Review

Gastric cancer & prospects of cancer in Saudi Arabia peninsula

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ABSTRACT

Gastric cancer is classified to be an aggressive disease with poor treatment outcome, as most cases remain undetected until later stages, wherein surgery and few chemotherapeutics become the only recommended treatment course. The process of cancer development is multistep involving many stages and types of precancerous lesions, and hence, routine monitoring becomes a necessity in those detected with these or exposed to risk factors. Studying the pattern of gastric cancer for any geographical region is also important to control mortality and focus on implementation of efficient management and treatment guidelines. The cause for gastric cancer can be genetic, racial as well as environmental, and hence the pattern of this malignancy differs across geographical regions and between the developing and the developed nations. In case of the Kindgom of Saudi Arabia, very few hospital-based reports have been published highlighting the pattern of gastric cancer, and the associated incidence and mortality rates. However, classified to be one of the most crucial cancer forms in Saudi Arabia, research pertaining to epidemiology, presentation and pathological features are limited. Studying gastric cancer occurrence from public health viewpoint is important also because eradication of causative agents like those that H. pylori has also shown been not reduce the risk of cancer development among individuals with atrophic metaplastic gastritis. In case of Saudi Arabia, many inherent risks for this malignancy exists like waterpipe smoking and shift in diet pattern from the traditional Mediterranean diet. Our review focusses on pattern of gastric cancer on a global scale in comparison to scenario in Saudi Arabia. The aim is to encompass all of the less stressed upon facts about this malignancy in the Kingdom, paving way for future work in this regards.

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Contents

1. Introduction

Global cancer burden continues to show an upward trend both in developed and developing nations even as technological advancements continue to aim towards reducing the gap between time-of-diagnosis and appropriate clinical management. Gastric cancer has emerged to be one of the most aggressive and heterogeneous disease, and though a steady decline in the number of affected has been recorded globally and reported as the second-leading reason of mortality world over (Ferro et al., 2014). The key therapeutic interventions have been surgery followed by adjuvant chemo radiati or chemotherapy and research for novel therapeutic options continue to be the need of the day. Though an improvement in survival of the affected has been noted about gastric malignancy, the median overall survival rate has been documented to still be less than a year (Cervantes et al., 2013).

The first mortality statistics recorded dates back to between 1760 and 1839 from Italy, and the earliest description of this disease to be noted in the 3000 BC was from early Egypt and till date it continues to be a lethal malignancy albeit with significant geographical, ethnic, gender as well as socioeconomic difference in its occurrence (Chan and Wong, 2017). As per GLOBOCAN 2012, cancer in the stomach has been predominantly in Africa and Asia, wherein 73% of the diagnosed have been recorded to be from Asia, among whom China alone harbours roughly 50% of the world's detected cases (Ferlay et al., 2013).

In US, the American Cancer Society's key estimated that the stomach cancer to be the principal reason of death till the 1930s, post which a steady decline was noted and probably attributed to the use of refrigerators for food storage (American Cancer Society, 2017). Statistics in the US highlight of the 22,220 cases detected positive annually, 10,990 are expected to die (Siegel et al., 2014). Apart from the US, wherein the decline was noted at a faster rate, high incidence countries like Japan and China recorded a slower pace in reduction of incidence rate, while in the UK a consistency in reduction was noted (Fitzsimmons et al., 2007). History has recorded the decline in incidence rate to be attributable towards identification of causative dietary and environmental factors, which happened prior to detection of link between *H. pylori* and the condition (Chan and Wong, 2017). Though contributing factors are many, men have been generally noted to bear higher risk, while the average risk has been documented to be 1 in 111 and of every 10 diagnosed, 6 have been recorded to be over 65 years of age (American Cancer Society, 2017).

