

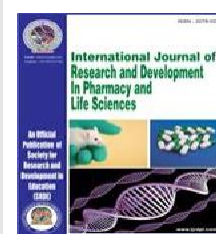


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Review Article

An overview on Gastric Carcinoma with its recent statistical ranges throughout the world

Venkatesh Goli, Om Sai Prakash Lanka, J.R. Tulasi*

Department of Pharmaceutical chemistry, Sir CRR college of pharmaceutical sciences, GNT Road, Shanthi Nagar, Eluru, India

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↑ Corresponding author at:

J.R. Tulasi (M. Pharm., Ph. D), Department of Pharmaceutical chemistry, Sir CRR college of pharmaceutical sciences, GNT Road, Shanthi Nagar, Eluru, India

E-mail: tulasikanumuri@gmail.com

ABSTRACT: Gastric cancer is the Fifth most common cancer and third most cause of cancer-related deaths in the world. The Decreasing number from the last two decades is the effect of the Healthy lifestyle, and Helicobacter pylori eradication, The review article pronounces the importance of mass screening and early detection in high risk population and summarizes the most important aspects of gastric cancers, which include epidemiology, risk factors, classification, tumor markers, diagnosis, prevention, ,treatment strategies for different stages of cancer and their five year survival rate. It also emphasizes global updated statistics of stomach cancer incidence, mortality rate and highly prevalent areas of this cancer to provide basic details to the researcher for identifying the need of developing more screening programs in high risk population and develop new treatments to improve the quality of life and survival rate in these people.

INTRODUCTION

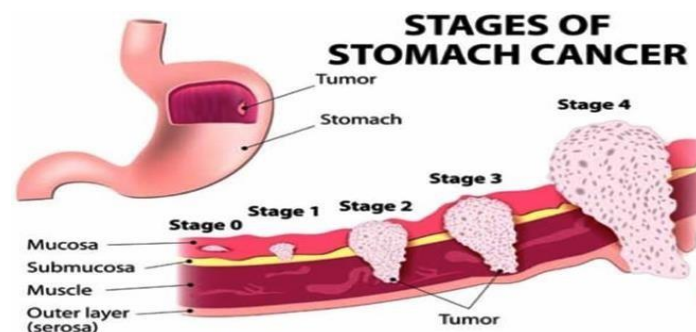
What is Stomach Cancer?

Cancer starts when cells in the body begin to grow out of control. Cells in nearly any part of the body can become cancer, and can spread to other areas of the body. Stomach cancer, also called **gastric cancer**, starts in the stomach.

Development of stomach cancer

Stomach cancers tend to develop slowly over many years. Before a true cancer develops, pre-cancerous changes often occur in the inner lining (mucosa) of the stomach. These early changes rarely cause symptoms and therefore often go undetected. The stomach cancer mostly effects in older people. The average age of people is diagnosed in 68. The stomach cancer in every 10 people, 6 peoples are diagnosed every year at the age of 65.

The risks of stomach cancer develop in man's lifetime is about 1 in 95, and women are about 1 in 154. But each person's risk can be affected by certain other factor. Cancers starting in different sections of the stomach may cause different symptoms and tend to have different outcomes. The cancer's location can also affect the treatment option [1].



Spread of gastric cancer:

- 1) Direct way
 - Muscularis, serosa
 - Adjacent organ: pancreas, colon, liver
- 2) Lymphatic way
 - Regional
 - Extensive – left supraclavicular node
- 3) Blood way
 - Via portal vein
 - Lung and bone
- 4) Transperitoneal
 - Indicates incurability
 - Anywhere in peritoneal cavity

- Can give rise to ascites
- Krukenbergt umour, sister joseph’s nodule

Stages of Stomach Cancer:

Stomach cancers can grow and spread in different ways. They can grow through the wall of the stomach and invade nearby organs. They can also spread to the lymph vessels and nearby lymph nodes. The stomach has a very rich network of lymph vessels and nodes. As the stomach cancer becomes more advanced, it can travel through the bloodstream and spread (metastasize) to organs such as the liver, lungs, and bones, which can make it harder to treat. The staging system most often used for stomach cancer is the American Joint Committee on cancer (AJCC)TNM system which is based on

- 1) Extent of tumor (T): How far cancer grown into five layers of stomach (Mucosa, Submucosa, Muscularis propria, Sub-serosa, Serosa)
- 2) The spread to lymph nodes (N)
- 3) The spread to distant sites(metastasis)-M

There are four stages of stomach cancer:

Stage	Pathophysiology	Prodiagnosis 5yr survival rate percentage	Treatment options
Stage 0 (T _{is} N ₀ M ₀)	Abnormal precancerous cells(dysplasia) are present in mucosa, but have not spread to other layers of stomach or lymph nodes. It is called cancer in situ	82 (82 out of 100 survived for 5 years if it is diagnosed at this early stage)	Surgery with either subtotal gastrectomy or total gastrectomy. Nearby lymph nodes are removed as well Endoscopic resection sometimes (done mostly in Japan)
Stage I			
Stage IA (T1N0M0)	Cancer spreads to next layer lamina propria, muscularis mucosa or sub mucosal layer	71	Total or subtotal gastrectomy, nearby lymph nodes are removed/ Endoscopic resection for some small T1a cancers
Stage IB (T1N1M0) or (T2N0M0)	Cancer spreads in to next layers of stomach and into one or two lymph nodes near the tumor,or to the muscularis or to the middle layer of stomach	57	Total or subtotal gastrectomy. Chemotherapy or Chemoradiation before surgery to shrink cancer. Lymph nodes removed. If cancer found in lymph nodes treatment with either chemoradiation, chemo alone or both
Stage IIA (T1N2M0) or (T2N1M0) or (T3N0M0)	Cancer developed into deeper layers of stomach like muscularis propria or subserosa layer and may have spread to lymph nodes sometimes	46	Surgery (Remove all or part of stomach, Omentum and nearby lymph nodes). chemo or chemoradiation before surgery in most patients.
Stage IIB (T1N3aM0) or (T2N2M0) (T3N1M0 or T4aN0M)	Cancer grown in mucosa and <i>laminaris purpuria</i> with spread to 7-15 lymph nodes/cancer grown into muscularis purpuria and spread to 3-6 lymph nodes/growing into sub serosa layer and spread to 1-2 lymph nodes/tumor grown into serosa but not spread to any organs	33	Treatment after surgery with chemo alone chemoradiation. If the person is too sick to have surgery, they may be treated with chemoradiation/ radiation therapy/chemo alone
Stage IIIA (T2N3aM0/T3N2M0/	Cancer growing into muscularis propria and its spread to 7-15 lymph nodes/Growing into subserosa layer and	20	Surgery (some may be cured by surgery while in others it helps to control cancer or relieve symptoms). Chemo before and

