Understanding the Epidemiology and Pathways to Care of Gastric Cancer in South Africa.

Anishka Ramadhar
2244064

Supervisor: Dr Mazvita Muchengeti
MB ChB (UZ), MSc (Wits) PhD (Bern)
Head of Department – National Cancer Registry

Co-supervisor: Prof Juliana Kagura
BHSc (Hons) (NUST), MSc (Med) (Wits), PhD (Wits)

Co-supervisor: Dr Natasha Khamisa
BA (Hons), Upgraded MPhil, PhD (Monash University)

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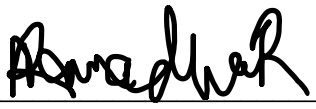
Declaration

I, Anishka Ramadhar, student number 224406, declare that this thesis is my own original, unaided work. It is being submitted for the degree of Doctor of Philosophy at the University of the Witwatersrand, Johannesburg, South Africa. It has not been submitted before for any degree or examination at any other University or institution.

Signed  on the

23 January 2025 in Durban, South Africa.

Dedication

My PhD is dedicated to my Mum:

This one is for you Mum, Shama Ramadhar, I love you and I thank you. Everything that I achieve will only be a fraction of all that you have and continue to achieve. Thank you for being my biggest cheerleader, critic, role model and irritating person. Jai Mata Di.

You really are the best!

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List of Abbreviations

Age standardized incidence rate (ASIR)

Age standardized mortality rate (ASMR)

Average annual percentage change (AAPC)

Computed tomography (CT)

Computer-assisted qualitative data analysis software (CAQDAS)

Confidence interval (CI)

Diagnosis and treatment pair (DTP)

Directly age-standardised event rate ($ASR_{(dir)}$)

Disability adjusted life years (DALYS)

Division of cancer control and population sciences (DCCPS)

Epidermal growth factor receptor (EGFR)

Epstein-Barr virus (EBV)

European Society for Medical Oncology (ESMO)

Familial adenomatous polyposis (FAP)

Figure (Fig)

Gastric adenocarcinoma (GAC)

Gastric cancer (GC)

Gastroenterologists (GI)

General practitioner (GP)

Global Cancer Observatory (GLOBOCAN)

Institute for Health Metrics and Evaluation's (IHME)

Healthcare professional (HCP)

Helicobacter pylori (H. Pylori)

Hereditary diffuse gastric cancer (HDGC)

Human development index (HDI)

International Agency for Research on Cancer (IARC)

International Prospective Register of Systematic Reviews (PROSPERO)

Kwazulu Natal (KZN)

Low - and middle-income countries (LMICs)

Microsoft Teams (MS Teams)

Mortality to incidence (M: I)

Multidisciplinary team (MDT)

National Cancer institute (NCI)

National Cancer Registry (NCR)

National Comprehensive Cancer Network (NCCN)

National Health Laboratory Services (NHLS)

Number (N)

Positron emission tomography (PET)

Prescribed minimum benefit (PMB)

Primary care clinicians (PCC)

South Africa (SA)

Statistics South Africa (STATS-SA)

Strengthening Reporting of Observational Studies in Epidemiology (STROBE)

Sub-Saharan Africa (SSA)

Surveillance research program (SRP)

Systematic review (SR)

Tumour Node and Metastasis (TNM)

Western Cape (WC)

World Health Organization (WHO)

Abstract

Introduction

Globally gastric cancer (GC) is the 5th most common and deadliest cancer. In sub-Saharan Africa (SSA) GC is the 10th most common and 9th deadliest cancer. In South Africa (SA), GC is the 14th and 10th most common cancer in females and males respectively. The aim of this thesis is to understand the epidemiology of GC in SSA and SA from available published literature, to determine the incidence and mortality rates for GC in the SA adult population from South African data registries and to explore the SA GC care pathway via primary data collection from healthcare professionals' (HCP) interviews.

Methodology

This explanatory mixed methods study comprises 3 research papers. Paper 1 is a systematic review (SR) on GC in SSA. Paper 2 is a cross-sectional study design using secondary data from cancer and death registries. Paper 3 is a qualitative study design using in-depth interviews. The study population for the paper 1 is primary SSA GC studies published between 1995 and 2022. In paper 2, data from the SA National Cancer Registry (NCR) from 2002 to 2020 were used for GC incidence rates and from Statistics South Africa (STATS-SA) from 2002 to 2018 for GC mortality rates. The study population for paper 3 comprises of 30 anonymised SA healthcare professionals (HCPs) that participated in a cancer care interview, across a variety of disciplines in the SA private and public healthcare sectors.

Results

The SR showed the overall crude pooled incidence was 1.20 GC cases per 100 000 (95%CI 1.15-1.26) people with 99.83% variability (I2 $p<0.001$). From the 29 high-quality population-based registry studies the crude pooled incidence was 1.71 GC cases per 100 000 people (95%CI 1.56-21.88) with 99.60% variability (I2 $p<0.001$). Paper 2 showed 22 391 GC cases and 20 212 GC deaths over the study period, with incidence increasing from the age of 40. Men had more than twice the GC ASIR than females at 0.39 and 0.15 GC cases per 100 000 people respectively in 2020. Men had more than twice the GC ASMR than females at 0.31 and 0.14 GC deaths per 100 000 people respectively in 2018. The average annual percentage change (AAPC) for ASIR (-0.8) and ASMR (-1.55) in the SA GC population was decreasing without statistical significance. Themes identified in paper 3 were referral and coordination processes in the GC care pathway, public versus private sector healthcare system differences, and the GC

care pathway challenges. The flow of GC care employs a multidisciplinary team (MDT) approach from diagnosis to treatment. Challenges include a low index of suspicion for GC by primary care clinicians (PCC) and *Helicobacter pylori (H. pylori)* detection.

