative care.⁴⁵ However, outcomes with early-stage cancers are much better, particularly with new endoscopic treatment techniques.⁴⁶ As such, screening to allow early detection and preventative treatment is recommended.

Risk Factors

Chronic inflammation of the esophagus develops due to gastroesophageal reflux disease (GERD) or other irritants. From this inflammation, intestinal metaplasia can occur in the distal esophagus, termed Barrett esophagus (BE). Continued irritation will lead to low-grade dysplasia, which will progress to high-grade dysplasia and then to adenocarcinoma. Furthermore, a recent study has begun to show genetic lineage between patients with GERD, BE, and esophageal adenocarcinoma (EAC).⁴⁷

Clinical risk factors for Barrett esophagus progression—Although GERD is the strongest risk factor, 15% to 45% of BE develops in patients with no symptoms of GERD. Furthermore, although GERD occurs in 15% to 20% of the Western population, only 10% to 15% of those patients have BE.⁴⁸ Although BE is clearly a precursor, it only progresses to EAC at a rate of 0.12% to 0.60% per year.⁴⁹ As such, other risk factors are looked for to determine who should be screened for BE (Box 1).

Men with BE develop EAC at more than twice the yearly rate of women, 0.28% to 0.13%, respectively.⁵⁰ Other clinical factors include increasing age, central obesity, and active smoking; essentially the same as risk factors for developing BE.⁵¹

Endoscopic risk factors for Barrett esophagus progression—Evidence of esophagitis or anatomic risk factors for worse reflux (ie, hiatal hernia) has been associated with increased progression from BE to EAC. Furthermore, most investigations into BE segment length suggest the increasing area of disease increases the risk for EAC. Finally, mucosal nodularity, ulcers, and strictures noted on endoscopy have been associated with increased risk of EAC. However, these probably indicate present high-grade dysplasia or EAC instead of risk of future development.

Histologic risk factors for Barrett esophagus progression—Rates of progression increase to about 1% per year for patients with BE that includes low-grade dysplasia and about 7% per year for patients with BE that includes high-grade dysplasia.⁵² The use of histology, however, is limited. First, biopsies of BE may miss dysplastic areas, leading to sampling error. Second, interpathologist and intrapathologist agreement in rating dysplasia is poor, leading to interpretative error.⁵⁰

Biomarkers are being developed to improve the accuracy of histologic assessment of BE. P53, a tumor suppression gene, is the most promising and immunostaining is currently recommended by the British Society of Gastroenterology guidelines.⁵³ Reid and colleagues⁵⁴ have promoted the use of aneuploidy and tetraploidy, evidence of genetic instability, as a marker of potential tumor progression. Kastelein and colleagues⁵⁵ demonstrated that both p53 overexpression (adjusted relative risk 5.6, 95% CI 3.1–10.3) and p53 loss of expression (adjusted relative risk 14.0, 95% CI 5.3–37.2) were associated with an increased risk of developing high-grade dysplasia or EAC. Other complex combinations of tumor markers are in development but require significant testing before they can be clinically used.

Screening Techniques

Screening can be broken down into (1) techniques to identify those in the population with BE and (2) techniques to identify those in the population with BE most likely to develop EAC, so they can undergo intensive surveillance and treatment.

Identifying Barrett Esophagus

Direct visualization—There are obvious benefits to endoscopic screening, such as direct visualization and the ability to take biopsies for histologic analysis. However, there are also

significant limitations, such as that the physical process of the technique is unappealing to patients, it requires an endoscopy suite, and the side effects of sedation. Cost is another limitation, directly because of the need for staffing, equipment, and so forth; and indirectly due to the patients' time off work and decreased productivity.⁵⁰

Capsule endoscopy is a noninvasive way to detect BE. However, the technique has low sensitivity, requires endoscopy to confirm diagnosis and obtain biopsies, and is not cost-effective compared with standard endoscopy.⁵⁶ Recently, a tethered capsule endomicroscope, which uses optical frequency domain imaging to provide cross-sectional architectural images of esophageal mucosa, allows identification of BE and dysplasia. Although this is reusable (overcoming some cost-effectiveness issues of capsule endoscopy), its accuracy is unproven and it is unclear patients would find swallowing a tethered pill more appetizing than a sedated endoscopic procedure.⁵⁷

Instead of standard endoscopy, ultrathin transnasal endoscopy (TNE) offers an endoscopy approach that avoids issues with sedation and can be performed outside an endoscopic suite. The procedure does seem to be effective. A meta-analysis of 5 studies (439 subjects) comparing TNE with standard endoscopy in the same subjects showed the pooled sensitivity and specificity of TNE in detecting BE was 91% and 96%, respectively.⁵⁸ However, even when a mobile unit brought TNE to patients' neighborhoods, only 48% were willing to undergo the procedure.⁵⁹ Furthermore, the technique has not gained widespread acceptance among physicians.⁶⁰