T4aN1M0/T4aN2M0/T4bN0M0)	spread to 3-6 lymph nodes/Spread to serosa layer and 1-2 nearby lymph nodes/Spread to serosa and 3-6 nodes/grown through stomach wall into nearby organs without spread to lymph nodes and distant sites		after surgery. Patients who don't get chemo before surgery and have some cancer left behind even after surgery are treated by chemoradiation
Stage IIIB (T1N3bM0/T2N3bM0 T3N3aM0/T4aN3aM0/T 4bN1M0/ T4bN2M0)	Cancer grown through muscularis mucosa and spread to 16 lymph nodes nearby/Grown through muscularis propria and spread to 16 nodes/tumor grown into subserosa and spread to 7-15 lymph nodes/grown into serosa and spread to 7-15 lymph nodes/grown through stomach wall to nearby organs and spread to 1-2 lymph nodes.	14	
Stage IIIC (T3N3bM0/T4aN3bM0 /T4bN3aM0/T4bN3bM0)	Grown into subserosa layer spread to 16 lymph nodes/grown into serosa layer and 16 lymph nodes/ grown through stomach wall to nearby organs and spread to 7-15 lymph nodes/. grown through stomach wall to nearby organs and spread to 16 lymph nodes	9	
Stage IV (ANYT/ANYM/M1	Cancer grows into any layers and might or might not have spread to nearby lymph nodes. It has spread to distant organs such as liver, lungs, brain or peritoneum	4	a cure is usually not possible. But treatment can help keep the cancer under control and relieve symptoms. This include surgery, total/subtotal gastrectomy .In some cases, a laser beam directed through an endoscope (a long, flexible tube passed down the throat) can destroy most of the tumor and relieve obstruction without surgery. If needed, a stent (a hollow metal tube) may be placed where the esophagus and stomach meet to help keep it open and allow food to pass through it. This can also be done at the junction of the stomach and the small intestine. Chemo and/or radiation therapy can often help shrink the cancer a

Types of stomach cancers

1) Adenocarcinoma

It is type of cancer which is originated at secretory cells which are found in tissue that lines the certain internal organs and which makes and releases substances in the body, such as mucus, digestive juices, or other fluids. The maximum percentage of about 90% to 95% cancers of the stomach are adenocarcinomas. Thus, the gastric cancer is always is an adenocarcinoma. These cancers develop from the cells that form the innermost lining of the stomach. it might be treated by chemotherapy, radiation, targeted therapy, or surgery.

2) Lymphoma

It is a type of cancer related to immune system issues which are found in the walls of stomach. The treatment depends upon type of lymphoma. It is originated in infection fighting lymphocytes of immune system. These are present in lymph nodes, spleen, thymus, bone marrow, and other parts of the body. There are two main types of lymphoma [2]:

- Non-Hodgkin: Most people with lymphoma have this type.
- Hodgkin

Non-Hodgkin and Hodgkin lymphoma involve different types of lymphocyte cells. Every type of lymphoma grows at a different rate and responds differently to treatment. Lymphoma is very treatable, and the outlook can vary depending on the type of lymphoma and its stage.

Symptoms:

- Swollen glands (lymph nodes), often in the neck, armpit, or groin that are painless
- Cough
- Shortness of breath
- Fever
- Night sweats
- Fatigue
- Weight loss
- Itching

3) Gastrointestinal stromal tumour (GIST)

It is a type of cancer is rarely seen in the earlier cells of walls of stomach called interstitial cells of cajal. Tumours in this type may be cancerous and also may be non-cancerous. Maximum GISTs are found in stomach in the digestive track. Although GISTs can be found anywhere in the digestive tract, most are found in the stomach.

4) Carcinoid tumour

It is type of cancer starts in the hormone making cells of stomach. Maximum number of tumours in this type don't spread other organs. Some of them starts in one of two areas like in both digestive system and lungs. That includes places like stomach, small intestine, colon, appendix, or rectum. It's not as common, but it might be start in pancreas, testes in males and ovaries in female.

Other cancers

Other types of cancer, such as squamous cell carcinoma, small cell carcinoma, and leiomyosarcoma, can also start in the stomach, but these cancers are very rare [\[3\]](#).

Signs and Symptoms of Stomach Cancer:

Early-stage stomach cancer rarely causes symptoms. This is one of the reasons stomach cancer is so hard to detect early. The signs and symptoms of stomach cancer can include:

- Poor appetite
- Weight loss
- Abdominal pain
- Vague discomfort in the abdomen, usually above the navel
- A sense of fullness in the upper abdomen after eating a small meal
- Heartburn or indigestion
- Nausea
- Vomiting, with or without blood
- Swelling or fluid up in the abdomen
- Blood in the stool
- Low red blood cell count (anaemia)

Above symptoms of cancer may also related to other types of diseases such as stomach virus and also seen in other types of cancers but it is necessary to diagnosed by a professional in case of any of the symptoms [\[4,5\]](#).

Risk factors:

Risk factors for GC may include:

1) Diet

It is one of the risk factor for stomach cancer by the recent research they concluded that diet with high meat and low leafy vegetables and smoked foods, salted fish and pickled foods are major risk factors and also substances such as cured meat containing nitrites and nitrates which are converted by bacteria such as *H. Pylori* into products which are carcinogenic in nature.

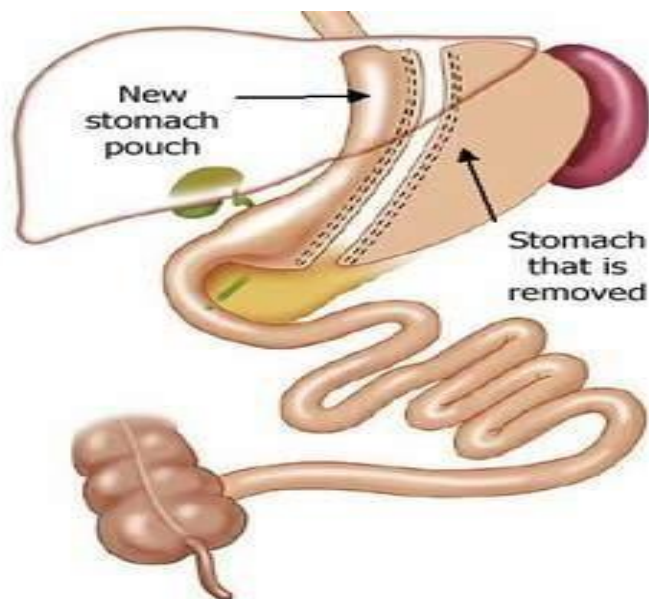
**2) Helicobacter pylori infection**

H.pylori infection is more common in stomach cancer by the recent studies it may be due to inherited from generation to generation linked with blood groups. The *H. Pylori* is involved about 90% of all gastric malignancies and its incidence varies according to age, ethnicity, and geographic location. *H. Pylori* gives the ranges from 30% to 70% by the age of 20 years and 70% to 90% by the age of 60 years approximately. It contributes to the development of gastric neoplasia by promoting inflammation in gastric mucosa, which may lead to the changes in sequential histopathology this may resulted in the development of gastric cancer. the *H pylori* strains with infection with *vacA*C1-, *vacA*M-1, and *cagA*- positive genotypes are associated with an approximate 6-fold increases in GC risk. Further studies are going on it.



