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Review Article

Gastroesophageal reflux to esophageal adenocarcinoma: pathogenesis, risk stratification, and precision surveillance

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ABSTRACT

Gastroesophageal reflux disease (GERD) is a global public health burden with a rising prevalence driven by urbanization, aging populations, and modifiable lifestyle factors. This narrative review delineates the progression from GERD to Barrett's esophagus (BE) and ultimately to esophageal adenocarcinoma (EAC), emphasizing the epidemiological trends, molecular mechanisms, and clinical implications. The global prevalence of GERD has surged by over 77% since 1990, affecting an estimated 800 million individuals, with notable geographic variability and underestimation in low- and middle-income countries owing to inconsistent diagnostic criteria and reporting. BE, a metaplastic transformation of the esophageal epithelium due to chronic reflux, is recognized as the only precursor of EAC. This progression involves a complex interplay between sustained inflammation, molecular dysregulation, and genetic mutations. Key signaling pathways, including NF-κB, IL6/STAT3, NOTCH, and Hedgehog, mediate epithelial remodeling and carcinogenic transformation. Dysplasia, particularly high-grade dysplasia (HGD), remains a key histopathological predictor of malignancy, complemented by molecular biomarkers such as TP53 mutations, aneuploidy, and gene expression alterations. This review also addresses clinical risk stratification, identifying high-risk cohorts based on segment length, obesity, smoking, symptom frequency, and genetic predisposition. Despite robust knowledge, gaps in surveillance persist, with current endoscopic screening failing to capture asymptomatic or under-recognized high-risk groups of patients. Non-endoscopic tools, such as Cytosponge and liquid biopsy, are promising adjuncts for bridging these gaps. A precision prevention approach, integrating molecular diagnostics, risk-based screening, and inclusive surveillance, is essential for mitigating the rising incidence of EAC and improving outcomes in at-risk populations.

Keywords: Gastroesophageal reflux disease, Barrett's esophagus, Esophageal adenocarcinoma, Metaplasia, Dysplasia, Risk stratification

INTRODUCTION

As of 2019, there were approximately 780 million cases of GERD globally, with an estimated 10-20% of Western populations and fewer than 5% of Asian populations. Over the past three decades, epidemiological statistics have shown a consistent rise in prevalence and incidence, primarily due to aging, population expansion, and lifestyle factors such as nutrition and obesity. There is significant geographic variation, with lower rates in underdeveloped nations and higher rates in developed and Westernized countries. However, accurate global estimates are complicated by differences in disease classification, reporting methods, and data quality. Diverse phenotypes, extraesophageal symptoms, and related premalignant disorders such as BE, which affects up to 5% of people in the US but only 1% worldwide, further complicate the epidemiology of GERD. These patterns highlight the need for established diagnostic standards and focused therapies, as well as the increasing public health implications of GERD in the country.[1,2]

Epidemiological framework for GERD prevalence was built on a 2005 comprehensive review by Dent et al which found a prevalence of 10-20% in Western countries and <5% in Asia.[1] With tropical Latin America displaying the highest age-standardized prevalence, Zhang et al claimed that the frequency of GERD has increased by 77.53% globally since 1990.[3] Bai et al further clarified these trends by examining non-malignant upper gastrointestinal diseases, including GERD, using GBD 2019 data supplemented by decomposition and frontier studies.[3]

Iranian-specific data from Delavari et al who approximated a week of global GERD prevalence of 21.2% in Tehran, which exceeded previous Asian estimates and matched Western nations, provided regional insights. Many studies examined lifestyle and preventable risk factors, mostly with an eye toward dietary triggers, including obesity, alcohol, smoking, hot and fatty foods.[4]

The diversity of GERD phenotypes complicates the estimation of its prevalence. The complex etiology and phenotypic variations of GERD have been well described by Fass et al, Marques de Sá et al and Sharma systematically examined BE, a premalignant disorder associated with GERD.[5-7] With considerable geographic diversity, they calculated that the prevalence of BE among GERD sufferers was 7.2%, approximately 1% globally.

Extraesophageal symptoms add to the epidemiological complexity, and methodological flaws in racial/ethnic reporting in GERD research limit our capacity to understand the variations.