Tissue sampling—Cytosponge is an abrasive sponge encapsulated in gelatin to form a pill attached to a tether. The patient swallows it, the gelatin capsule dissolves, and the sponge is pulled back up through the esophagus, capturing mucosa for analysis. The cytosponge does have good sensitivity and specificity at 73.3% and 93.8%, respectively, with a BE segment with circumferential length greater than or equal to 1 cm; and 90.0% and 93.5%, respectively, with a BE segment with circumferential length greater than 2 cm.⁶¹ Furthermore, cost-effectiveness analysis demonstrated benefit in men older than 50 years with GERD, with a potential reduction of EAC by 19%.⁶² However, patient tolerability still seems to be an issue; only 18% of subjects offered the test were willing to proceed in the initial studies.⁵⁸

Unfortunately, tests with blood, urine, or stool to detect those at risk for EAC have not been developed. A promising noninvasive test, however, involves electronic nose technology, in which a device uses reactable compounds to detect different volatile organic compounds in breath samples. In a study of 85 subjects undergoing surveillance for dysplastic BE (43 with biopsy proven active BE and 42 without), the test had 86% specificity and 90% sensitivity. More encouraging, the test had 98% acceptance rate in recruitment.⁶³ This technology could represent an acceptable, easily used, cost-effective mechanism to screen large populations for BE or EAC.

Identifying Dysplastic Barrett Esophagus

Customarily, random biopsies (taken in 4 quadrants around the circumference of the esophagus) along the BE segment are obtained to try and identify dysplasia. As previously

noted, however, this is limited by sampling and interpretative errors. To improve the efficiency of sampling, electronic high-resolution chromoendoscopy (usually narrow band imaging) has been used to obtain better, more detailed, imaging of the vasculature and mucosa. Although randomized controlled trials did not show an increased diagnostic yield for high-grade dysplasia or adenocarcinoma, a meta-analysis of 843 subjects in 14 studies demonstrated an increased diagnostic yield of 34% (95% CI 20%–56%, $P<.0001$) compared with standard endoscopy.⁶⁴

In-procedure histology-level imaging through probe-based confocal endomicroscopy (pCLE) has been shown to enhance detection of BE-associated dysplasia compared with standard endoscopy.⁶⁵ pCLE is limited, however, because it has a very limited field of view, requires administration of intravenous fluorescent agents, and needs endoscopists to make a histologic diagnosis. Research in topical fluorescent agents to allow for simplified pCLE is ongoing.

Another optical technique is volumetric laser endomicroscopy (VLE), which uses a frequency domain optical coherence tomography device that can generate wide-field cross-sectional views of the entire distal portion (6 cm) of the human esophagus. The benefits of VLE are that it allows for comprehensive assessment of a significant length of esophageal mucosa and submucosa. However, VLE can effectively distinguish normal squamous epithelium from BE only when highly trained pathologists use specific scoring systems.^{66, 67} This has prevented widespread application of the technology.

Current Screening Guidelines

No major society recommends general population screening for BE or EAC. Screening is recommended by the American Gastroenterology Association, the British Society of Gastroenterology, the ASGE, and the American College of Gastroenterology for certain high-risk groups (Box 2). If BE is found, then 4 biopsies every 2 cm (for at least 8 biopsies) should be obtained to assess for dysplasia. If Los Angeles grade B, C, or D esophagitis is found, then repeat screening in 8 to 12 weeks after twice a day proton pump inhibitor treatment is recommended to ensure there is no underlying BE. Otherwise, if no BE is found, then repeat screening endoscopy is not recommended.⁶⁸

If no dysplastic BE is found, guidelines still suggest endoscopic screening every 3 to 5 years with 4-quadrant biopsies every 2 cm is reasonable.⁶⁸ For patients with indeterminate dysplasia, 2 expert pathologists should confirm the diagnosis. Repeat endoscopy with biopsy samples should be obtained in 3 to 6 months. If dysplasia persists, then endoscopic surveillance yearly with 4-quadrant biopsies every 1 cm is recommended.⁶⁸

Once low-grade dysplasia is found, endoscopic treatment can be considered. Otherwise, yearly endoscopic surveillance with 4-quadrant biopsies every 1 cm should be pursued. If high-grade dysplasia is found and confirmed by 2 expert pathologists, then endoscopic or surgical treatment should be pursued.⁶⁸

Even with these complex screening guidelines, 90% of individuals diagnosed with BE will die from an unrelated condition. Worse, 93% of EA cases are not detected by current

screening algorithms, presenting at an advanced stage.⁵⁴ To try and further improve efficiency of BE screening, risk predication models have been developed (Table 2).