Refrigeration of food became a pivot and continues to be the most popular contributing source for decline as apart from preventing fungal and bacterial contamination, it also reduces the need for salt-based preservation techniques apart from maintaining the freshness of fruits and vegetables that preserves their antioxidants; the natural anticancer agents (Chan and Wong, 2017). Scientific studies have documented dietary patters, apart from food preservation techniques and accessibility of fresh vegetables and fruits to be risk factors for gastric cancer (Karimi et al., 2014). The high incidence rate including mortality among both men and women in Japan has been attributed principally to the dietary pattern involving consumption of salted foods like pickled vegetables, dried and salted fishes in a study published by Tajima and Tominaga (1985), who also documented the relative risk for this condition to be 2.60. Studies have also identified high-salt diet to augment the effect of *H. pylori* infection towards development of gastric carcinogenesis (Nozaki et al., 2002).

For diagnosing gastric cancer, studies reveal demarcating cancerous lesions both by histopathology and endoscopy continues to add difficulty and thus emerges as a challenging clinical issue (Saka et al., 2016). *H. pylori*, a class I human carcinogen has been clearly associated with development of noncardia gastric cancers which are majorly associated with poor sanitation, overcrowding and poor socioeconomic status (de Martel et al., 2013). Infection by this gram-negative bacterium however has been shown to contribute towards 2.9% incidence through a retrospective study published by Uemura et al. (2001).

In this review article, we focus on highlighting the updated scenario of gastric cancer in Saudi Arabia, along with the backdrop of discussing the probable causatives along with the clinical features and treatment options currently being followed. Lacunae exists in connecting the causatives with the preventives and our review attempts to get all the triggers in a single report connecting it to the published statistics as well as proven risk reduction strategies. The aim is to identify modifiable factors, which can aid in efficient diagnosis and disease management.

2. Scenario in Saudi Arabia

The Kingdom of Saudi Arabia, with an estimated population size of 32.94 million in the year 2017, is the second largest Arab state after Algeria and comprises of Jordan, Iraq, Kuwait, Bahrain, Qatar, UAE, Yemen and Oman. The capital of the Kingdom; Riyadh harbours around 22% of the population of the whole country. The healthcare sector in Saudi Arabia involves primarily the Government, which works through the Ministry of Health (MoH) and a number of semi-public and private organizations. With free healthcare services being provided by the Government, accompanied by a motto of "from womb to tomb", it continues to be a priority sector in the Kingdom. With the proposal to spend over 13.5% of the total government budget for health and social development as allocated in the year 2017, it marks one of the fastest growing populous regions of GCC (Gulf Cooperation Council), thus indicating a natural upward trend in need of healthcare services in future. Though huge spending in healthcare has been noted for decades now, the quality still lacks international standards and the development is mired by a lot of adversaries like dependency on imports, business environment, and many such more (https://www.e-marmore.com/Blog/Infrastructure/April-2017/Healthcare-in-Saudi-Arabia-Will-the-future-tide). However, with reports on improved liquidity and a focus to expand the private sector's contribution towards the economy, the healthcare sector has been predicted to grow at a CAGR of 12.3% till the year 2020 (http://www.oxfordbusiness-group.com/news/big-changes-ahead-saudi-arabia%E2%80%99s-health-care-sector).

Health survey reports of Saudi Arabia indicate non-communicable ailments to bear a major healthcare burden and a CDC report of the year 2016, indicates cancer to also be one of the contributors apart from accidents and other chronic ailments. The Saudi Arabia Cancer Incidence Report of 2013 highlights a total number of 15,653 cases to be recorded in that year alone; in which 14,796 were adult cancers. The major or top ten malignancies recorded include cancer of the breast, colorectal, lung, etc. among many others including leukemia and lymphoma. Statistics of gastric cancer alone as per the Saudi Arabia Cancer Incidence Report of 2013, indicates an incidence rate of 2.7% among all the newly diagnosed cases in the year 2013 in Saudi Arabia. Stomach cancer in occurrence has been ranked 12th among women and 9th among men. Studies which have documented the prevalence of stomach cancer between the year 1997–2007 in Oman have detected this malignancy to be the second most common among females from that region of the Kingdom and also indicates Oman to bear the highest burden of stomach cancer among all the GCC regions (Al-Mahrouqi and Parkin, 2011). The study that aimed to document

Table 1
Frequency and Mortality in various Populations.