Conclusion

This thesis demonstrated the high variability of GC incidence across SSA. Differential exposure to risk factors may explain the incidence and mortality differences observed among the SA population groups. There is a need for further primary data collection and exploration, and cancer care studies in SSA. Accurate estimation of the SA GC burden is crucial for public health policies and GC control measures. Thorough staging upon GC diagnosis provides a basis for a vigorous treatment plan, enhanced decision making on surgery and treatment administration. These steps will facilitate the effective flow of the GC care pathway and provide patients with a solid understanding of their disease and prognosis. An effective care pathway may assist in identifying a potential for cure or increased quality of life early in the patients' treatment plan. A national consensus for a MDT GC care, emphasising early diagnosis to aid in a robust treatment plan for improved patient outcomes is warranted. This consensus will aid in public health strategies for a uniform and patient-specific approach for GC care in SA.

Chapter 1: Introduction

1.1 Background

Globally, cancer is the second leading cause of death, with 20 million new cancer cases and 9,7 million deaths in 2022 (13). Global Cancer Observatory (GLOBOCAN) demographic estimates show that by 2050, the yearly number of new cancer cases will reach 35 million (13). About 1 in 5 people develop cancer in their lifetime, and approximately 1 in 9 men and 1 in 12 women die from the disease (34). Lung cancer was the most common cancer with 2.5 million new cases (12.4% of the total new cases). Female breast cancer was second (2.3 million cases, 11.6%), followed by colorectal cancer (1.9 million cases, 9.6%), prostate cancer (1.5 million cases, 7.3%), and GC (970 000 cases, 4.9%) (35).

Globally GC is the fifth most common cancer and cause of cancer-related death. The development of GC comprises of multiple factors, numerous stages, and progressive histopathological phases (1). In many GC cases, the first stage of development starts with *Helicobacter pylori* (*H. pylori*) infection, followed by chronic hypertrophic gastritis, intestinal metaplasia, dysplasia, and eventually aggressive carcinoma (2).

In 2022 GC attributed to 659 853 cancer deaths and 968 350 new cancer cases (13). Globally, the GC ASIR for males is 12.8 per 100 000 people and 6 per 100 000 people for females, with 627 229 and 341 121 new cases for males and females respectively (13). The 5-year relative survival rate for GC decreases with severity and spread of the disease (23). The American Cancer Society 2023 report indicates that the 5-year survival rate for localised GC is 72%, regional GC is 33% and distant GC is 6% (23). The American and European GC 5-year survival rate is between 25% and 28% if cancer is diagnosed in the later stages (23).

Anatomically, GC can be classified into cardia GC and non-cardia GC subtypes. Cardia GC is in the upper stomach near the oesophagus (close to the heart) and non-cardia GC occurs in the mid and distal stomach (6). Cardia GC comprises of two different aetiologies, the first being similar to gastroesophageal reflux and resembles oesophageal adenocarcinoma, and the other is similar to *H. pylori* atrophic gastritis with a resemblance to non-cardia GC (7).

The International Agency for Research on Cancer (IARC) acknowledges that the primary cause of GC is *H. pylori* infection and *H. pylori* is a group 1 carcinogen (3, 43). *H. pylori* may cause a

3-to-5-fold increase in the development of GC; however, GC only appears in 1-4% of patients infected with *H. pylori* (4). This indicates that many factors may contribute to GC development in cases both with and without *H. pylori* infection. In Africa, the role of *H. pylori* in GC development is multifactorial, with lifestyle, diet, genetic predisposition, and other pathogens all contributing to or accompanying *H. pylori* infection (5).

Epidemiological and clinical data for GC in SSA and SA are sparse (13). Gastric cancer survival rates are lower in developing countries in SSA due to late-stage detection compared to developed countries (24). Developing nations claim 70% of the global GC cases (24). South Africa has a private and public healthcare system that both diagnose and treat GC (39). Gastric cancer is a prescribed minimum benefit (PMB) condition in the Diagnosis and Treatment Pair (DTP) code 950C in the private health sector (39). Prescribed minimum benefits for the diagnosis, treatment and care are the same in both the private and public health systems (39).

The goal of the following literature review is to provide thorough insights into GC, covering global, SSA and SA GC epidemiology, anatomy of the stomach, pathophysiology, clinical presentation, risk factors, GC staging and healthcare pathways. This comprehensive dive into GC endeavours to create awareness of this disease to increase knowledge on GC and encourage further research to benefit HCPs and to better understand the GC patient journey for improved patient outcomes. The implications of GC epidemiological knowledge on a regional and national level and understanding the care pathway will influence current practice to improve the incidence and mortality of GC patients, investigate signs and symptoms with a heightened suspicion of GC and encourage widespread best practice on a public health level that can advance health policies for GC treatment and management.

1.2 Literature review

Gastric cancer epidemiology

Globally 1 in 127 females and 1 in 54 males will develop cancer within their lifetime (lifetime defined as 0-74 years) (10). One in 175 females and 1 in 74 males will develop GC within their lifetime. (10). Gastric cancer contributes 4.9% of all new cancer cases worldwide with about a million incident cases diagnosed each year, and 6.8% of all cancer deaths. Globally GC is the 5th most common cancer, among males GC accounts for about 427 421 deaths yearly and 8.6%

(1 in 12) of all cancer deaths [10, 13]. Among females GC accounts for about 232 432 cancer deaths yearly [10].