3) Previous stomach surgery:

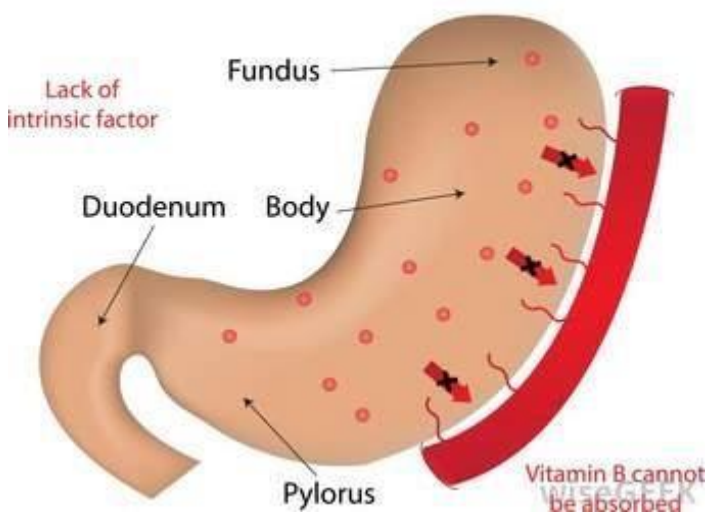
In this factor Stomach cancers are more likely to develop in the people who have the part of their stomach removed to treat non-cancerous diseases such as ulcers and this leads the stomach makes less acid, which allows more nitrite-producing bacteria to be present. Reflux or backup of bile from the small intestine into the stomach after surgery might also add to the increased risk. Finally these cancers are typically developed for many years after the surgery.



4) Pernicious anemia:

In this factor certain cells in the stomach lining normally make a substance called **intrinsic factor** (IF) which makes us to absorb vitamin B12 from the food and if the lack of IF leads to end of vitamin B12 absorption that effect body ability to make the RBC and also other problems this leads to decrease RBC count thus this condition is called as pernicious anemia.

Pernicious Anemia



5) Epstein-Barr virus (EBV) infection:

EBV has been linked with some forms of lymphoma. It may also found that in the cancer cells of about 5% to 10% of people with stomach cancer. These people tend to have a slower growing, less aggressive cancer with a lower tendency to spread. This infection has been found in some stomach cancer cells, but it isn't clear that if this virus is actually causes stomach cancer. further studies is going on this infection.



6) Certain occupations:

Where the workers are working under the coal, metal, and rubber industries may seem to have a higher risk of getting stomach cancer.

7) Common variable immune deficiency (CVID):

In this factor people are with CVID deficiency have increased risk of gastric cancer. The immune system of someone with CVID can't make enough antibodies in response to germs. People with CVID deficiency have frequent infections as well as other problems including atrophic gastritis and pernicious anemia. They are also more likely to get gastric lymphoma and stomach cancer [\[6-20\]](#).

Treatment:

1) Chemotherapy drugs and combinations

Some studies are testing new ways to combine treatments already known to be active against stomach cancer or other cancers. Several chemotherapy drugs are approved and used to treat stomach cancer, and some are used together in combination with each other. Newer chemotherapy (chemo) drugs are also being studied. For example, S-1 is an oral chemo drug related to 5-FU. This drug is commonly used for stomach cancer in some other parts of the world and continues to be studied. New ways of giving chemo are also being studied. Other studies are testing the best ways to combine chemo with radiation therapy, targeted therapies, or immunotherapy. A good deal of effort is being directed at improving the results of surgery by adding chemo and/or radiation therapy either before or after surgery. Some studies are also looking at benefits of giving chemo during surgery. Several clinical trials are in progress.

2) Targeted therapies

This is a kind of treatment which is an advanced treatment in chemo therapy. In this type of therapy chemo drugs are targeted on cells that divide rapidly. They work more efficient than chemo therapy on cancerous cells. They also tend to have less severe side effects than chemo drugs.

3) Drugs that block HER2:

Some stomach cancers have too much of the HER2 protein on the surface of their cells, which helps them grow. Drugs that target this protein might help treat these cancers. Trastuzumab is already approved for use against advanced stomach cancer. Other drugs that target HER2, such as lapatinib, pertuzumab, and emtansine are now being studied in clinical trials.

4) Drugs that block EGFR:

EGFR is another protein found on some stomach cancer cells that helps them grow. Panitumumab is a drug that targets EGFR that is being tested against stomach cancer. This drug is already FDA-approved to treat some other cancers.

5) Other targeted drugs:

Other drugs target different parts of cancer cells. For example, another targeted drug being studied against stomach cancer is apatinib. Most research is going on this area is looking at combining targeted agents with chemotherapy or with each other.

6) Immunotherapy:

Immunotherapy is an approach that uses drugs to try and help the body's immune system fight the cancer.

In 2017, the pembrolizumab became the first immunotherapy agent approved to treat stomach cancer in some patients whose treatment did not work or stopped working. Pembrolizumab is an immune checkpoint inhibitor and targets PD-L1, a protein found on some stomach cancer cells [21-27].

Screening test:

Screening means checking your body for **cancer** before you have symptoms. Getting **screening** tests regularly may find breast, cervical, and colorectal (colon) **cancers** early, when treatment is likely to work best.

Stomach cancer Screening:

Upper endoscopy with random gastric biopsies (small samples of tissue) is currently the best method to screen for stomach cancer. Unfortunately, diffuse gastric cancer often is not apparent on endoscopy, and biopsies are often negative.

Hereditary diffuse gastric cancer is nearly impossible to detect at an early stage, however, the recommended procedure to prevent stomach cancer is a total gastrectomy, or complete removal of the stomach. Although this procedure is complicated and commonly leads to weight loss, diarrhoea, altered eating habits, and vitamin deficiency, it is possibly the only method to prevent stomach cancer in these families.

Some screening tests are used because they have been shown to be helpful both in finding cancers early and in decreasing the chance of dying from these cancers. Other tests are used because they have been shown to find cancer in some people; however, it has not been proven in clinical trials that use of these tests will decrease the risk of dying from cancer.