Country	Frequency (%)		Mortality (%)		Reference
	Men	Women	Men	Women	
China	14.59	7.85	14.8	11.3	Zheng et al. (2013)
Japan	11.4	5.7	3.9	1.8	Taniyama et al. (2017)
United States	2.1	1.2	2.1	1.5	Siegel and Miller (2017)
Saudi Arabia	3.84	2.41	3.29	2.05	Alahmadi et al. (2016)

the epidemiology of gastric cancer between Oman and GCC regions calculated the age-adjusted frequency rates to be 10.1 per 100,000 for males and 5.6 per 100,000 for females respectively. Table 1 highlights the mortality and incidence rate of gastric cancer, among women and men in comparison to other parts of the world.

A publication by Mohammad et al. (2009) which documented the incidence and frequency of stomach cancer in Oman in comparison to those recorded in other GCC regions, identified early-onset stomach cancer to have a low incidence rate in Saudi Arabia, UAE and Kuwait, in comparison to Oman while the relative risk was reported to be borderline in Bahrain. This study also noted regional variation in incidence frequency with coastal regions harbouring higher number of affected in comparison with the inland city. The most potent reason cited for this difference would be differential rate of exposure to trigger factors; wherein people from coastal region principally consume higher amounts of salt-preserved fish.

2.1. Pathology and subtypes

As per the Saudi Arabia Cancer Incidence Report of 2013, of the 2.7% incidence rate recorded for gastric cancer, Adenocarcinoma morphology was detected at the highest rate of 42.1% and 38% among men and women respectively. The signet ring cell carcinoma type followed this, while the carcinoid and the mucinous adenocarcinoma were recorded at much lower frequencies of 2.1% and 1.7% each among men and women respectively. A study publication by Mohammad et al. (2009) on the cancer incidence in Oman in the year 2007, recorded malignant gastric lymphomas to account for 5–10% of all the stomach cancer cases detected.

A study, which focussed on publishing the incidence of gastric cancer in Southern region of Saudi Arabia, identified intestinal adenocarcinoma to be the most frequent in occurrence at 75% followed by malignant lymphomas and diffuse adenocarcinoma at frequencies of 14% and 11% respectively. Further analysis in to documenting the most common part affected led to identifying the gastric antrum to be the major affected at 47%, followed by the gastric corpus at 27%, the cardia and fundus at 14% and 12% respectively (Hamdi and Morad, 1994). A recent hospital-based study published in the year 2016 from the King Faisal Specialist Hospital-Jeddah Saudi Arabia documented the incidence of gastric cancer in their institute. This retrospective analysis included 47 patients diagnosed between the years 2002–2013 and identified 91.5% of the cases to bear the intestinal type and 68.1% of the cases exhibited poorly differentiated type malignancy. This study concluded the underrepresented fact that gastric cancer is one of the deadliest cancers in Saudi Arabia though the frequency of affected is detected to be low in comparison to the world over (Alahmadi et al., 2016).

2.2. Postulated causatives

Gastric cancer until date continues to be classified as an aggressive, multifactorial condition marked by poor prognosis and poses difficulty to cure. Studies which focused on documenting the stages of development of precancerous lesions of the intestinal cancer type identified the following steps; chronic gastritis, atrophy, intestinal metaplasia, dysplasia, finally culminating in cancer (Correa et al., 1975). H. pylori infection coupled with excessive salt intake have been detected to be the principle triggers for atrophy and development of initial stages of gastritis. Smoking status, nutrition, bacterial infections as well as occupational exposure are the broad category of causatives widely documented.