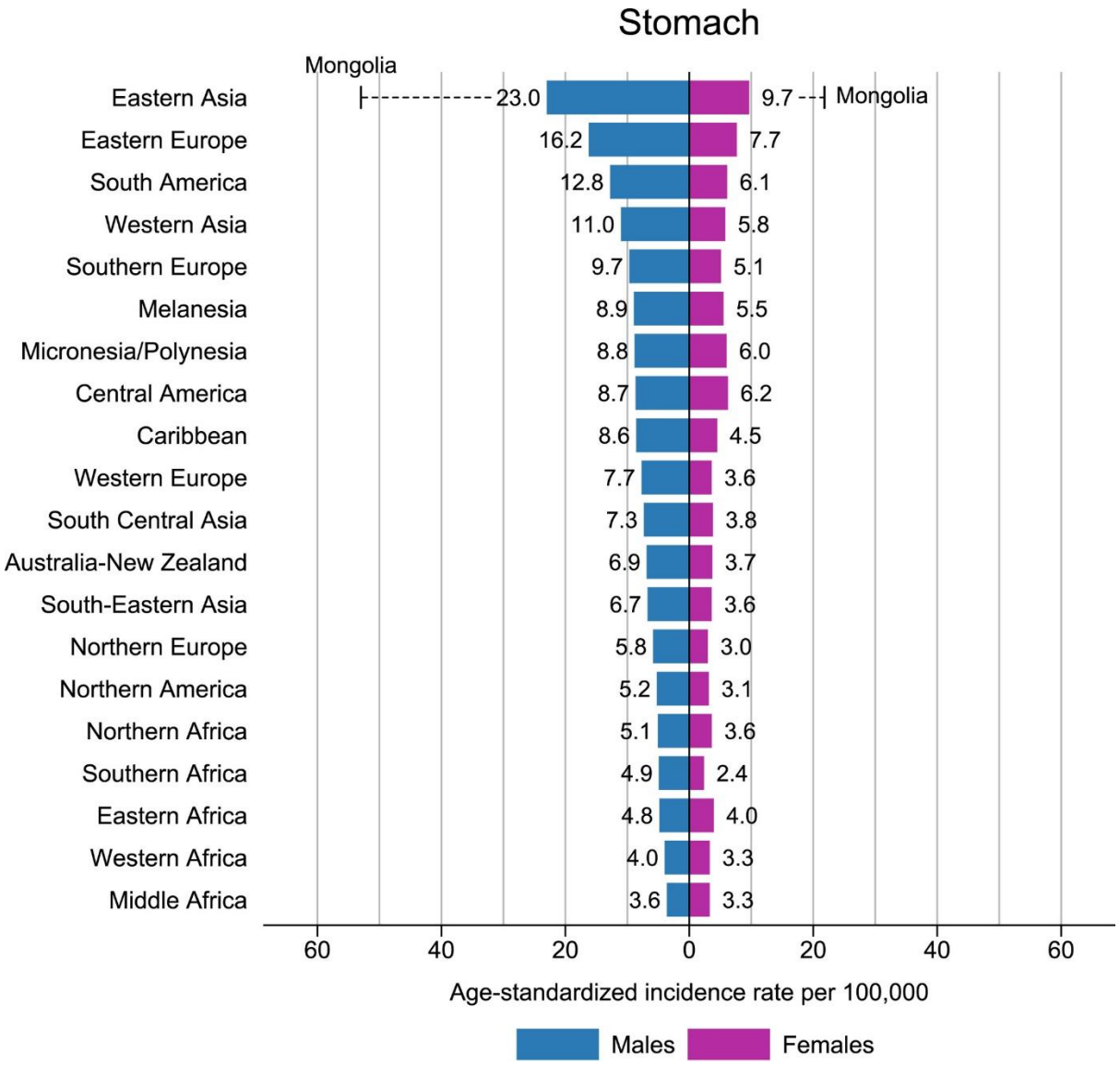


Figure 1: Bar chart of the region-specific incidence age-standardized rate by sex for stomach cancer in 2022. (Source: GLOBOCAN 2022)

Figure 1 from the GLOBOCAN 2022 report shows the GC ASIR is the lowest in Africa compared to the rest of the world. In 2020, the African continent showed 32 402 incident cases of GC (3% incidence rate), 27 945 GC deaths (3.6% mortality rate) and a 5-year prevalence of 44 192 cases (2.4%). In the 2022 WHO report with GLOBOCAN data, SSA had 23 481 GC incident cases with an ASIR of 3.9 cases per 100 000 people, and 20 681 GC deaths with an ASMR of 3.5 cases per 100 000 people. The SSA ASIR for males in 2022 was reported as 4.4 cases per 100 000 cases and 3.5 cases per 100 000 people in females [56].

The 2022 SA NCR report indicated that in SA, GC makes up 1.13% of all cancers in females and 1.92% of all cancers in males. In SA, GC is the 14th and 10th most common cancer in females and males respectively (12). The low GC survival rates and limited treatment options in developing countries like SA indicates that the key to reducing GC mortality is to reduce GC incidence (13).

The 50-year trend of GC globally shows a steady decline in incidence and mortality (15), which is similar to SA where the SA National Cancer Registry (NCR) yearly reports and Statistics South Africa (STATS SA) data show a slow but steady decrease in GC incidence and mortality over the past 20 years (14). Globally the decline in GC incidence and mortality rates may be due to improved diet, less use of tobacco and alcohol, improved food preservation methods such as the increased use of refrigerators, reduction in *H. pylori* infection, and earlier screening and detection of GC which leads to better treatment options (15).

Anatomy of the stomach

Gastric cancer refers to cancer of the stomach which is located below the diaphragm in the upper abdomen. The role of the stomach is to store ingested food and facilitate the digestion process. The stomach consists of the inner oblique, middle circular and outer longitudinal muscles layers which are involved in peristalsis for the further breakdown of food. The serosa, muscularis externa, mucosa, and submucosa are the 4 layers of the stomach wall, the submucosa supports the mucosal layer which contain glands for gastric secretions. The cardia connects the oesophagus to the proximal part of the stomach and the pylorus connects the stomach to the small intestine via the duodenum (38).