Emphasizing need for context-specific care and worldwide relevance of GERD, Hunt et al presented global recommendations combining clinical and epidemiological data.[8]

Table 1: Impact of clinical, molecular, and diagnostic parameters on BE and EAC.

Category	Factor/tool	Impact on progression or detection	Reference
Clinical	GERD frequency	Increases BE risk (OR 3.56)	9
	Barrett's segment length (LSBE)	Higher risk of dysplasia and EAC	10 and 11
	Obesity (BMI >30)	Increases risk via metabolic and reflux mechanisms	12
	Smoking	Increases BE (OR 1.41) and EAC (OR 2.15) risk	13
Molecular	p53 mutation	Correlates with HGD and EAC risk	14 and 15
	Aneuploidy	Predicts malignant progression	14
	Hub gene upregulation (e.g., MMP1, COL1A1)	Indicates early neoplastic remodeling	16
Non-endoscopic tools	Cytosponge-TFF3	Non-invasive BE detection in primary care	17
	Liquid biopsy	Detects ctDNA; emerging early detection tool	18
Surgical intervention	Antireflux surgery	May reduce progression; evidence mixed	19 and 20
Surveillance approach	Risk-based endoscopic surveillance	Improves detection in high-risk patients	21,22

The global evidence base is substantial, supported by extensive datasets such as the GBD and comprehensive systematic reviews; however, it is constrained by variability in GERD definitions, diagnostic criteria, and reporting standards among studies. Numerous prevalence studies depend on symptom-based questionnaires devoid of confirmatory tests, jeopardizing accurate classification. Geographic variations in data availability, particularly in low- and middle-income countries, hinder thorough global assessments. The incorporation of extraesophageal symptoms and premalignant states introduces complexity, although they are frequently reported inconsistently. The global prevalence of GERD is increasing, with lower rates in Western countries and Asia than in other regions. This is due to lifestyle changes and urbanization, resulting in a total global burden of 800 million. The growing prevalence of GERD necessitates the establishment of standardized diagnostic criteria and targeted interventions that address modifiable risk factors and improve data collection in underrepresented regions.[23-26]

ESOPHAGEAL ADENOCARCINOMA

EAC originates from glandular cells in the lower esophagus and typically evolves from BE, a condition more prevalent among older males with risk factors such as chronic GERD, obesity, smoking, and a positive family history.[27,28] Over recent decades, Western populations have experienced dramatic increases in EAC incidence-up to 600% over 30 years-largely attributed to lifestyle-related factors including obesity and GERD.[27,29,30] Although the majority of EAC cases occur in older age groups, emerging evidence indicates a rising incidence in younger males, particularly those aged 40-49 years, as highlighted by a population-based study from Japan that reported annual increases exceeding 7%.[31] However, in Western countries, BE and EAC remain relatively rare in individuals under 50, and current screening guidelines are primarily directed at older males with multiple risk factors.[27,28] Advances in nonendoscopic screening methods, such as circulating microRNAs and minimally invasive esophageal sampling techniques, show promise for earlier detection of BE and EAC, though their specific utility in young males remains to be fully established.[18,32,33]

BARRETT'S ESOPHAGUS

BE is a condition in which the healthy lining of the esophagus undergoes a transformation, frequently as a result of chronic acid reflux, into a tissue that is more akin to that of the intestine. BE is the sole known precursor of EAC, a malignancy with an obviously terrible prognosis, thus this metaplastic transition is important.[34,35] Early detection and focused therapy depend on an awareness of which molecular and histological signals indicate the change from BE to EAC.

Histologically, the sequence is well known: normal squamous epithelial → intestinal metaplasia (BE) → low-grade dysplasia → HGD → invasive cancer.[14] Currently the most consistent histological marker showing higher cancer risk is dysplasia, especially high-grade. But depending just on microscopic inspection has drawbacks because pathologists' subjective assessment varies and sample errors exist.[14,15]

Emerging as indispensable allies to histology, molecular markers provide more objective, early signals of malignant change. Detectable by immunohistochemistry, abnormal p53 protein expression is one of the most clinically recognized molecular indicators; it is linked with TP53 gene mutations and represents progression risk.[15,36] Another sign linked to higher risk of advancement is aneuploidy, or aberrant DNA content, found by flow cytometry.[15] Other genetic changes linked have loss of heterozygosity at chromosome 17p (harboring TP53), mutations in tumor suppressor genes such p16, and anomalies in genes controlling cell cycle and adhesion, including cyclin D1 and E-cadherin.[14,15]

Recent proteomic studies have revealed variations in protein expression profiles along development. For instance, dysplastic and malignant tissues showed higher expression of DNA repair proteins (MSH6) and nuclear export proteins (XPO5), implying their relevance in carcinogenesis.[16] These proteins reflect the intricacy of molecular mechanisms driving development by being involved in micro-RNA trafficking and DNA damage repair pathways.