2.2.1. Bacterial infection by Helicobacter pylori

Discovered in the year 1983, H. pylori infection has been associated with pepetic ulcer as well as gastric cancer, wherein the risk ratio for the later has been documented to range from between 1.0 and 5.1 (Watanabe et al., 1997; Yatsuya et al., 2004). A three-year prospective study of 303 children from Saudi identified the prevalence of the infection to be 49.8% and regions of Jeddah and Riyadh contributed in majority. Poor living and socioeconomic conditions were majorly attributed to be the cause (Hasosah et al., 2015). Over 3 billion people accounting to roughly 50% of the world's population from developing countries have been postulated to be affected by H. pylori infection (Salih, 2009). The fact that the infected generally progress without clinical symptoms or development of peptic ulcers and only bear indications of superficial chronic gastritis leads to high infection rates as per WHO (Rothenbacher and Brenner 2003). Of the infected, 17% approximately have been postulated to eventually develop peptic ulcer and a very less frequency of just 1% that in numbers translates to approximately 30 million may progress towards development of gastric cancer (Malaty, 2007). Another hospital-based study from the Saudi Arabian Medical City of Riyadh documented a study to determine the relationship H. pylori and different gastrointestinal ailments in 150 outpatients. The prevalence of the infection was detected to be extremely high among the tested, and a strong association with duodenal ulcer was noted. Gastric ulcer was detected at a frequency of 20%, while duodenal ulcer, gastritis and gastric cancer were detected at frequencies of 24%, 33.3% and 2% respectively (Alhussaini, 2016).

2.2.2. Lifestyle factors

The contribution of lifestyle factors towards risk of gastric cancer has been consistently studied and researched upon in many high-risk countries even before the discovery of the H. pylori association. Studies have shown over 30% of cancer deaths to be preventable through controlling and modification of lifestyle factors like diet and exposure to carcinogens (Alshammari et al., 2015).

Smoking & alcohol consumption has been documented to be the most crucial factors for gastric cancer, as alcohol is a known gastric irritant and smoking tobacco been documented to prompt progress of precursor gastric lesions (Nagini, 2012; Gonzalez and Lopez-Carrillo 2010). Studies in Japan indicate a 28.4% risk among cigarette smokers independent of H. pylori infection, while in case of China, smokers have been detected to harbour an 80% risk (Shikata et al., 2008; Moy et al., 2010). The association between smoking and increased cancer risk has been noted in the Middle East. The prevalence of smoking has been noted to be highest in the Saudi at 19.1% and 8.3% frequencies among men and women respectively as per a survey carried between years 1996 and

2001 (Hussein, 2010). Water pipe smoking or shisha is popular among the Middle East and has been proven associated with a lot of short-term and long-term health impact, gastric cancer risk being one among the many. A large-scale cohort study in Iran identified a three times higher risk for gastric cancer in waterpipe smoking post adjustment for cigarette smoking and many other risk factors (Sadjadi et al., 2014).

The carcinogenicity of nitrous compounds is well documented and it either occurs naturally in some vegetables or is added externally as a preservative in cured meat, instant foods, etc. Dietary nitrate is converted to the carcinogenic form of N-nitroso compounds due to gastric acidity, thus increasing the risk of cancer. High intake of preserved fish as well as vegetables has hence been linked to the risk of gastric cancer (Jakszyn and Gonzalez, 2006). Studies have documented traditional Yemeni food to majorly include fresh fruits and vegetables along with unprocessed wheat products. However, a rapid change in dietary pattern has been noted in the last decade dominated by animal protein, hot spices, canned and fermented foods; all known risk factors for gastric carcinoma (Al-Samawi and Aulaqi, 2012). Studies have also documented a high starch and low protein diet to favour mechanical damage to the gastric mucosa due to acid-catalyzed notarisation (Berretta et al., 2012).

2.2.3. Genetic factors

Genetic variants in many genes like the tumor suppressor TP53 as well as COX-2 have been detected in spontaneous cases of gastric cancer. Deletion in the TP53 gene has been associated with over two-third of gastric cancer cases (Kumar et al., 2013). TP53 mutation and overexpression has been noted in over 50% of gastric cancer cases (Forbes et al., 2011). A study by Nasif et al. (2013), evaluated circulating TP53 antigen in the sera of gastric cancer patients as a tumor marker. This study detected TP53 expression in 62.5% of the nuclei in carcinoma cells in patients, thus concluding P53 concentration to be a useful marker for gastric cancer (see Fig. 1).