The stomach can adjust its capacity to accommodate various dietary volumes up to approximately 1.5 litres. Hydrochloric acid and gastric enzymes for metabolism of all food groups are secreted by a mucosal layer lining the inner stomach, which allows for continued digestion and nutrient absorption in the intestines. The celiac trunk supplies the stomach with blood with vascularisation by arterial branches and a complex lymphatic drainage system. The sympathetic and parasympathetic nerves of the autonomic nervous system innervate the stomach (38).

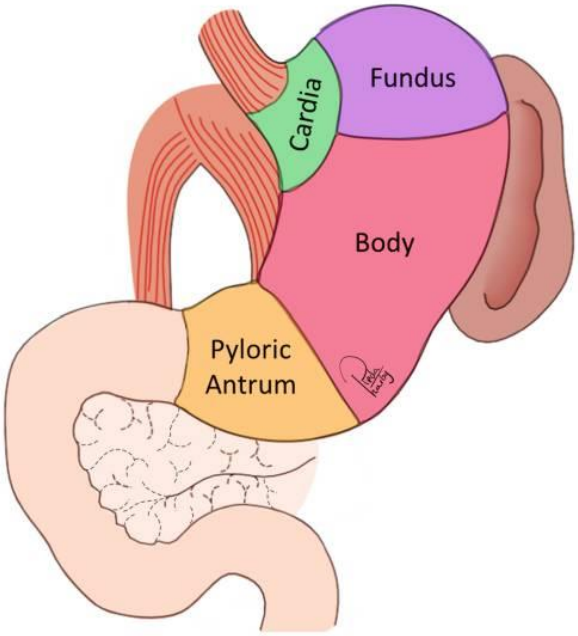


Figure 2: Anatomy of the stomach (42)

Gastric cancer pathophysiology

The pathophysiology of GC is initiated by genetic mutations followed by a series of processes leading to a complex disease. Genetic mutation causes may include *H. pylori* and Epstein-Barr virus (EBV) infection, inflammation, hazardous environmental exposure, or genetic predisposition. The cellular alterations resulting from gene mutations promote proliferation of these altered cells in the stomach lining. The genetic mutations which accumulate in genes that manage cell division, growth and repair are the cornerstone of malignancy. Continuous cell proliferation and reduced automated cell death resulting from genetic mutations cause precancerous lesions (40).

Malignant cells infiltrate neighbouring cells, tissues and vasculature, and metastasise into nearby lymph and organs and eventually into distance organs. Gastric tumours foster angiogenesis which supplies malignant cells with essential oxygen and nutrients for the growing tumour to thrive. Cancer cells have an evolved defence system allowing them to progress and spread by evading the body's immune system. Errors in the cell signalling pathways - controlling cell proliferation, survival and metabolism - including the epidermal

growth factor receptor (EGFR) pathway and PI3K-AKT-mTOR cascade, also contribute to GC formation. Mutations in EGFR, PI3K, and tumour suppressor gene PTEN causes abnormalities in the cell signalling pathway leading to flawed cell signalling, metabolism and growth which are attributes of GC (41).

Gastric cancer may present differently in individuals and these differences start with peculiar cellular characteristics and follow distinct trajectories for its heterogenous presentation. Intestinal and diffuse GC are subtypes of GC with intestinal GC being better differentiated and having a better prognosis than the diffuse type (42).

Clinical presentation of GC

The clinical features of GC may differ between patients as most patients only present with GC in the later stages of disease. Common symptoms GC patients may present with include dyspepsia, dysphagia, weight-loss, vomiting, abdominal pain, indigestion, postprandial pain, and melaena (16). In the early stages of GC clinical signs are usually ignored or absent, in late-stage GC diagnosis, an epigastric mass may be felt, and a noticeable left supraclavicular node may be present. Ascites, jaundice, hepatomegaly, or acanthosis nigricans are other conditions that may arise in late-stage GC presentation (17).

Patients present late with GC due to patient related factors such as delayed HCP visit, self-diagnosis of initial symptoms, considering symptom severity more important than the presence of symptoms, and self-treatment (31). Health system related delays in GC diagnosis and treatment are due to incorrect medical diagnosis at initial clinician visits (low index of suspicion by clinician) or radiological evaluation, which leads to delay or failure to process biopsies and endoscopies (32). Delays within the healthcare system in the laboratories and radiology departments, poor interpretation of results and confounding symptoms of existing diseases also contribute to the late diagnosis and treatment of GC (33).

Risk factors

Gastric cancer may have varied risk factors, origins, and presentations (8). Literature shows the common risk factors for the development of GC may include diets, infectious diseases, and genetics.

A diet high in salt, read meat, alcohol, tobacco and chilli increases the likelihood of GC development in SA men and women (8, 48). High alcohol and tobacco consumption are risk factors for many types of cancer and especially GC as they promote the formation of lesions in the lining of the stomach and these lesions may become malignant (9). A generous consumption of fresh fruit, vegetables and vitamin rich food increases the quality of gut and overall health and is conducive to a healthy gastric system which may be protective or prevent early onset of GC.

Infectious risk factors for GC include *H. pylori* and EBV. *Helicobacter pylori* infection leads to gastric ulcers, gastritis, duodenal ulcers, gut inflammation and dyspepsia which are all symptoms of GC, and which may result in GC without treatment and eradication (3, 16). Globally, chronic *H. pylori* infection is a leading risk factor for GC due to the bacteria taking over the stomach lining leading to continued inflammation (3). Gastric cancer may form from continued chronic inflammation of the stomach lining (9).

Hereditary GC increases the risk of GC for individuals from the same genetic line, and chances of developing GC are increased with genetic alterations related to hereditary diffuse gastric cancer (HDGC) syndrome (8). Genetic predisposition to GC stem from genetic mutations such as germline mutation (alteration in CDH1 on chromosome 16q22), Lynch syndrome, Familial Adenomatous Polyposis (FAP) and Li Fraumeni Syndrome (9).