Studies at the genomic level expose a varied mutational terrain in BE with multiple mutations even in non-dysplastic tissue. Some patients may have fast malignant transformation in response to large-scale chromosomal abnormalities including copy-number changes and genome doubling events (chromothripsis).[36] This genetic instability emphasizes how difficult it is to forecast progression based just on histology.

From normal esophagus through BE to EAC, bioinformatics techniques examining gene expression profiles have found "hub genes," increasingly upregulated from normal esophagus. Involved in extracellular matrix remodeling, cell adhesion, and immunological responses, key genes include COL1A1, TGFBI, MMP1, COL4A1, NID2, MMP12, and CXCL 1. These genes not only indicate therapeutic targets but also possible biomarkers for progression since medications blocking pathways linked to them may halt or stop development of cancer.[37]

Including molecular markers into clinical practice seeks to enhance risk assessment. Under evaluation to complement histology and inform surveillance and treatment decisions are tools like wide area transepithelial sampling with three-dimensional computer-assessed analysis (WATS3D), tissue cypher (a multiplexed biomarker assay), and mutational load analysis (BarreGen). Many molecular markers need more confirmation even if they show great potential before general clinical use.[36,37]

This review explores the progression from GERD to BE and EAC, focusing on the increasing incidence of EAC in young males. It highlights current gaps in surveillance and early detection, particularly the lack of tailored strategies for emerging high-risk groups. The review underscores the need for risk-adapted screening protocols and biomarker-based approaches to improve early diagnosis and outcomes.

FROM GERD TO BARRETT'S: EPIDEMIOLOGIC AND MOLECULAR EVOLUTION

The pathophysiological mechanism by which GERD leads to intestinal metaplasia in BE is multifactorial, integrating insights from clinical, histopathological, and molecular domains. Central to this process is the chronic injury inflicted by repeated exposure of the esophageal epithelium to refluxate containing gastric acid and bile acids. Evidence from Mukaisho et al demonstrates that duodenal fluid rich in bile acids induces mucosal injury and sustains a pro-inflammatory environment through activation of the epidermal growth factor receptor (EGFR) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling pathways, thereby fostering carcinogenic progression.[38] Maslenkina et al further elaborate that reflux-induced epithelial damage prompts a cytokine storm, culminating in an inflammatory microenvironment highly conducive to metaplastic transformation.[39] In this context, chronic inflammation is not merely a byproduct of reflux injury but a key pathological driver, initiating a shift from the native stratified squamous epithelium to a columnar intestinalized phenotype.

Multiple molecular signaling pathways are implicated in orchestrating this phenotypic shift. As highlighted by Maslenkina et al aberrant activation of signaling axes such as NOTCH, Hedgehog, NF-κB, and IL6/STAT3 plays a pivotal role in regulating epithelial remodeling and stem cell fate.[39] In particular, suppression of NOTCH signaling correlates with intestinal differentiation, while the

Hedgehog pathway, aberrantly activated under reflux conditions, contributes to epithelial remodeling. Bile acids also activate NF-κB signaling, promoting the expression of pro-inflammatory cytokines and reinforcing the chronic inflammatory state. Meanwhile, IL6/STAT3 signaling enhances epithelial proliferation and survival, further facilitating the establishment of metaplastic epithelium.[39]

The cellular origins of Barrett's metaplasia remain a subject of ongoing investigation but are essential to understanding the underlying pathogenesis. Que et al propose several potential progenitor cell sources, including basal cells of the squamous epithelium that undergo transdifferentiation, esophageal submucosal gland cells and their ducts, proximal gastric stem cells, and residual embryonic cells at the esophagogastric junction.[40] The metaplastic transition may occur through transdifferentiation-direct conversion of squamous cells to columnar cells-or via transcommitment, involving reprogramming of undifferentiated progenitor cells toward a new lineage. This transformation is conceptualized as an aberrant wound-healing response, wherein chronic mucosal injury activates latent developmental pathways, leading to intestinal metaplasia as a maladaptive but regenerative mechanism.[40]

