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EDITORIAL

Progress in gastric cancer

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Every year there are nearly 1 million new cases of gastric cancer worldwide, making it the third leading cause of cancer related deaths worldwide and prompting the World Health Organization to declare it a public health concern [1]. Although some forms of gastric cancer are decreasing due to better surveillance, detection and treatment, there are other forms of gastric cancer that are increasing in incidence, for example, the 70% increase in the incidence of non-cardia gastric cancer in 25–39 year olds in the United States, showing that despite progress in many areas, there is still much to be elucidated [2].This article will survey the main contributors to these advances, including better understanding of gastric cancer etiology, screening programs, and improvements in treatment and progress in our understanding of this heterogeneous cancer.

One major factor in the global decline in gastric cancer incidence is the discovery in the 1980s that *H. pylori* infection causes gastric ulcer disease, which can progress to gastric cancer. This public health advance won Drs. Barry Warren and Robin Russell the Nobel Prize. Patients with symptoms of gastric ulcers are now routinely tested for *H. pylori*, which is treatable with antibiotics. Nonetheless, this pathogen remains a major cause of gastric cancer in developing countries.

Decreased rates of gastric cancer can also be attributed, at least in Western countries, to improvements in diet. Increased consumption of fresh vegetables and fruits, and reduced consumption of preserved foods high in salt, has decreased the incidence of many cancers. However, diet remains a contributor to gastric cancer risk in areas such as East Asia and Eastern Europe, where traditional cuisines feature salt-preserved foods, pickled vegetables, and in the latter region, cured and smoked meats; all of these foods are linked both epidemiologically and mechanistically to gastric cancer. Nonetheless, different regions of the world have vastly different survival rates, owing partly to timing of detection and screening programs. Countries without established screening programs have poorer overall survival compared to countries with aggressive government sponsored screening programs, largely due to earlier detection. Screening recommendations are generally recommended based on incidence in the population.

The etiology for differences in incidence of gastric cancer in various regions of the world has been a source of great controversy and disagreement. For example, certain countries, such as Japan and South Korea, have a nearly 10 fold higher incidence of gastric cancer compared to countries like the United States. Some groups have attributed differences in incidence to genetic factors, however emerging data from genetic analysis are not finding specific mutations associated with racial subgroups. In fact counter arguments demonstrate that in pockets of the Western world, such as Italy, Eastern Europe and Chile, gastric cancer rates approach those seen in high-incidence Asian countries. Other groups argue that diet is an important predisposing risk factor for gastric cancer, citing high salt diets and those high in nitrites, including smoked or grilled foods, as being responsible for the increased incidence in some countries. Although many studies cite the relation of healthy diets high in vegetable and fruits and low in sodium and red meat, as being protective against many types of cancer, the dietary differences are insufficient to explain the differing incidence of gastric cancer among global regions. Genetics have also been posited as a reason for geographic variation in gastric cancer rates, but genetic analyses have not yet found compelling risk-correlated mutations associated with ethnic groups.

A key step forward in understanding the complex epidemiology of gastric cancer was the discovery of a mutation causing familial gastric cancer by Dr. Parry Guilford in 1998 [3]. His team found that a mutation in the tumor suppressor gene CDH1, encoding E-cadherin, was responsible for inherited gastric cancer in a Maori kindred. Germline

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loss-of-function mutations in E-cadherin increase the lifetime risk of developing diffuse (sometimes called signet ring) gastric cancer, which is very aggressive, as well as lobular breast cancer. This advance has enabled investigations of how a genetic form of gastric cancer develops and progresses, as well as genetic testing in patients with family history to identify those in need of intensive monitoring and preventive care.

The discovery of the genetic basis for one subtype of gastric cancer paved the way for the concept that all tumors fall into recognizable clinical subtypes. The establishment of these three categories also followed mounting evidence that outcomes and survival were related to the anatomic location and histopathology of gastric cancer [4]. Gastroesophageal or GE junction cancers are more aggressive and have poorer survival compared to distal intestinal-type cancers, both of which are distinct from the rarer diffuse or signet-ring type gastric cancers. GE junction cancers are associated with esophageal reflux and obesity, whereas distal cancers are related to *H. pylori* infection and ulcers; diffuse cancers are non-inflammatory and tend to be familial. This concept has been rapidly adopted around the world, and will likely lead to improvements in care, as each subtype's responses to various therapies can now be distinguished.

A further augmented classification system that is proving very important for advancing gastric cancer treatment arose from the US Cancer Genome Atlas project [5]. That study defined four molecular subtypes: Epstein Barr virus (EBV)-related tumors, microsatellite unstable tumors, genomically stable tumors and tumors with chromosomal instability. While most EBV-related cancers are located in the gastric body and those with chromosomal instability were especially frequent at the GE junction, these subtypes do not clearly correspond to the three clinical classifications and are not associated with different outcomes. Nonetheless, this genetic information promises to lead to molecularly targeted therapies, as they have distinct signaling dependencies.

Regardless of subtype, early detection is key to improving survival, as evidenced by the success of Japan and South Korea's aggressive government-sponsored screening programs, where rates of gastric cancer are among the highest in the world. These public health efforts likely help explain the continuing enhancement in global gastric cancer survival.

Changes in the treatment of gastric cancer are also already improving outcomes. The mainstay of treatment remains curative resection, but several large-scale, randomized prospective trials have shown that various perioperative therapies enhance survival by 10–15% for patients with locally advanced gastric cancer. The first of these was the MAGIC trial, which found that perioperative treatment with chemotherapy (epirubicin, cisplatin, and fluorouracil) both before and after surgery improved disease-specific survival. Most recently, a randomized trial showed that perioperative chemotherapy with FLOT (docetaxel, oxaliplatin and fluorouracil/leucovorin) further improved survival (results were presented at the 2017 American Society of Clinical Oncology meeting). Other effective regimens include post-operative chemotherapy with S-1 [6] or capecitabine-oxaliplatin [7] and post-operative chemotherapy and radiation [8].

Gastric cancer staging and resection have also progressed remarkably in the past 5–10 years. In many parts of the world, including the US, staging practices now include diagnostic laparoscopy prior to planned resection to identify patients with metastatic disease who would not benefit from resection and instead need systemic therapy. Even more revolutionary is the broad adoption of laparoscopic or robotic gastrectomy for appropriately selected patients with gastric cancer. Many large retrospective and several prospective randomized studies in different countries have shown that these surgical approaches are oncologically equivalent to open surgery, with fewer complications and decreased recovery time. Laparascopic gastrectomy has been proven effective even for some locally advanced tumors (KLASS-2 trial). Though thorough resection of advanced tumors requires an open technique, the rapid acceptance of less invasive surgery for most cases has been encouraging, and new and better technologies continue to emerge.

Overall, there has been tremendous progress in the understanding and treatment of gastric cancer. Many environmental and genetic factors influencing gastric cancer development have been identified, and further elucidation promises to aid prevention and lead to new therapies. Improvements in perioperative treatment will hopefully be refined based on genetic understanding to enable individualized treatment. Revolutionary improvements in laparoscopic and robotic resection for appropriately selected patients will be augmented by image-guided technologies and advances in automation.

Compliance with ethical standards

Conflict of interest The author declares that she has no conflict of interest.

Research involving human participants and/or animals This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study formal consent is not required.

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