PRIMEVIEW

GASTRIC ADENOCARCINOMA

nature REVIEWS DISEASE PRIMERS

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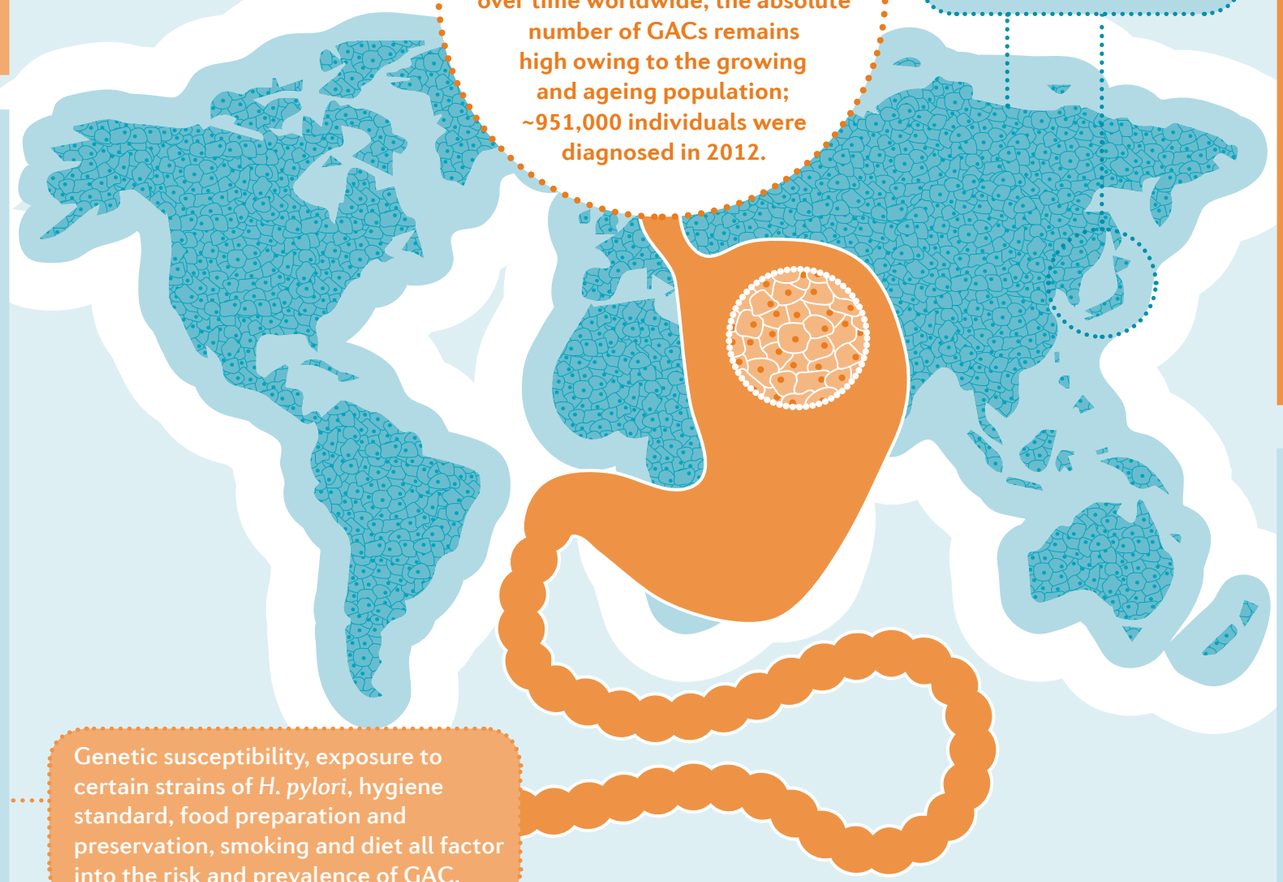
Gastric adenocarcinoma (GAC) accounts for ~95% of cancers originating in the stomach. Typically classified according to its location, GAC has heterogeneous phenotypes, molecular features and associated risk factors, including *Helicobacter pylori* infection.

EPIDEMIOLOGY

Globally, GAC is the fifth most common cancer type, occurring twice as often in men as in women. Although incidence has gradually declined over time worldwide, the absolute number of GACs remains high owing to the growing and ageing population; ~951,000 individuals were diagnosed in 2012.