Prevention

Control of clinical risk factors is the first step in prevention of EAC. Therefore, smoking cessation and prevention or treatment of obesity are important interventions. Treatment of GERD is also important because reduction of the irritating effects of stomach acid may prevent the development of dysplasia or EAC.⁶⁹ Proton pump inhibitors may prevent the development of EAC in patients with BE who do not have heartburn symptoms.^{70–72} However, the use of antireflux surgery is only recommended to prevent GERD symptoms, not to improve BE outcomes.⁶⁸

Population studies have shown aspirin users have lower incidence of EAC.^{73, 74} Preliminary data indicate that nonsteroidal antiinflammatory drugs inhibit inflammatory pathways in the esophagus. Due to its side-effect profile, further data are needed before aspirin can be recommended as a preventive agent.⁶⁸

Being at much higher risk of progression to BE, treatment to eliminate dysplastic BE is thought to be justified. Historically, this meant esophagectomy. Fortunately, endoscopic treatments can now be provided that significantly reduce treatment morbidity. Nodular lesions in dysplastic BE can be resected through either endoscopic mucosal resection or endoscopic submucosal dissection.⁷⁵ Pech and colleagues⁷⁶ compared endoscopic resection to esophagectomy in a multicenter retrospective cohort study and found complete remission in 98.7% of subjects treated with endoscopic resection. Few subjects undergoing endoscopic resection had complications, whereas 32% had major complications after esophagectomy.

Flat dysplastic BE is treated with radiofrequency ablation (RFA), which uses a high-frequency electromagnetic field from regularly spaced electrodes in an endoscopically attached ablation catheter to produce superficial thermal injury. In a multicenter, sham-controlled, randomized trial, complete eradication of dysplasia was achieved in 91% of cases with low-grade dysplasia and in 81% of cases with high-grade dysplasia.⁷⁷ Recent data have shown decreased progression to high-grade dysplasia and to EAC in patients with low-grade dysplasia who received RFA.⁷⁸ RFA is a relatively safe procedure, particularly compared with esophagectomy.⁷⁵

ESOPHAGEAL SQUAMOUS CELL CARCINOMA

Although no longer the dominant form in the West, esophageal squamous cell carcinoma (ESCC) remains the most prevalent form of esophageal cancer worldwide. Rates of 100 cases per 100,000 person-years are found in Southeastern Africa and the so-called Asian esophageal cancer belt (Turkey, Iran, Kazakhstan, and Northern and Central China).⁷⁹

Risk Factors

The most important risk factors for ESCC are environmental. Smoking seems to increase the risk of developing the disease.⁸⁰ A study from Taiwan showed smokers have an OR of 4.2

and former smokers an OR of 3.4 compared with never smokers for developing ESCC.⁸¹ It does seem that in higher risk regions, smoking is less of a risk factor.⁷⁹

Alcohol is another important risk factor, with increasing relative risk from 2 to 8, depending on the volume of alcohol consumed.⁸⁰ Certain areas of increased alcohol consumption do seem to be hotspots for the disease, though alcohol consumption is low in several high-incidence regions of the world.⁷⁹

Eating dietary products high in nitrogenous components was shown to have an OR of 2 for individuals who eat foods rich in such compounds compared with those who do not.⁸⁰ The areca nut, commonly chewed like tobacco in India and Southeast Asia, has an OR of 2.3 for developing ESCC in chewers versus nonchewers.⁸⁰ Wood burning for heating and cooking has been associated with ESCC in Africa, Iran, and Brazil.⁸² This may be related to increased exposure to polycyclic aromatic hydrocarbons.⁸³

A genetic basis for ESCC was suggested by family predominance in high-incidence areas and is associated with autosomal dominant diseases such as tylosis.⁷⁹ A Chinese population dataset that included 453,852 single nucleotide polymorphisms (SNPs) from 1898 squamous carcinoma subjects and 2100 control subjects was used to identify candidate causal SNPs revealed 3 strong possible genetic pathways to developing ESCC.⁸⁴ Genome-wide association studies have shown SNPs for alcohol dehydrogenase 1B (rs1229984), aldehyde dehydrogenase 2 family (rs671), and a region of chromosome 20 (C20orf54).^{79, 85}

Screening Techniques

It is thought that esophageal squamous dysplasia is the precursor lesion to ESCC, though there are no prospective studies that assess the relationship between dysplasia and ESCC.⁸⁶ Chromoendoscopy with Lugol staining is the gold standard for the diagnosis of precancerous squamous lesions.⁷⁶ The sensitivity and specificity of white-light endoscopy for the detection of high-grade dysplasia and cancer is 62% and 79%, respectively, compared with a much higher sensitivity of 96% when using Lugol chromoendoscopy.⁸⁷