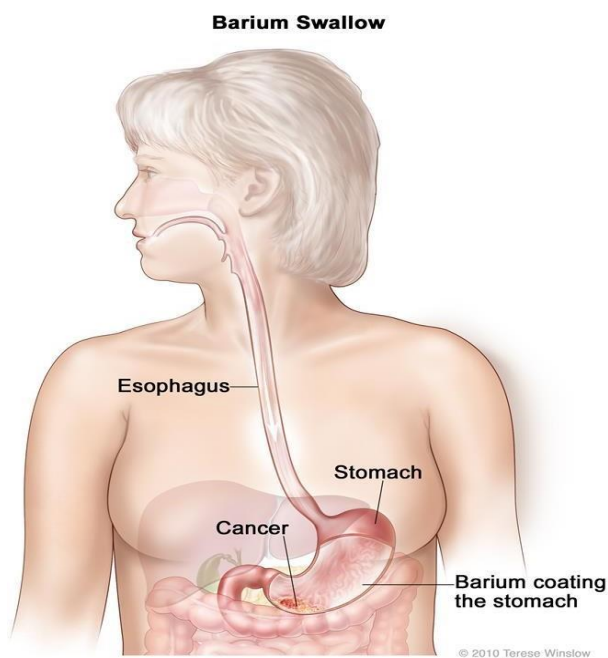
S. No.	Screening Test	Diagnosis	Diagnosed at age of	Advantages	Dis advantages
1.	Colonoscopy, sigmoidoscopy, and high-sensitivity faecal occult blood tests (FOBTs)	prevent colorectal cancer	50-75	Helps to detect colon cancer	Unable to see your whole colon and may not detect or remove all polyps Colonoscopy is still needed if cancer is detected
2.	Low-dose helical computed tomography	This test screen for lung cancer which reduce deaths among heavy smokers	55-74	Helps to detect lung cancer	A small, but difficult to quantify, risk of cancer associated with multiple follow-up CT scans
3.	Mammography	screen for breast cancer which reduce mortality	40-74	This method is good for detecting DCIS and calcifications	Double reading of mammogram leads to increase in cost of detection Risk of false alarm
4.	Pap test and human papillomavirus (HPV) testing	reduce the incidence of cervical cancer allow abnormal cells to be identified and treated before they become cancer	21-65	Can be used in patients with systemic disorders where biopsy is contraindicated	Not useful in non-epithelial lesions

Other Screening Tests	Diagnosis	Advantages	Dis advantages
1. Alpha-fetoprotein blood test	Try to detect liver cancer early in people at high risk of the disease	This test is designed for mothers who wish to confirm their low potential for Down's syndrome and neural tube defects	It may not be suitable for everybody.
2. Breast MRI	This imaging test is used for women who carry a harmful mutation in the <i>BRCA1</i> gene or the <i>BRCA2</i> gene; such women have a high risk of breast cancer	Breast MRI does not use ionizing radiation, and it is the best method for determining whether silicone breast implants have ruptured.	A very irregular heartbeat may affect the quality of images obtained using techniques that time the imaging based on the electrical activity of the heart, such as electrocardiography (EKG).
3. CA-125 test	detect ovarian cancer early, especially in women with an increased risk of the disease	Used to determine levels of a tumour marker that may be elevated in cases of ovarian cancer.	Shows false positive as well as false negative.
4. Clinical breast exams and regular breast self-exams	Routine examination of the breasts by women themselves has not been shown to reduce deaths from breast cancer	Reduces the risk of dying from breast cancer.	Periods of waiting and anxiety when additional examinations are required.
5. PSA test	able to detect prostate cancer at an early stage	Earlier cancer detection; eliminates PSA elevations due to BPH	Limited data at present on influence of non cancerous conditions.
6. Skin exams	people who are at risk for skin cancer examine their skin regularly or have a health care	If cancer is diagnosed at early stage, treatment is more likely to successful.	It lead to unnecessary worry and investigations when there is no cancer present.
7. Transvaginal ultrasound	This imaging test, which can create pictures of a woman's ovaries and uterus, is sometimes used in women who are at Increased risk of endometrial cancer	Helps to see if there is any abnormality in the uterus.	There is no known risks of having trans vaginal ultra sound.
8. Virtual colonoscopy	This test allows the colon and rectum to be examined from outside the body. However, it has not been shown to reduce deaths from colorectal cancer.	Virtual colonoscopy has less risk of colon tearing, or perforation, than conventional colonoscopy.	Virtual colonoscopy is not as sensitive as colonoscopy for finding polyps less than 10mm in size.

Scientists study screening tests to find those with the fewest risks and most benefits. Cancer screening trials also are meant to show whether early detection (finding cancer before it causes symptoms) decreases a person's chance of dying from the disease. For some types of cancer, the chance of recovery is better if the disease is found and treated at an early stage. Clinical trials that study cancer screening methods are taking place in many parts of the country. Several types of screening tests have been studied to find stomach cancer at an early stage. These screening tests include the following:

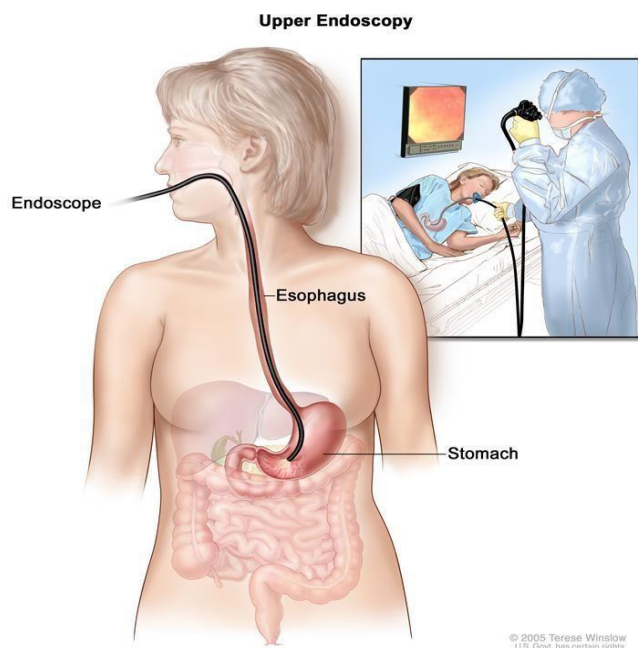
Barium-meal photofluorography:

It is series of x-rays of the oesophagus and stomach. In this screening method the patient drinks a liquid that contains barium (a silver-white metallic compound) which coats the oesophagus and stomach as it is swallowed. Photographs are taken of the x-ray images. Those photographs are processed to make the organs easier to see and then made into a film. This makes it possible to see the motion of the organs while exposing the patient to less radiation.



- **Upper endoscopy:**

It is a procedure to look inside the oesophagus, stomach, and duodenum (first part of the small intestine) to check for abnormal areas. An endoscope is passed through the mouth and down the throat into the oesophagus. An endoscope is a thin, tube-like instrument with a light and a lens for viewing. It may also have a tool to remove tissue, which is checked under a microscope for signs of disease.



- **Serum pepsinogen levels:**

A test that measures the levels of pepsinogen in the blood. Low levels of pepsinogen are a sign of chronic gastric atrophy which may lead to stomach cancer [28].

UGI series:

This is a mass screening method for gastric cancer. This method was introduced in Japan in 1960s. The sensitivity of UGI series ranged from 60 to 80% whereas the true positive rate were 90%. This UGI series resulted in a 40 to 60% reduction in gastric cancer. This reminds an accepted method for the national gastric cancer screening programs in Japan and Korea.