Clinical and epidemiological findings reinforce the mechanistic links between GERD and BE. A meta-analysis conducted by Taylor and Rubenstein encompassing over 10,000 patients from 26 studies revealed a fivefold increase in the odds of developing long-segment BE (LSBE) among GERD patients.[41] Notably, this strong association is less evident for short-segment BE (SSBE), suggesting that the chronicity and severity of reflux exposure are critical determinants of metaplastic response. These epidemiological trends align with molecular evidence, underscoring the necessity of prolonged reflux-induced injury to fully instigate epithelial transformation.

From a histopathological standpoint, the diagnosis of BE is predicated on the identification of intestinal metaplasia characterized by goblet cells, as emphasized by Falk and Spechler.[42,43] However, distinguishing true Barrett's epithelium from intestinal metaplasia of the gastric cardia remains diagnostically challenging due to overlapping histological and molecular features. This ambiguity underscores the complexity of interpreting reflux-associated intestinalization and reinforces role of chronic mucosal injury in initiating the metaplastic cascade.[40,42,43]

Recent genomic and transcriptomic analyses further deepen our understanding of BE pathogenesis. Peters et al provide evidence of reflux-induced mutagenesis in stem cells, which may not only stabilize the metaplastic phenotype but also predispose to neoplastic progression.[44] This molecular perspective supports the model in which chronic exposure to refluxate results in both genetic alterations and epigenetic reprogramming, thereby anchoring the intestinal phenotype and amplifying the risk of malignant transformation.[44]

Despite these insights, limitations in the quality of evidence persist. Much of the mechanistic understanding stems from animal models and narrative reviews, with limited direct applicability to human pathology. While large-scale meta-analyses offer robust epidemiological associations, they fall short in elucidating cellular mechanisms. Molecular pathway studies are often conducted *in vitro* or in non-human systems, and few have been validated in human tissues or through longitudinal analyses. The study by Taylor and Rubenstein, although comprehensive, is not immune to heterogeneity and diagnostic inconsistencies across included studies.[41]

In synthesis, the progression from GERD to intestinal metaplasia in BE is orchestrated by a complex interplay of chronic reflux-induced injury, sustained inflammation, and molecular reprogramming of esophageal progenitor cells. Persistent exposure to acidic and biliary refluxate damages the esophageal squamous epithelium and triggers inflammatory signaling, particularly through pathways such as NOTCH, Hedgehog, NF-κB, and IL6/STAT3. These pathways mediate changes in stem cell behavior and epithelial identity, culminating in development of columnar intestinal-type mucosa. Cellular origin of this metaplasia is likely heterogeneous, involving contributions from basal squamous cells, submucosal gland progenitors, and possibly residual embryonic cells. Clinically, this process correlates with long-standing GERD, particularly in patients with LSBE and carries implications for neoplastic transformation. Moving forward, delineating the precise origin of the metaplastic epithelium in human subjects and developing targeted interventions to modulate these molecular pathways remain critical goals in preventing BE and its progression to EAC.[10,41]

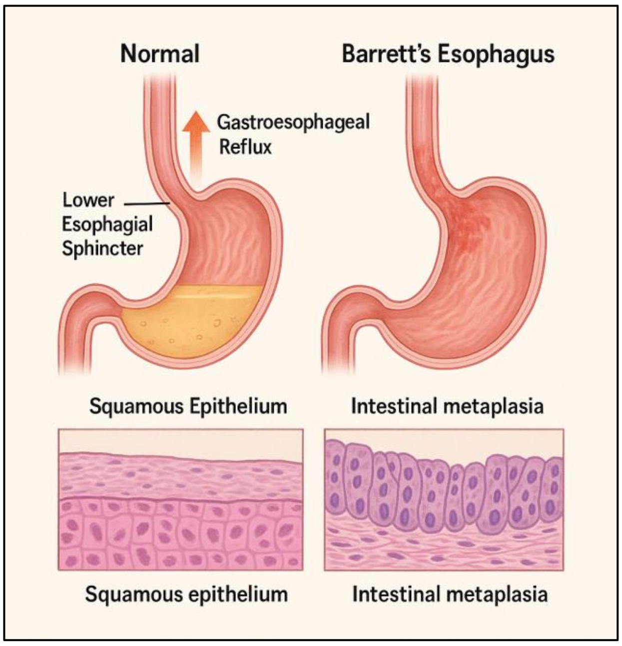

Figure 1: Pathogenic and molecular continuum from GERD to EAC: a multilevel risk stratification mode.