Cytology techniques without endoscopy and tissue or serum markers of risk have been suggested as alternative screening techniques.⁷⁶ Although several nonendoscopic techniques to obtain esophageal cytology exist, these techniques have a sensitivity of only 24% to 47% for dysplasia-cancer and 18% to 44% for cancer, making them unsuitable for screening.⁸² Very few studies looked at serum biomarkers but those that exist suggest these could be used in the future.⁸²

Screening Guidelines

Due to low incidence in Western countries, screening is clearly not effective. However, guidelines do exist in high-incidence regions (30 cases per 100,000 persons per year), such as in Northern China.⁷⁶ Based on economic parameters and management, a comparison study between 12 different existing screening methods in high-risk or high-incidence areas of squamous cell carcinoma in China demonstrated 2 endoscopic screening strategies that were cost-effective.⁸⁸ In areas with low income levels and limited health care access, the investigators recommended 1 screening endoscopy at age 50 years, with 5-year follow-up

for low-grade dysplasia and 3-year follow-up for high-grade dysplasia. In areas with higher incomes and better health care access, they recommended 3 screening endoscopies at 5-year intervals starting at the age of 40 years, with the equivalent monitoring of low-grade and high-grade dysplasia.

Prevention

Prevention of ESCC requires avoiding the environmental factors that increase the risk of developing the disease. Avoidance of smoking, alcohol, and high-risk food products is important.⁷⁷ Good screening programs may help with prevention in high-incidence areas but is not cost-effective in most of the world.

SUMMARY

Gastric adenocarcinoma, EAC, and ESCC are among the most prevalent and deadly of malignancies worldwide. Screening and prevention programs will be critical to finally improving outcomes in these diseases. For gastric adenocarcinoma, screening in high-risk populations has significantly reduced disease mortality. More research is needed to determine how to screen high-risk individuals in low-risk populations. For EAC, though BE is a clear precursor lesion, more work is needed to develop truly efficient and effective techniques to improve mass screening programs. Meanwhile, for most populations, screening for ESCC is not effective. However, avoidance of toxic environmental risk factors is critical to reducing the incidence of this deadly illness.

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Box 1 Risk factors for developing Barrett esophagus

GERD⁵⁰

Male sex⁵¹

Increasing age⁸⁹

Central adiposity (visceral adipose tissue area, increased waist-to-hip ratio, or waist or abdominal circumference)⁹⁰

Family history of dysplastic BE or EAC⁹¹

Smoking⁹²

Box 2 High-risk groups recommended to undergo Barrett esophagus screening

1 of:

1. Men with >5 y GERD
2. Men with > weekly GERD symptoms (heartburn or acid regurgitation)

And

2 of:

1. Age >50
2. Central obesity (waist circumference >102 cm or waist-to-hip ratio >0.9)
3. White race
4. Active or history of smoking
5. First-degree relative with BE or EAC

Data from Qumseyra BJ, Wang H, Badie N, et al. Advanced imaging technologies increase detection of dysplasia and neoplasia in patients with Barrett's esophagus: a meta-analysis and systematic review. Clin Gastroenterol Hepatol 2013;11(12):1562–70.e1-2.

KEY POINTS

- Gastric adenocarcinoma, esophageal adenocarcinoma, and esophageal squamous cell carcinoma are among the most prevalent and deadly of malignancies.
- Screening in high-risk populations has significantly reduced the mortality of gastric adenocarcinoma; however, screening efficacy for high-risk individuals within low-risk populations is unclear.
- Although esophageal adenocarcinoma has a clear precursor lesion (Barrett esophagus), clearly effective screening techniques and programs are still being developed.
- Screening for esophageal squamous cell carcinoma is not cost-effective; however, avoidance of environmental risk factors (smoking, alcohol abuse) can prevent the disease.

Table 1

Risk factors for developing gastric cancer

Nonmodifiable Risk Factors	Modifiable Risk Factors
Race or ethnicity (East Asian or Pacific Islander)	<i>H pylori</i> infection
Age (>45 y)	Tobacco smoking
Family history	Obesity (body mass index >30)
Sex (Male) Genetics	High salt diet
	Low fruit or vegetable diet

Table 2

Risk predictor models for presence of Barrett esophagus

Model	Variables	Area Under the Receiver Operating Characteristic Curve (AUROC)
Thrift Clinical Model ⁹³	Age, sex, smoking status, BMI, highest level of education, and frequency of use of acid-suppressant medications	0.61
Michigan Barrett Esophagus pREdiction Tool ⁹⁴ (http://mberet.umms.med.umich.edu/)	Weekly GERD, age, waist-to-hip ratio, and pack-years of cigarette smoking	0.72
Thrift Combined Biomarker Model ⁹⁵	Biomarkers: IL12p70, IL6, IL8, IL10, and leptin Clinical: GERD frequency and duration, age, sex, race, waist-to-hip ratio, and <i>H pylori</i> status	0.85