H. PYLORI SEROLOGY:

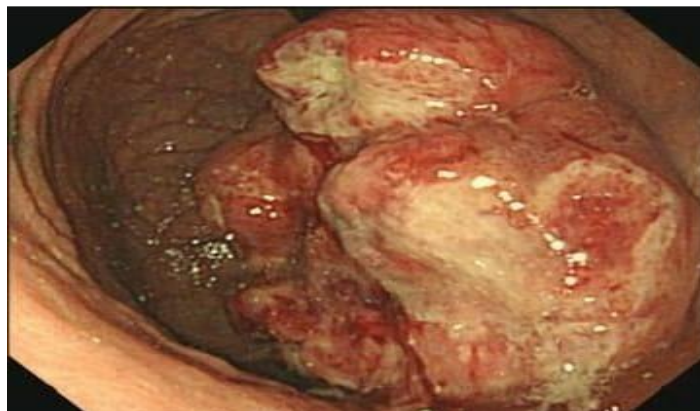
H. pylori serology as a screening test for gastric cancer is limited by low sensitivity and a failure to detect premalignant lesions. Even through *H. pylori* virulence factors such as *cag A*, *vac A*, *bab A*, may increase its sensitivity for gastric cancer detection, their sensitivity is still low. Therefore, *h.pylori* serology is not useful as a standalone screening test.

SERUM PG TESTING:

PG is a pepsin it is produced in gastric layer. This is the one of the methods to know the gastric cancer. PG is classified in to 2 diff

isozymes PG1 and PG2. PG1 is produced by cells in the gastric fundus and PG2 is produced by the cells throughout the stomach. The limitations of using serum PG include variable proposed cut off values and lack of sensitivity and variability of PG1 and PG1/2 ratio, lack of sensitivity, these are depending on age, sex, and race.

GASTRO FIBER SCOPY(GFS):



GFS or double contrast upper gastro intestinal series (UGIS), has been used in Korea since 1996. The aim of this study was to assess whether there have been major changes in clinicopathologic features of gastric cancer by introducing gastric cancer screening. This method is a complete exploration of the stomach, allowing to inspect the antropyloric area without difficulty [29,30]

STATISTICS:

Stomach cancer

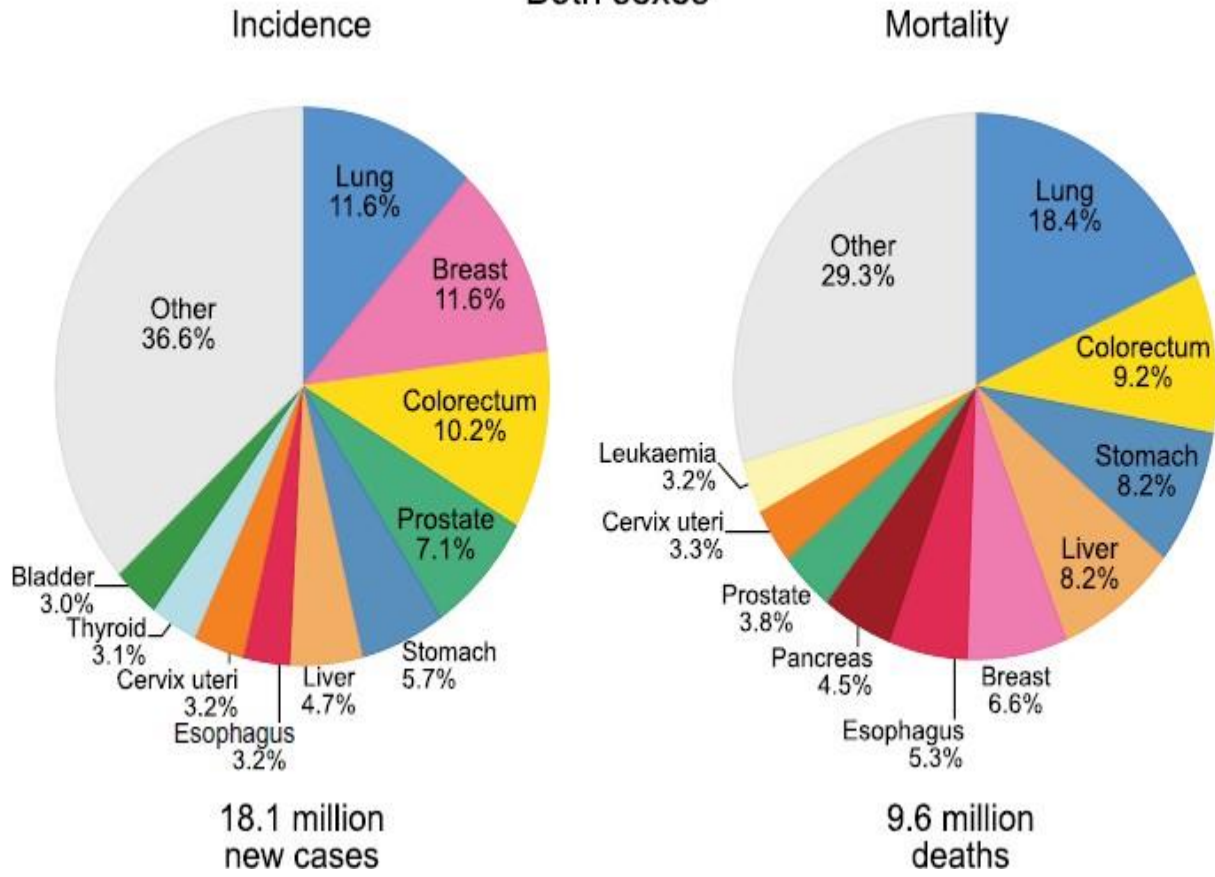
Stomach cancer remains an important cancer worldwide and is responsible for over 1,031,700 new cases in 2018 and an estimated 787,200 deaths (equating to 1 in every 12 deaths globally), making it the fifth most frequently diagnosed cancer and the third leading cause of cancer death. Incidence and death rates are slightly higher in men (684,000 new cases and an estimated 513,000 deaths) compared to females (352,600 new cases and an estimated 273,000 deaths) as can be seen in the pie charts and bar charts given below. It is most commonly diagnosed and leading cause of cancer deaths in countries like eastern Asia, eastern Europe, south America, west Asia, southern Europe. etc followed by others. The regional dominance can be accounted to the hereditary mutation they carry, *H. Pylori* infection or due to the common food habits (smoked or salted food, low fruit diet) they possess.

CONCLUSION

H. pylori eradication and healthy lifestyle declined the number of new cases and mortality rate steadily over the past few decades, but it still remains the alarming source for the global researchers to focus on new screening strategies for early and cost effective diagnosis as it is mostly asymptomatic, and develop some new targeted and immune therapy to improve the quality of life and survival rate among them. The results of Japan and Korean mass screening program also lays foundation for need of screening guidelines, strategies and public awareness programs particularly among high risk population.