BARRETT'S ESOPHAGUS TO ADENOCARCINOMA: RISK STRATIFICATION AND PROGRESSION PATHWAYS

The progression of BE to EAC is influenced by a combination of clinical, molecular, and genetic risk factors. Key determinants include the length of the Barrett's segment, the presence and grade of dysplasia, chronic GERD symptoms, male sex, obesity, tobacco smoking, and genetic predispositions. Antireflux surgery may potentially reduce progression risk in BE patients, but the evidence remains inconclusive. Surveillance strategies tailored to high-risk patients are essential, with the integration of clinical, endoscopic, molecular, and genetic assessments critical for optimal management.[11]

Barrett's segment length and dysplasia grade

Kim et al found that long-segment BE (LSBE, ≥3 cm) significantly increases the risk of progression to dysplasia and EAC when compared to short-segment BE (SSBE, <3 cm).[11] Despite this, clinical management often overlooks segment length, potentially underestimating risk in LSBE patients. The review suggests more aggressive management and shorter surveillance intervals for LSBE patients, a recommendation that aligns with findings by Kuipers and Spaander which confirmed the correlation between segment length, HGD and cancer risk, along with male sex and age.[45]

Krishnamoorthi et al conducted a meta-analysis of 1,441 patients with BE indefinite for dysplasia (BE-IND) and reported a progression incidence of 1.5 per 100 person-years to HGD/EAC, emphasizing the importance of dysplasia grading in risk stratification.[4] This progression risk rises from indefinite to low-grade dysplasia and HGD.[13]

GERD and symptom frequency

GERD symptoms, particularly when occurring weekly, have been shown to increase the likelihood of developing BE. Antonios et al found that frequent GERD symptoms increase the odds of BE by 3.56-fold (95% CI 2.03-6.25).[9] Chronic acid reflux plays a key role in inducing the metaplastic changes characteristic of BE. However, as Ness-Jensen points out, approximately 40% of EAC patients do not report prior GERD symptoms, indicating that silent reflux may contribute to the pathogenesis of EAC.[46] This suggests that relying solely on symptomatology is insufficient for precise risk stratification.

Obesity and metabolic factors

Schlottmann et al reviewed the mechanisms linking obesity, particularly central adiposity, to BE and EAC risk. These include increased GERD prevalence, altered adipokine profiles (low adiponectin, high leptin), insulin resistance, and microbiota alterations.[12] Antonios et al confirmed that obesity (BMI >30) significantly raises the risk of BE (OR 1.23; 95% CI 1.09-1.39).[9] These findings highlight the metabolic factors that contribute to carcinogenesis in BE beyond acid reflux alone.

Tobacco smoking and alcohol use

Smoking is consistently identified as a major risk factor for both BE and EAC. Antonios et al reported an odds ratio (OR) of 1.41 (95% CI 1.30-1.51) for BE and 2.15 (95% CI 1.85-2.43) for EAC with tobacco use.[9] Alcohol consumption is also linked to BE (OR 1.37; 95% CI 1.10-1.71), though its role in progression to EAC remains less clear. The carcinogenic effects of tobacco are well-documented, with DNA damage and mutation accumulation in the esophageal epithelium contributing to BE and EAC development.

Genetic predisposition

Callahan et al reviewed the emerging evidence on genetic variants associated with BE and EAC risk.[47] Genome-wide association studies (GWAS) have identified loci related to inflammation, cell proliferation, and DNA repair, although the full genetic contribution is yet to be comprehensively understood. This area represents a promising frontier for personalized risk assessment and surveillance.