Chronic inflammation of the stomach lining from prolonged gastritis or severe anaemia also increases the risk of GC. Patients who have undergone gastric surgery for other health conditions are high risk for GC in the remaining gastric space (6). The risk of developing GC increases as individuals age with males being more susceptible than females (8).

Gastric cancer staging

The size and spread of cancer are described by staging which comprises the Tumour Node and Metastasis (TNM) staging and numbered staging. The TNM evaluation determines the numbered staging from 1 to 4 (44). The TNM staging used by the American Joint Committee on Cancer (AJCC) is accepted globally for GC staging and is endorsed by the National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology (ESMO) (53). Staging recommendations for GC from the eighth edition of the AJCC Cancer

Staging Manual – based on data from more than 25 000 GC patients - comprise clinical TNM (cTNM) staging (newly diagnosed, untreated patients), pathologic TNM (pTNM) staging (gastric resection without previous treatment), and post neoadjuvant pathologic TNM (ypTNM) staging (patients receiving preoperative therapy) (54).

T1 indicates the tumour has grown into the stomach wall, T1a is within the mucosal (inner) layers, T1b is through the mucosa into the submucosal layer. T2 indicates tumour growth into the stomach muscle layer, T3 indicates growth into the outer stomach lining, T4a indicates growth through the stomach wall and T4b indicates growth into nearby organs or tissue (44, 45).

Nodes (N) define the cancer spread into the lymph nodes. N0 indicates no malignant cells in the lymph nodes, N1 indicates malignant cells in 1 or 2 lymph nodes close to the stomach, N2 indicates malignant calls in 3 to 6 proximity lymph nodes, N3a indicates malignant cells in 7 to 15 proximity lymph nodes and N3b indicates malignant calls in 16 or more proximity lymph nodes (45).

Metastasis (M) describe the spread of GC to other body parts, M0 indicates GC has not spread to other body parts, M1 indicates spread of GC to other body parts (44, 45).

Baseline GC staging offers details to develop treatment plans and predict patient prognosis (53). Diagnostic tools such as endoscopic ultrasound (EUS), computed tomography (CT), Positron emission tomography (PET) CT, and laparoscopy (detects peritoneal disease) improves the accuracy of baseline GC clinical staging (53). Lack of screening programmes in countries with low GC incidence results in late-stage diagnosis (54). Globally more than 50% of GC patients are diagnosed in the advanced stage which results in poor outcomes (53). Measures of poor outcome include tumour size, metastases, and positive lymph nodes. In localised resectable GC patients, outcomes are governed by the surgical stage GC (53, 54).

Gastric cancer in SSA is diagnosed in the advanced stages of disease due to late presentation of the patient to PCCs and HCPs not investigating early enough to diagnose GC in the beginning or intermediate stages (49, 50). South Africa is similar to SSA in that most of the GC cases are diagnosed in stage 3 and stage 4 due to late presentation, difficulties in the health systems for diagnostic workup and difficulties in accessing healthcare centres by most of the population (46, 51).

Healthcare pathways

Integrated health systems care pathways are patient and HCP-built, both the patient and the healthcare worker provide insight into the diagnosis and management of diseases from the first point of medical contact of the patient to final outcomes (28). Health-related care pathways are used globally for a spectrum of various healthcare conditions to construct patient-centric care practices. Therapeutic areas without established care pathways experience late diagnosis, restricted and inadequate treatment, and poor quality of life for patients and their caregivers. A smooth flow is required for the development of care pathways ranging from the participants in the multidisciplinary care team, equal geographical representation and equilibrium between subject matter experts, palliative care workers and digital healthcare (28).

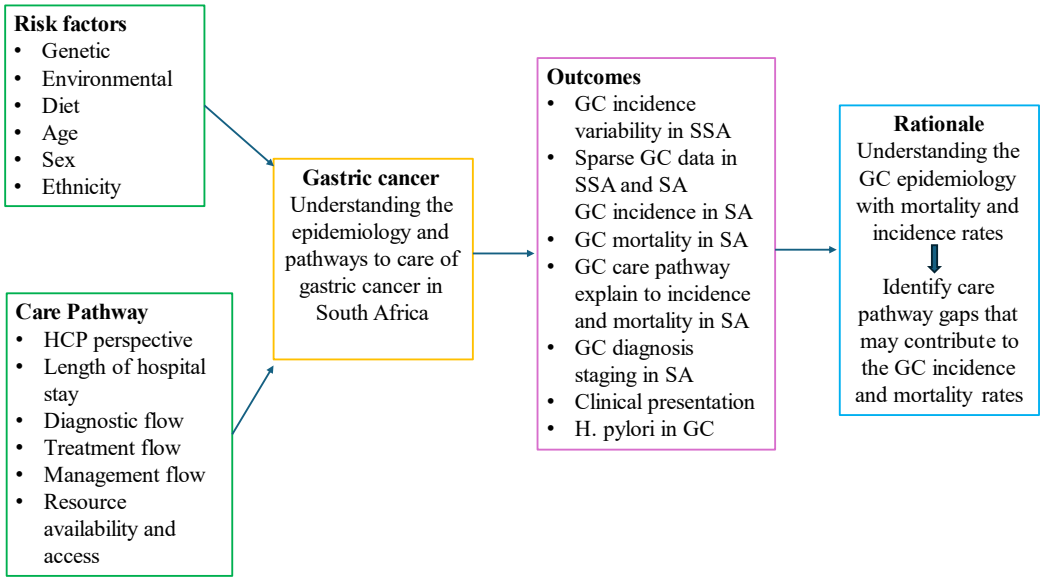
The purpose of care pathways is to improve the patient care and GC outcomes in patients and streamline the diagnosis and treatment processes for the healthcare workers in SA (29). The care pathway should highlight essential points in the patients GC journey and the subsequent care correlating to those events. After exploration of GC care in SA, a GC Care pathway once created, needs to be robust enough for global comparisons to standardise care to nations with the most improved GC outcomes (29). Integrated health system care pathways offer patient focussed care, benefitting the multidisciplinary medical and auxiliary team, the patient, their family, and their caregivers. The is currently no guideline directed, standardised approach for GC care published in SA and specific to SA (46, 51). Once a GC care pathway is established and standardised, there may be regular advancements in clinical practice, improvement in treatment and management, and opportunities for further research for GC in SA (30).