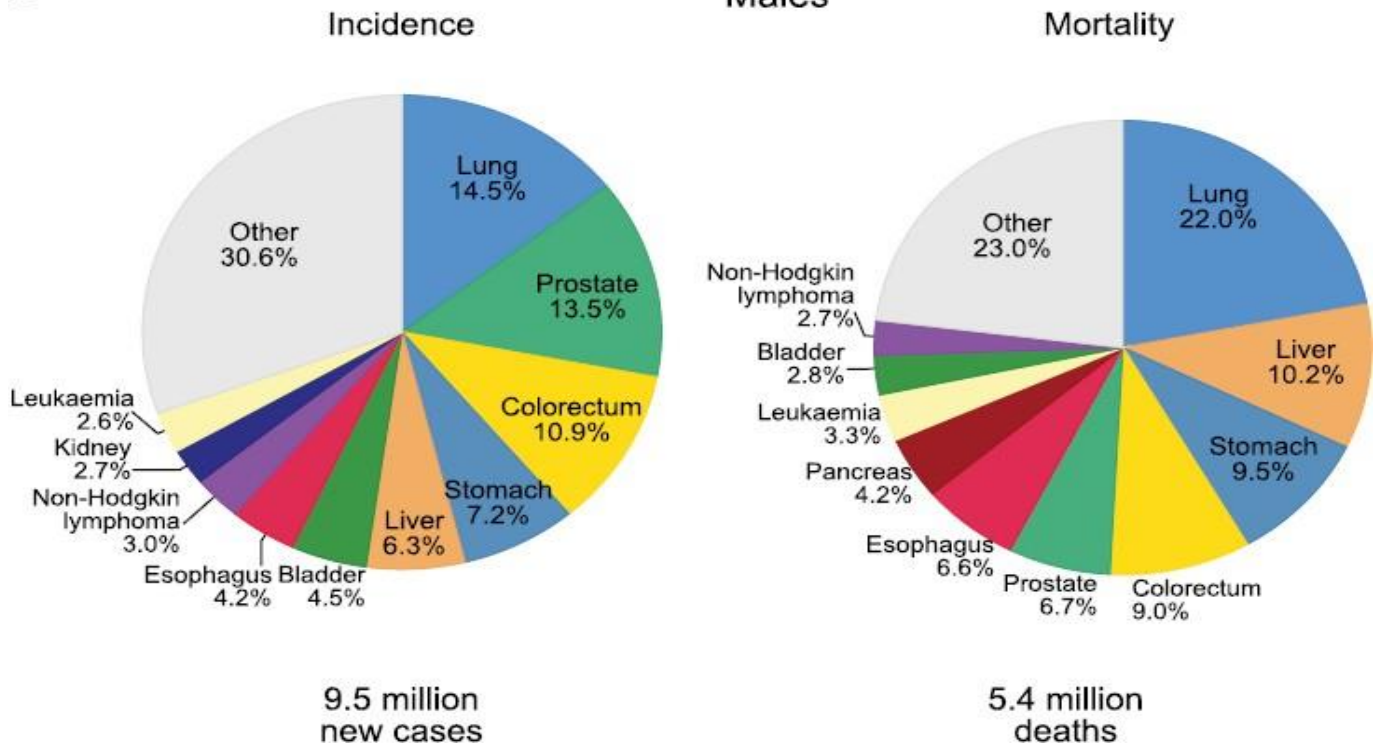
A

Both sexes



B

Males



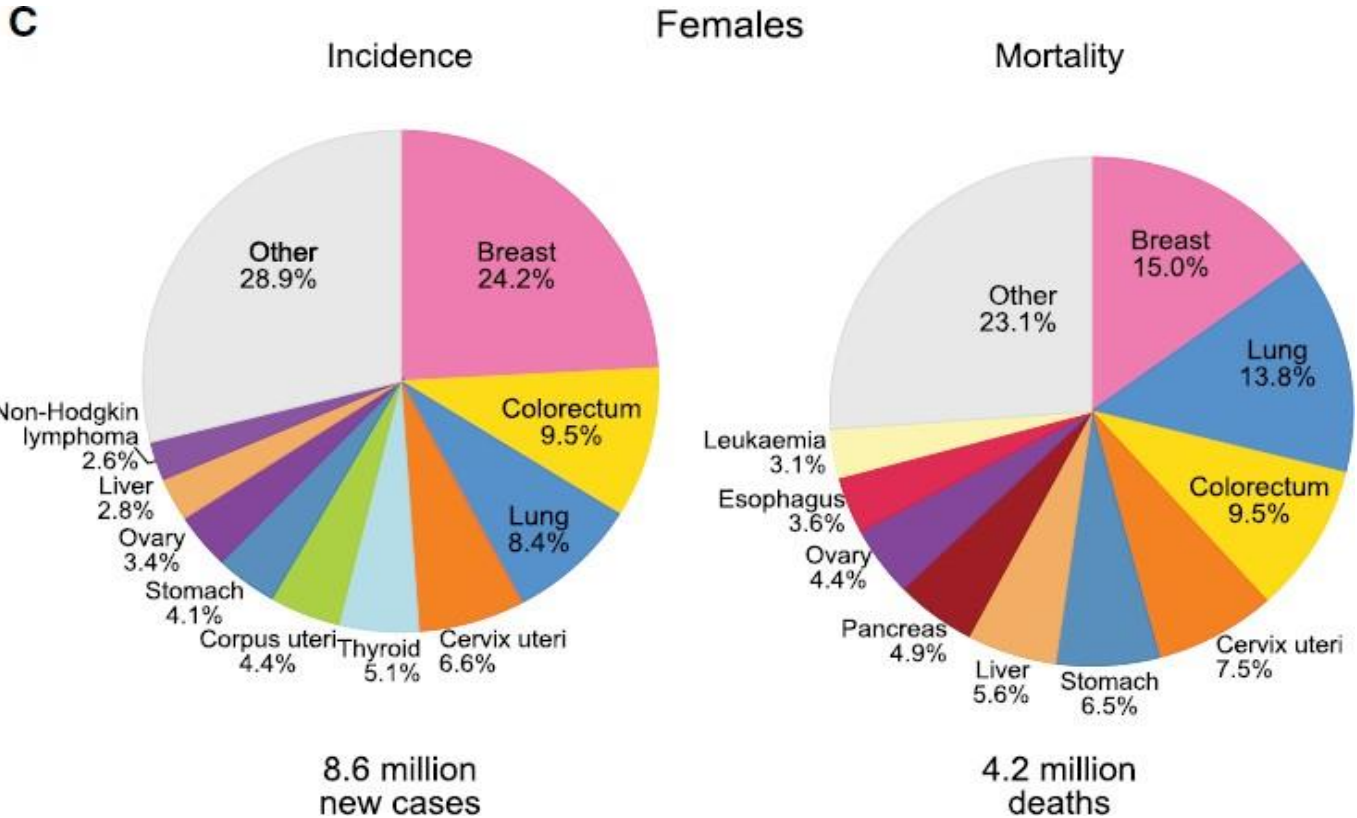
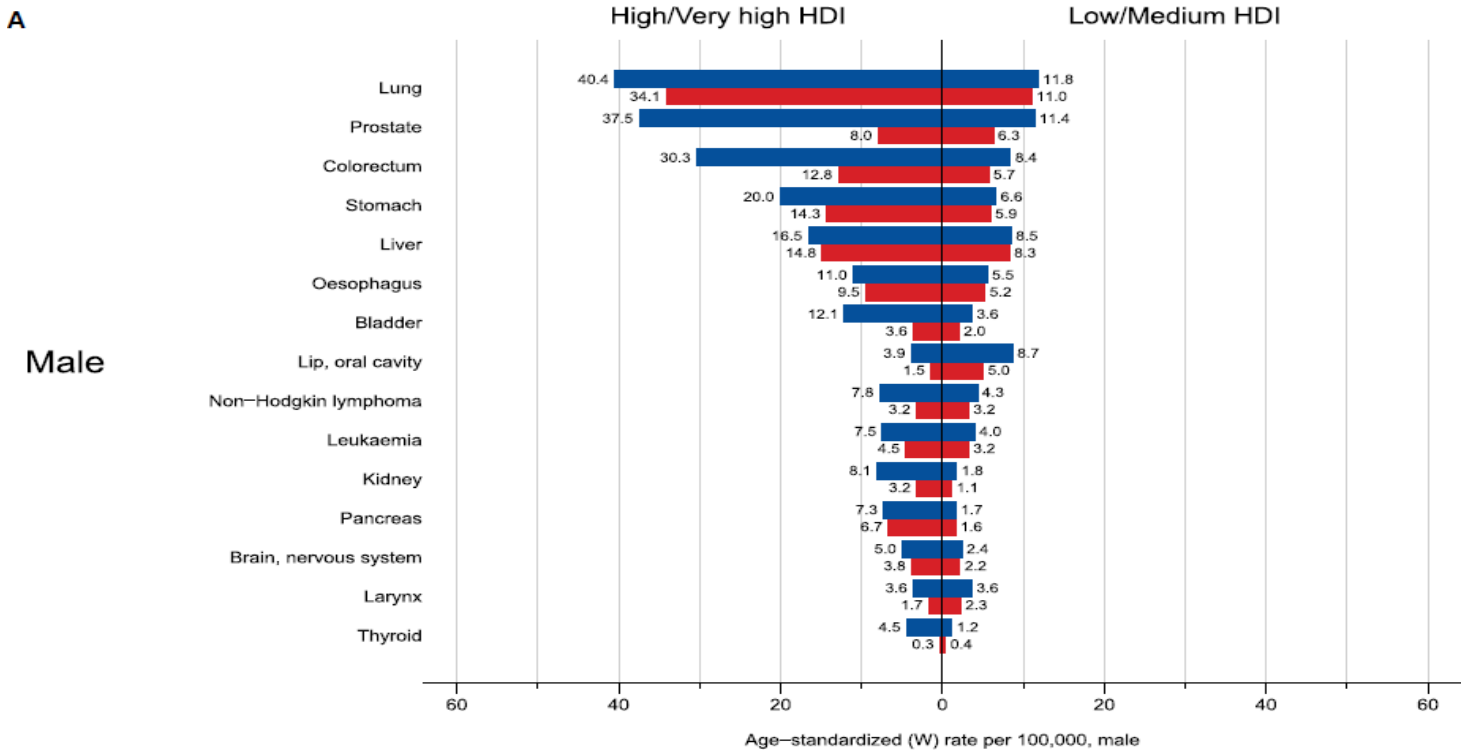