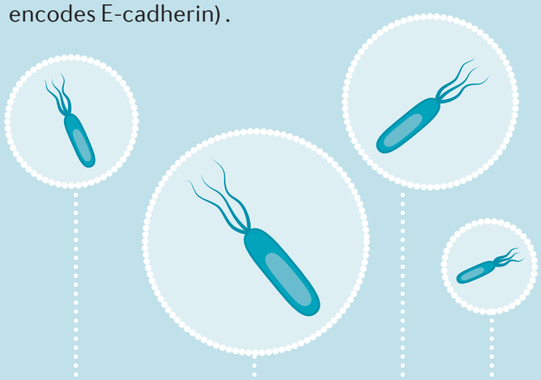
Endemic areas with high rates of GAC include the countries of Eastern Europe, many South and Central American countries, Iran, Russia and countries of Eastern Asia. Incidence is highest in Japan and South Korea.



Genetic susceptibility, exposure to certain strains of *H. pylori*, hygiene standard, food preparation and preservation, smoking and diet all factor into the risk and prevalence of GAC.

MECHANISMS

Numerous signalling pathways (such as those mediated by various growth factors) are amplified in GAC, leading to aberrant and uncontrolled gene expression, cell proliferation, cell survival and angiogenesis. In addition, the majority (66%) of GACs have at least one mutation in cell cycle-related genes. GAC cells also commonly display stem-like features, mediated by mutations in Hippo, WNT and Hedgehog signalling. Other common mutations in GAC affect the epigenetic machinery (chromatin remodelling and histone methylation), cell adhesion and focal adhesion (for example, mutations in *CDH1*, which encodes E-cadherin) .



! The majority of endemic GAC cases may be related to *H. pylori* infection, which contributes to carcinogenesis and progression by promoting chronic inflammation. A pro-inflammatory milieu leads to oncogenic activation, aberrant methylation (and silencing of tumour suppressor genes) and production of reactive oxygen and nitrogen species, which promote DNA damage.

SCREENING

Japan introduced screening in high-risk individuals in the early 1980s, and is the only country to do so. Most commonly, barium radiography — in which the ingested barium appears white on radiography, highlighting the presence of gastrointestinal abnormalities — is used, but endoscopic screening has recently been introduced. Screening has resulted in a dramatic shift in stage at diagnosis and a reduction in GAC-related mortality.

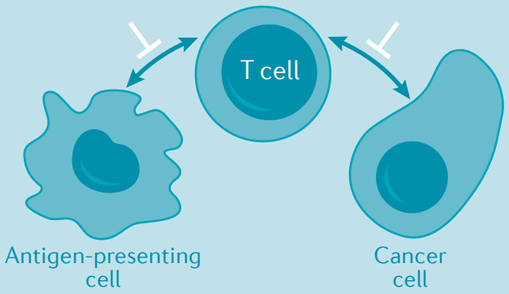
! Primary prevention of GAC involves reducing or eliminating exposure to carcinogens, eradicating *H. pylori*, adopting healthier lifestyles and using aspirin as a chemopreventive agent.

MANAGEMENT

Once diagnosed, the clinical stage of the GAC can be used to guide initial treatment; early-stage tumours can be surgically resected or treated endoscopically, whereas tumours with locoregional spread will require better staging information to guide treatment. If a total resection is desired, the pathology of the resected tumour will guide the type of adjuvant therapy sought. Patients unfit for surgery or who present with unresectable, widespread disease are offered chemotherapy or chemoradiotherapy.

OUTLOOK

Because early-stage GAC is highly treatable (with a 5-year survival rate of ~95%) and advanced-stage GAC is highly lethal (with a median survival of just ~9–10 months), research efforts have focused on strategies to detect GAC early and treat metastatic disease. For example, several GAC-associated antigens are in development as diagnostic biomarkers. In addition, several immune checkpoint inhibitors are being assessed for use in GAC, building on success in other cancer types. Indeed, enthusiastic clinical trial participation, and tumour tissue and blood donations for research, are needed for progress in the near future.



Written by Mina Razzak; designed by Laura Marshall

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