1.3 Conceptual Framework

This conceptual framework was informed by literature on GC globally, in SSA and in SA. Literature on GC included GC risk factors, *H. pylori*, clinical presentation, staging, data on incidence, mortality, and treatment and GC care according to guidelines.

For this study GC incidence and mortality data was analysed from all SSA countries where available. Gastric cancer incidence and mortality data was analysed from South African cancer and death registries. Risk factors were investigated to explain the incidence and mortality trends in the population groups of South Africa. Comparisons were made between the SA and SSA incidence and mortality rates. The SA GC care pathway was mapped to understand if the flow from GC diagnosis to treatment explains the incidence and mortality findings in SA.

The conceptual frame is adapted from the 2013 Canadian Cancer Risk Management Model: evaluation of cancer control published in the international journal of technology assessment in health care by Evans W.K. et al (55).



1.4 Problem statement

Gastric cancer is one of the leading causes of non-communicable disease deaths and cancer related deaths in the world, SSA and SA (5, 12, 13). Epidemiology of the disease portrays GC as a global and national health challenge with a high mortality rate regardless of the steady decline in incidence rates (13, 15). The complexity of the gastric tract and stomach – due to the 3 muscle layers and 4 layers of the stomach wall, the digestion and absorption of food and abundance of microorganisms in the cavity - plays a vital role in the development, region, staging, and spread of the disease (38). Genetic alterations and chronic inflammation are central to the GC pathophysiology (40). *H. pylori* infection and dietary choices are risk factors of global concern and addressing these factors may change the trajectory of GC incidence (3).

Over 3 billion individuals of the global population are infected with *H. pylori*, with the greatest burden in developing countries. The problem with an *H. pylori* infection rate is that hundreds of millions develop gastric peptic ulcers at some point in their lifetime, and tens of millions of those patients may develop gastric cancer, this resulting from ulcers introduced by *H. pylori* (25).

Gastric cancer claims many lives globally, in SSA and SA, but there are very limited organised records and investigation into these data in SSA and SA (10, 20). The scarcity of GC data and data analysis in SSA and SA results in inaccurate GC epidemiology and a poor understanding of the disease burden, which is problematic for healthcare planning to reduce the disease burden and improve patient outcomes.

There are no literature comparing the GC landscape in SA with the rest of SSA and the world, which inhibits the GC diagnostic and treatment approaches from being standardised. Standardised care allows HCPs to methodically contemplate all diagnostic and treatment approaches for all patients and minimise both treatment variation and treatment delay for optimal patient care (52). Gastric cancer data in SSA have not been aggregated to provide a collective perspective of GC incidence, mortality and treatment in the region or to perform comparative analysis between areas within the region (18, 20). Data on GC incidence and mortality are noticeably absent in SSA and SA (13). Accurate GC epidemiology is missing in SA regarding demography, geography, GC staging, treatment and management (13). This missing information does not provide a comparison for future SA GC studies and possible conclusions cannot be drawn from regional data to explain findings from SA data analysis.

The SA GC mortality rate exceeds the incidence rate which indicates that not all incident cases are being reported and mortality might be better recorded than incidence (12, 47). Extensive GC data by sex, population group, and geographical location exists in SA but have not been previously explored for incidence and mortality trends. Gastric cancer treatment and management is offered at public and private healthcare facilities (39) and the effectiveness and success of these treatment and management regiments cannot be measured without incidence and mortality trends for the SA GC population and different population groups.

A GC care pathway in SA has not previously been mapped (39, 46). There is no standardised consensus published for the care pathway for GC patients in SA (39, 46). The GC care pathway will help clinicians, researchers and policy makers to understand the challenges and successes in diagnosis, treatment and care for optimal patient management. The pathway will enable clinicians to make the correct referral decision for timely diagnosis and treatment options.

1.5 Study justification

Most GC studies in the developing countries are disadvantaged due to referral bias and the absence of reliable updated cancer registries (10, 20). The study of GC requires robust, well maintained cancer registries, ongoing epidemiological studies, and constant investigation into the pathogenesis of GC (18). In SSA especially, synergies between the multivariable risk factors such as diet, social influences, infectious diseases, and genetics should be explored to further understand the incidence and mortality of GC. (18). Literature shows that GC is highly variable across the SSA region (13). The importance of confirming this variability via a systematic review of primary data across SSA is to show that the literature supports the data from the region. This GC variability in SSA may be explained by the GC risk factors being different for the various locations within the SSA region. The differences in GC incidence among the countries of SSA may be used to investigate possible risk factors in the sub-Saharan African context. The SSA GC incidence will form a solid base of comparison for SA GC incidence and mortality analysis findings. These discoveries are critical for public health planning by customising the treatment and management approaches to specific GC situations at various locations. This analysis will allow for a better understanding of the GC disease burden in SSA. The implications of location-specific GC treatment and management may allow for the GC disease burden to be addressed via compartmentalisation and if patient outcomes are improving in smaller areas, this may result in larger regional improvements in the GC disease burden.