Fig. 1: pie charts showing distribution of cases and deaths for the 10 most common cancers in 2018 for (A) Both Sexes, (B) Males and (c) Females. Area reflects the total number of cases or deaths in each type of cancer Source: GLOBOCAN 2018



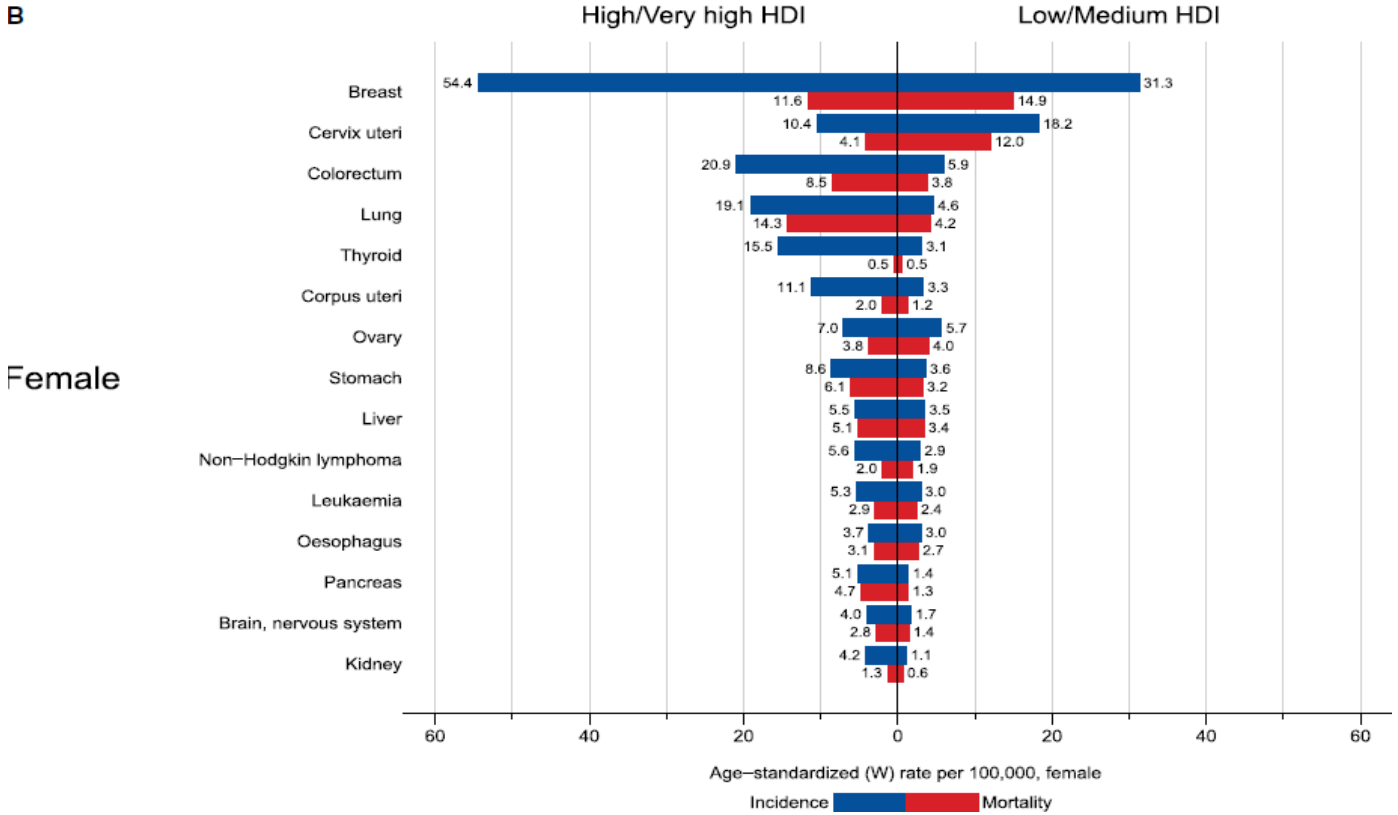


Fig. 2: Bar charts of incidence and mortality Age-Standardized rates in high/Very high human development index (HDI) regions versus Low/Medium HDI regions among (A)Men (B) Women in 2018 are shown in descending order of the overall age-standardized rate for both sexes among 15 most common cancers