2.3. Clinical features & treatment options

As per reported by the Saudi Oncology Society clinical management guideline series for stomach cancer, the median age of diagnosis has been noted to be 65 years for males and 60 years for females. This detailed guideline discusses gastric cancer in a multidisciplinary form as esophagogastric junction tumor. This is classified into three types covering 5 cm area on either side of the gastro-esophageal junction. Type II and Type III which encompasses tumor extending 1 cm in proximal and 2 cm in distal region of the junction and those with extend >2 cm below the gastro-esophageal junction to be treated as gastric cancer (Kandil et al., 2014). For metastatic disease, no standard of care exists in literature for treated conditions of third line or beyond. Genetic factors, environment, demographics as well as cultural indices contribute towards the heterogeneity of this condition, though the major factor towards disease progression and further management has been attributed towards environmental factors (Al Saghier et al., 2013). Prognosis of this condition depends majorly on the stage of diagnosis, and the subsequent surgical and curative options endorsed.

Experimental studies have proven development of gastric cancer to be a sequential process beginning with accumulation of genetic and epigenetic alterations in oncogenes, tumor suppressor genes, DNA repair genes, etc. of epithelial cells (Nagini, 2012). As per Saudi Oncology Society clinical management guidelines, the staging of the disease is to done as per The American Joint Commission on Cancer (AJCC) pathological staging system. Surgical options available for treatment include gastrectomy or endoscopic resection as well as laparoscopic gastrectomy. Gastrectomy has been documented to be the most popular mode associated with a high 5-year survival rates (Katai et al., 2010). For treatment of *H. pylori* involved cancer, eradication of the same followed by endoscopic resection of early gastric cancer has been associated with reduced risk of occurrence of metachronous cancers (Fukase et al., 2008). The adjuvant therapy involves systemic chemotherapy, radiotherapy or intraperitoneal chemotherapy, though surgical excision of the tumor mass is considered the only curative option (Dicken et al., 2005).

Adjuvant radiotherapy is also considered as important as studies have documented up to 80% of the affected patients to experience local recurrence. Many randomized trials have also shown post-operative survival benefit with combined chemo radiation therapy (Macdonald et al., 2001). The chemotherapeutics approved as per the Saudi Oncology Society clinical management guideline include epirubicin, cisplatin, 5-fluorouracil, docetaxel, FOLFOX, at
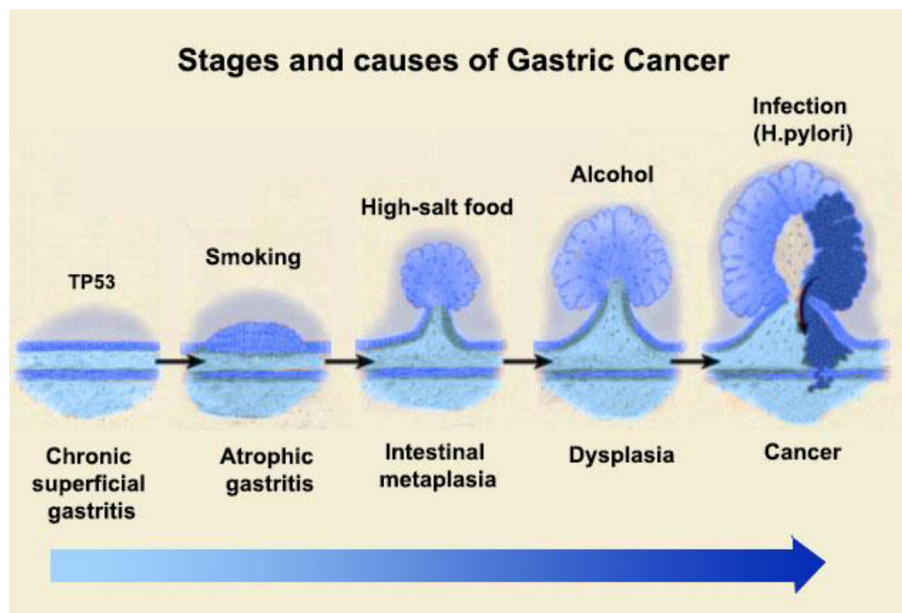