Role of antireflux surgery

Two systematic reviews/meta-analyses (Rayner and Gatenby and Maret-Ouda et al) assessed the effect of antireflux surgery on BE progression.[19,20] Rayner et al analyzed 962 patients over 3,736 patient-years and reported an annual incidence of EAC of 0.18% post-surgery, with 8% progression and 35% regression of Barrett's features.[19] Maret-Ouda et al found a non-significant trend towards reduced EAC risk after surgery compared to medical therapy (IRR=0.76; 95% CI=0.42-1.39), although the risk remained elevated compared to the general population (IRR=10.78).[8,20] These findings suggest that while anti-reflux surgery may provide some protective benefit, it is not curative/ preventive on its own.

Surveillance and cost-effectiveness

Inadomi and Saxena discussed the cost-effectiveness of screening and surveillance, noting that endoscopic eradication therapy is cost-effective for HGD but not for non-dysplastic BE.[21] Wani and Gaddam emphasized the challenges of risk stratification in surveillance programs, which must account for variability in progression rates and biomarkers.[22] Kuipers and Spaander recommended targeted surveillance based on segment length, dysplasia grade, and patient demographics to improve outcomes.[45]

Molecular and pathophysiological insights

Peters et al reviewed the molecular mechanisms of BE and its progression to EAC, focusing on inflammatory pathways, oxidative stress, and genomic instability as key factors in malignant transformation.[44] Beydoun et al reinforced these findings, noting the role of inflammatory and growth factor pathways, mitochondrial changes, and pepsin exposure in carcinogenesis.[48]

Special populations

Tullie et al reported a high prevalence of BE (5.0%) and EAC in patients with repaired esophageal atresia, a cohort with chronic reflux and altered esophageal anatomy.[49] Dunn et al highlighted the development of Barrett's-like metaplasia in the esophageal remnant post-esophagectomy, underscoring the importance of reflux and mucosal injury in metaplastic progression.[50]

Chemoprevention

Mehta et al reviewed chemopreventive strategies, finding that proton pump inhibitors (PPIs) have not convincingly reduced cancer risk, while NSAIDs and dietary agents show potential in preclinical and epidemiological studies.[51] Ness-Jensen acknowledged some evidence for PPIs in preventing EAC but also noted limitations due to asymptomatic cases and incomplete surveillance.[46]

The progression of BE to EAC is influenced by various risk factors, including Barrett's segment length and dysplasia grade. The presence of GERD symptoms increases the risk, but silent reflux complicates risk prediction. Modifiable risk factors include obesity and tobacco smoking. Genetic predisposition is an emerging factor for personalized risk assessment. Personalized surveillance strategies are essential for early detection and intervention.

CURRENT GAPS IN SCREENING AND SURVEILLANCE: WHO ARE WE MISSING?

The American college of gastroenterology (ACG), American gastroenterological association (AGA), and European society of gastrointestinal endoscopy (ESGE) have established guidelines for gastrointestinal endoscopy. The ACG recommends starting CRC screening at age 45, while the AGA advocates for colonoscopy as the preferred one-step method. The ESGE focuses on colonoscopy as the primary screening method for average-risk populations, but does not specify an exact starting age. The ACG and AGA generally agree on screening high-risk populations, but differ in specific recommendations.

Critical assessment of limitations in current surveillance

Endoscopy-based surveillance limitations

For CRC screening, the ACG stresses colonoscopy as the gold standard, even though it is quite expensive and invasive. Despite the possible hazards and invasiveness of upper endoscopy, it also recognizes the difficulties in using it for GC screening. The ACG acknowledges the value of a high-quality endoscopic examination in identifying GPC in high-risk individuals in spite of these obstacles.[17,52]

Limitations of symptom-driven strategies

Symptom-driven strategies for gastrointestinal cancer screening often result in delayed diagnosis. Patients with symptoms such as dyspepsia or gastrointestinal bleeding may undergo endoscopy, but asymptomatic individuals at risk of cancer are likely to be overlooked. A study showed that most patients with BE (a precursor to EAC) were diagnosed after experiencing symptoms like heartburn or dysphagia, rather than through screening.[53] Similarly, many GC patients are diagnosed at advanced stages due to the absence of early symptoms.[54]

Disparities in access, diagnostic delays, and under-recognized high-risk populations