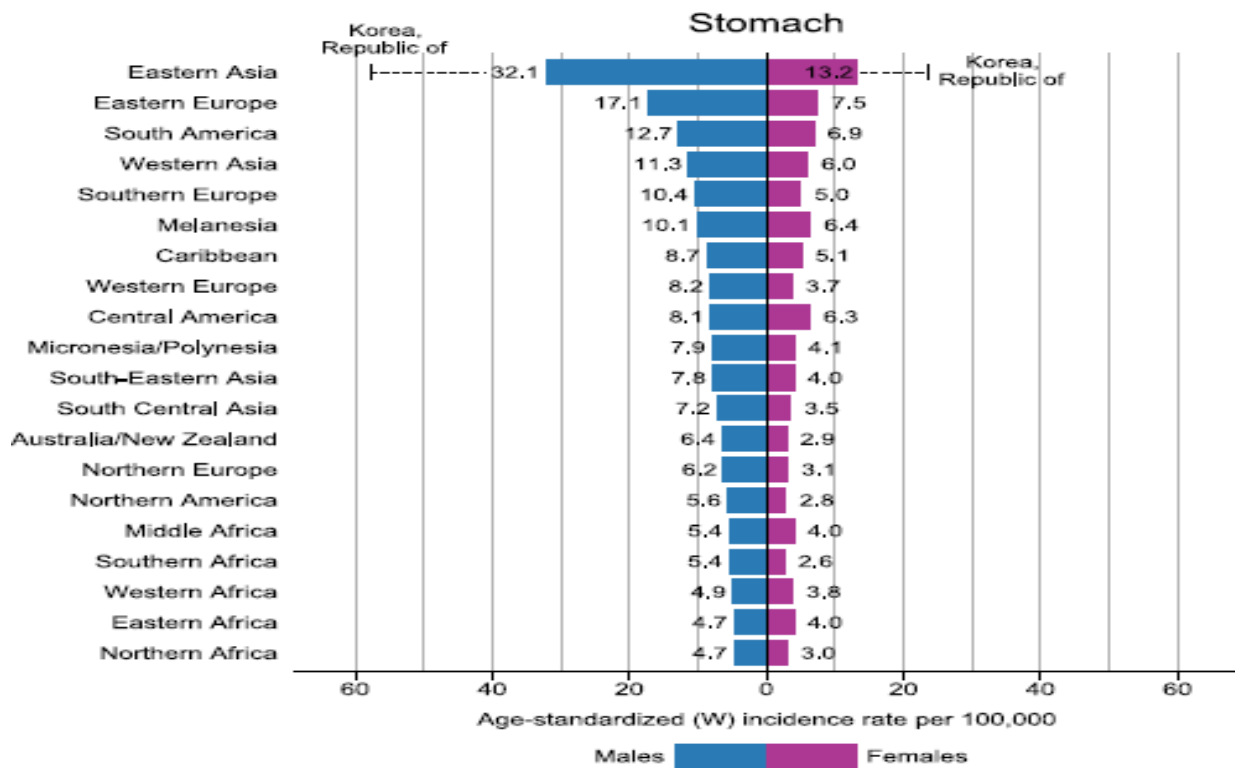


Fig. 3: Bar chart of region-specific incidence Age-Standardized rates by sex for cancers of the stomach in 2018 Rates are shown in descending order of the world Source: GLOBOCAN 2018

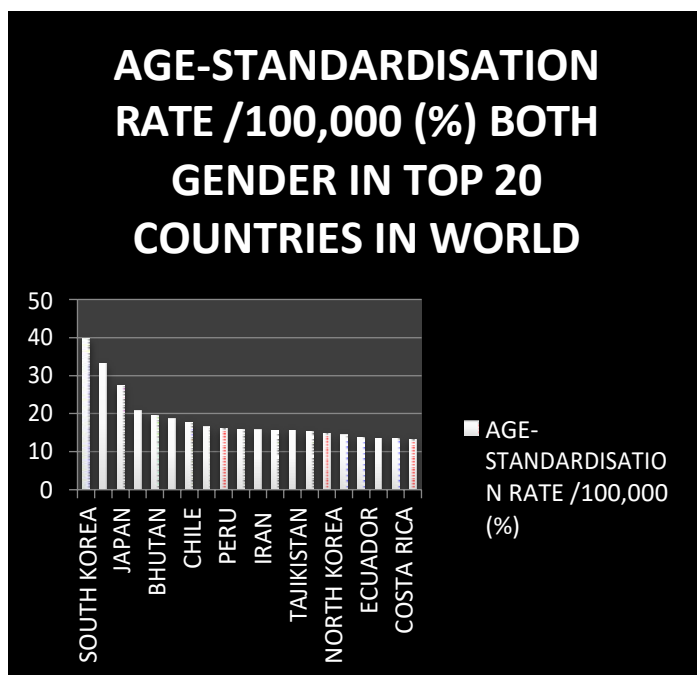


Fig. 4: The age-standardisation rate per 100,000 percent of males in top 20 countries all over the world.

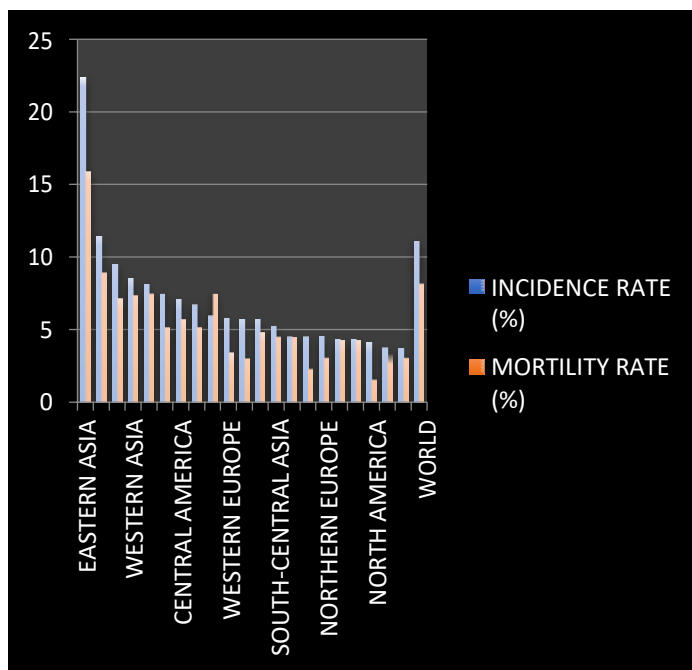


Fig. 5: Worldwide incidence rates on stomach cancer based on both genders

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