The epidemiological analysis of GC in SA, from the incidence and mortality trends, will allow for a better understanding of the landscape and burden of the disease in SA. This study will analyse GC patterns which may assist in predicting future GC trends. The occurrence of GC in patients across different populations, ages and demographics can be compared for severity and progression. These trends may influence diagnosis, health policies, care pathways and management of GC. The implication of identifying GC trends may allow proper diagnostic workups at initial HCP visits instead of delaying the diagnostic progress and eliminating generic treatment only for symptom relief. Further implications of identifying GC trends is to inform healthcare departments of these trends to initiate national programmes for GC awareness campaigns to HCPs and to the public, for improved healthcare seeking behaviour. Examination of these GC trends is essential to obtain an understanding of the regression or progression in effective GC control in SA especially regarding risk factors and risk reduction.

Data on GC diagnosis and care is sparse in SA, yet SA has a high GC mortality to incidence ratio and most patients are diagnosed very late [1, 46]. Exploring CG care pathways may reveal possible explanations for the delayed diagnosis and high mortality to incidence ratio. Once a care pathway is mapped it will provide a comparison of the SA care pathway to international standards set in guidelines and will uncover the gaps that can be corrected in the referral pathway for faster time to diagnosis and treatment, to improve patient outcomes. Improved patient outcomes may result in decreasing the burden of disease as the GC incidence and mortality rates may drop with enhanced treatment and management of GC patient. The GC care pathway analysis will also highlight the successes of the process which can later form part of a standardised referral and management protocol for GC patients.

1.6 Research aim and objectives

1.6.1 Overall aim

To determine of the epidemiology of GC in SSA and SA, incidence and mortality rates for GC in the South African adult population, and to explore the care pathway of GC in SA.

1.6.2 Specific objectives

Study papers:

Paper 1: Gastric Cancer in Sub-Saharan Africa – A Systematic Review of Primary Data

Primary objective: A systematic review on all available data on GC in SSA to achieve an estimate of the pooled GC incidence rate to describe the incidence rates and rate variability of GC in adults in SSA countries.

Secondary objective: To describe treatment and mortality of GC in adults from SSA.

Paper 2: Gastric Cancer in South Africa – Incidence and Mortality Trends

Objective 1:To determine GC incidence rates and incidence trends in South Africa from 2002 to 2020 to examine the trends on age, gender and ethnicity.

Objective 2:To determine the mortality rates and mortality trends for GC from 2002 to 2018 in South Africa to examine mortality trends on age, gender and ethnicity.

Paper 3: Exploring the Gastric Cancer Care Pathway in South Africa

Primary objective: to map the South African gastric cancer care pathway from diagnosis to the various healthcare professionals involved in the GC patient journey.

Secondary objective: to explore the barriers and facilitators to the flow in the GC care pathway.

Publications:

Paper 1: Gastric Cancer in Sub-Saharan Africa – A Systematic Review of Primary Data

Published in the eCancer Journal: Ramadhar, Anishka et al. "Gastric cancer in Sub-Saharan Africa - a systematic review of primary data." *Ecancermedicalscience* vol. 18 1680. 7 Mar. 2024, doi:10.3332/ecancer.2024.1680

Paper 2: Gastric Cancer in South Africa – Incidence and Mortality Trends

Status: Under review by the Journal of Cancer Epidemiology

Paper 3: Exploring the Gastric Cancer Care Pathway in South Africa

Status: In final review with the African Journal of Primary Health Care and Family Medicine.

Chapter 2: Methodology

2.1 Study design

This thesis consists of a sequential mixed methods study design. The study comprises 3 research papers. Paper 1 is a systematic review on GC in SSA from 1995 to 2022. Paper 2 is a cross-sectional study design using secondary data from the SA NCR and STATS SA data bases. Paper 3 is a qualitative study design using in-depth interviews from HCPs.

This sequential mixed method study design was chosen for ease of flow of the study papers where each paper will form the base of the subsequent paper and findings from the study papers can explain the results of previous papers.

The SA NCR has contains data for GC from 2002 and the last year for complete GC data at the time of study analysis was 2020, the STATS SA data was chosen in a time period that matched the NCR data. Hence, the inclusion of primary data for the SR in the first paper spanned 1995 to 2022 to align with period for the second paper.

2.2 Study population

The study population for this research project encompasses a vast range of data starting from GC research studies from primary data collection in SSA for a systematic review on GC incidence, to anonymised secondary GC patient data on GC incidence and mortality to identify trends in the SA adult GC population by gender and ethnicity, to primary data collection from HCPs in SA via in depth interviews.

The study population for the paper 1 is primary GC studies on GC in adults in SSA, published between 1995 and 2022. The paper 2 study population is the South African population since the NCR and STATS SA are national cancer and death registries respectively. The population included adults GC patients from all demographics across SA. The disease of interest will be GC patients recorded from the years 2002 to 2020 for GC incidence calculations and from 2002 to 2018 for GC mortality calculations. The study population for paper 3 comprised of 30 anonymised SA healthcare workers including general practitioners, gastroenterologist, nurses, surgeons, oncologist, pathologists, dieticians, and palliative care specialists, that participated in a cancer care qualitative interview, across a variety of disciplines in the SA private and public healthcare sectors, who treat or manage GC patients.

2.3 Data collection and sources

Paper 1:

The systematic review for the first paper will be compiled using online, primary data studies, available on search engines and databases such as PubMed, Google Scholar, Medline, Ovid, EBSCOHOST, EMBASE, Cochrane and Scopus from the years 1995 to 2022. The primary investigator extracted the data 2 reviewers verified the data extraction.

Paper 2:

Routinely collected, anonymised data from the SA NCR for the study analysis of GC in SA, by age, population group and gender. Statistics SA data was utilised for analysis of mortality trends. Data from the NCR and STATS SA are publicly available. Data variables from the NCR include diagnosis age, gender, ethnicity, geographical location, morphology, and topography. Data variables from STATS SA include mortality age, gender, ethnicity, geographical location, and cause of death.