Fig. 1. Highlights the stages of development of gastric cancer along with the proven causatives.

different stages for as adjuvant as well as palliative treatment. Use of immunotherapy for treatment of gastric cancer has also been investigated in one of the largest phase II trials; KEYNOTE-059. This study carried out in three different cohorts, detected an objective response rate of 12%, for pembrolizumab among the pre-treated patients. PD-L1 or the programmed death-ligand 1 expression was also associated with a 16% response rates in comparison to 6% among those negative for expression. This study also noted a good promising response among the newly diagnosed metastatic cancer cases of both the other cohort involving the combination therapy arm and the pembrolizumab alone arm (Wainberg, 2017- ESMO 2017). Use of targeted therapy like Trastuzumab which is an anti-HER2 (anti-Human epidermal growth factor receptor 2) antibody, has also shown marginal efficacy in HER2 positive gastric cancer cases. The ToGA (Trastuzumab for Gastric Cancer) trial has highlighted this agent to improve 5-year overall survival among patients with high HER2 protein expression (Wagner et al., 2006).

3. Future prospects

Infection control by *H. pylori* continues to be stated as one of the major goals as it proved to significantly reduce gastric carcinogenesis and mild gastritis without intestinal metaplasia or severe dystrophy (Tsukamoto et al., 2017).

Diet as discussed extensively in this review, without doubt proven to play an important role in the ethology of this malignancy. A nine-year study covering over ten European countries including a cohort analysis of 485,044 women and men between the age of 35–70 years old, compared different dietary patterns ensuing risk of gastric cancer. Data generation was done by comparing with a typical Mediterranean diet pattern, upon which only 449 cases were diagnosed within the cohort. This study indicated a significant 33% risk reduction upon indulgence in a typical Mediterranean diet than anything otherwise, and meat consumption associated with increased risk (Buckland et al., 2010).

Raw vegetables and fruits intake proven and linked to a decrease the risk for gastric cancer by numerous scientific studies. Published case-control studies in various parts of the world like Asia and Europe. Have found intake of vegetables and fruits to reduce risk by 40% and 30% respectively (Lunet et al., 2007). Another EPIC study involving 683 gastric adenocarcinoma patients with a 11-year follow-up detected intake of citrus fresh fruits to confer protection against the risk of diffuse and cardia gastric cancers (Gonzalez et al., 2012). The micronutrients found in vegetables and fruits like vitamin C, lycopene and selenium. have been shown to be powerful antioxidants and thus potent anticancer agents. Studies have shown serum vitamin C levels to be inversely proportional gastric cancer associated mortality (Liu and Russell, 2008). Another randomized study from Japan among patients with chronic gastritis reported reduced rate of progression of gastric mucosal atrophy with vitamin C (Sasazuki, et al., 2003). Carotenes which are another class of lipid-soluble compounds are present in rich amounts in vegetables and fruits has been detected to be a potential free radical scavenger, especially in late stage of gastric carcinogenesis, and has an effect opposite to that of salt. An interventional trial in China identified cancer mortality rates to be considerably reduced over a period of 5.25 period among patients accompanied with vitamin E, selenium and beta-carotene (Ge et al., 2012).

4. Conclusion

The most crucial aspect in controlling cancer burden in any country involves identifying the fuelling factors and enforcing appropriate measures including early detection, promotion of healthy lifestyle, routine screening programmes, etc. Also, existing published literature on stomach cancer from Saudi Arabia indicate great difference in incidence rate across different regions, which highlights the need for maintenance of better cancer registries and also invest in more research to understand and tackle the cause for disparity. Labelled the deadliest form of cancer in this region, the need for better curative approaches with effective diagnostic and treatment strategies become the need of the hour. The plethora of scientific publications on gastric cancer until date indicate nutritional chemoprevention can be the best policy for prevention of gastric cancer.

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