Disparities in access

Racial and ethnic minorities face significant barriers to accessing gastrointestinal cancer screening. African Americans have one of the highest CRC incidence rates in the U.S., yet their screening rates are lower than those of whites. Studies suggest that African Americans are less likely to undergo colonoscopy and more likely to experience diagnostic delays, contributing to higher CRC mortality rates.[17] Similarly, immigrants from high-incidence regions and U.S. populations with high GC incidence, such as East Asian individuals and Latino groups, may struggle to access screening services due to language barriers, lack of health insurance, and limited awareness of screening importance.[55,56]

Diagnostic delays

Diagnostic delays exacerbate the prognosis of gastrointestinal cancers. A study found that delays in diagnosing BE were associated with increased risks of EAC.[57] For GC, delays in diagnosis often lead to advanced-stage disease at presentation, reducing treatment efficacy and survival rates.[8] The ACG highlights that in the U. S., GC screening and surveillance for high-risk racial and ethnic populations are ethically and clinically justified but emphasizes that efforts to address screening disparities are critical.[58]

Under-recognized high-risk populations

Some high-risk populations are often overlooked in screening programs. For example, individuals with autoimmune atrophic gastritis (AAG) have an elevated risk of GC and type 1 neuroendocrine tumors. However, the ACG notes insufficient evidence to make formal recommendations on endoscopic surveillance for AAG patients.[17] Additionally, individuals with gastric polyps, particularly those with hyperplastic polyps larger than 10 mm, may be at increased risk of GC but lack clear surveillance guidelines.[58]

Non-endoscopic tools as scalable screening methods

Cytosponge: The Cytosponge is a non-endoscopic tool for detecting BE. Patients swallow a capsule attached to a string, which releases a sponge that collects esophageal cells when pulled out. Studies have shown that Cytosponge combined with biomarker testing can effectively identify individuals with BE, with high sensitivity and specificity. Its simplicity and non-invasiveness make it a promising screening method for primary care settings.

Cytosponge-TH disseminated in primary care (Cytosponge-TH delle) study demonstrated that Cytosponge test is effective in identifying BE in primary care.[58]

Liquid biopsy: Liquid biopsy involves analyzing circulating tumor DNA in blood to detect early-stage cancers. Research indicates that liquid biopsy has potential for gastrointestinal cancer screening, particularly for CRC. For example, multi-target stool DNA test combines fecal immunochemical testing with DNA marker analysis, improving detection rates for early-stage CRC. Additionally, blood-based liquid biopsies are being explored for GC screening, though their diagnostic accuracy and cost-effectiveness require further validation.[59]

Table 2: Comparison of recommendations in ACG, AGA, and ESGE guidelines.

Guideline	Recommendation for CRC Screening	Recommendation for GC screening	Recommendation for GPC surveillance	Reference
ACG	Begin screening at age 45 with any test; colonoscopy is the preferred one-step screening method	Routine upper endoscopy screening not recommended for the general U.S. population; focused screening of high-risk populations may address GC disparities	Systematic gastric biopsies according to the updated Sydney protocol are recommended for individuals at increased risk of GPC or suspected GPC	17
AGA	Begin screening at age 45 with any test; special efforts needed to boost screening among African Americans	Insufficient evidence to make recommendations for upper endoscopy screening for GC/GPC in high-risk U.S. populations	Endoscopic surveillance may be considered for individuals with certain hereditary genetic syndromes or a first-degree family history of GC	53 and 54
ESGE	Colonoscopy is the primary screening method for average-risk populations	Upper gastrointestinal endoscopy is recommended for high-risk populations, such as those with a family history of GC or hereditary genetic syndromes	High-definition white-light endoscopy and image-enhanced endoscopy are suggested for patients undergoing upper endoscopy for GPC evaluation	60

CONCLUSION

EAC is a global disease characterized by chronic mucosal injury, inflammatory signaling cascades, and molecular alterations. Conventional clinical markers are insufficient for predicting disease progression. To address this, surveillance paradigms must consider silent reflux and incorporate emerging molecular tools. Innovations like Cytosponge-TFF3 test and liquid biopsy approaches offer non-invasive alternatives, while artificial intelligence can improve diagnostic accuracy. Addressing disparities in access to care and a transition towards precision medicine requires multidisciplinary collaboration, robust data infrastructure, and harmonization of diagnostic standards.

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