Paper 3:

Primary data collected from healthcare professionals via qualitative in-depth interviews were collected for the third paper to map the GC care pathway. The interviews were directed at general practitioners (GPs), oncologists, nurses, surgeons, pathologists, gastroenterologists (GI), nutritionists, and palliative care specialists in the private and public sector that contribute to GC treatment and care. The GP was the first point of contact and chain-referral sampling was used based on the referrals from the GP for other HCPs involves in GC care.

2.4 Statistical analysis

Paper 1:

Upon acceptance of the study protocol, an International Prospective Register of Systematic Reviews (PROSPERO) registration commenced to register the systematic review on their review register. The PROSPERO registration number is CRD42022341498. The research question was based on the objective of the systematic review which was to determine the incidence rates and rate variability of GC in SSA and to describe the mortality and treatment of GC in SSA. The search terms included primary studies on adult GC patients in the 54 SSA countries between the years 1995 and 2022. Final search terms were used in search engines including PubMed, Medline, Google Scholar, Embase and Cochrane. The final search results underwent a title review to assess if the abstracts contain relevant information for the study. Relevant articles were found via the abstracts, located from search engines and stored by incidence, mortality, treatment, and background. Entire articles were reviewed to assess which

findings were eligible to be included in the paper. Summaries on the findings were created and stored based on incidence, mortality, treatment, population group and outliers. The PRISMA 27-item checklist was used for the study inclusion criteria. The articles were graded from 1 to 4 according to the data quality defined by the data source and the histology confirmation. One was the rank provide to articles containing the highest quality data and four was the rank provided to articles with the lowest data quality. A meta-analysis from the crude data was performed to determine the overall GC incidence in the whole of SSA, subgroup analysis by region and by countries with the highest quality data. Stata 15 statistical software package was used for the meta-analysis to calculate the overall incidence rate of GC in SSA and the regional GC incidence rates for North, South, East and West Africa.

Paper 2:

Stata 15 statistical software package was utilised for all data cleaning, management, and analysis. Trends and AAPC in GC incidence rates and mortality rates was described for the different age and population groups using the Joinpoint Regression statistical software. (26). Age-standardisation - using the Segi world standard population of 1960 - for gastric cancer enhances the comparability of GC incidence and mortality from different populations by accounting for the effects of differences in age structure. The directly age-standardised event rate ($ASR_{(dir)}$) for GC incidence or mortality for the study populations, is calculated by using the event rates (r_i) (incidence or mortality rates) for each age group of the study population to the standard population sizes for each age group (N_i):

$ASR_{(dir)} = \sum N_i r_i / \sum N_i$

$ASR_{(dir)}$ is a weighted mean of the r_i using the N_i as weights. The age-standardised rate is expressed per 1,000 or 100,000 population (27).

Paper 3:

The analysis for this paper was done from qualitative in-depth interviews from HCPs that diagnose, treat and manage GC patients. The interviews with the HCPs were done via Microsoft Teams (MS Teams) and Google Meet which were recorded for optimal data transcription and extraction. The qualitative analysis comprising of narrative analyses (based on experiences) and thematic analyses (based on themes) was done using the MAXQDA software programme. The qualitative interview guide was piloted by a GP, oncologist, and GI surgeon to increase the accuracy and relevance of the questions for further dissemination to HCPs.

The outcome of paper 3 is the mapped GC care pathway which outlines the journey of the GC patient from the PCC to treatment or further HCP referrals at each step, and challenges and successes experienced. Analysis of these steps revealed the GC care pathway, treatment gaps and intervention requirements in the care process.

2.5 Selection criteria

Paper 1:

Inclusion: primary data studies on GC in SSA, published between January 1995 and March 2022 were considered. Country inclusion was in accordance with The World Bank definition of SSA comprising 54 countries. All attempts to access texts and data were made, including contacting corresponding authors of publications.

Exclusion: GC studies outside of SSA, paediatric GC studies, benign gastric tumours, and benign neoplasms. Studies without accessible full text in either French or English language were excluded.

Paper 2:

Inclusion: South African adult male and female patients who have been histologically diagnosed with primary gastric cancer between 2002 and 2020 and SA adult male and female patients who have died from primary GC between 2002 and 2018.

Exclusion: GC patients histologically diagnosed before 2002. Paediatric patients.

Paper 3:

Inclusion: GPs, oncologists, nurses, surgeons, pathologists, GIs, nutritionists and palliative care specialists, that treat GC in the private and public healthcare sector from the Western Cape, Gauteng and KwaZulu Natal provinces which are the most densely populated provinces in SA.

Exclusion: gastric cancer patients and HCPs that do not treat GC.

2.6 Ethical clearance

The systematic review was registered on PROSPERO with registration number CRD42022341498 before commencement of research. Permission to use the NCR data was

requested from the NCR. Cancer mortality data by population group was requested from STATS SA. Ethics clearance was obtained from the Wits Human Research Ethics Committee (Medical) before the commencement of research, and for the collection of primary data via HCP interviews. The ethical clearance certificate number is M220752 (Appendix 3). An electronic consent form was provided to all interview participants for the third research paper to seek informed consent prior to participating in the survey.

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Chapter 3: Gastric Cancer in Sub-Saharan Africa – A Systematic Review of Primary Data

Anishka Ramadhar[1], Phoebe N Miller MS MD[2], Mazvita Muchengeti MBChB MSc[1] PhD[3], Juliana Kagura MSc PhD[1], Kathryn Chu MD[4], Cameron Gaskill MD MPH[5]

[1] Division of Epidemiology and Biostatistics, School of Public Health, University of the Witwatersrand, Johannesburg, South Africa

[2] University of California San Francisco, San Francisco, CA, USA

[3] National Cancer Registry, National Health Laboratory Service, Johannesburg, South Africa

[4] Stellenbosch University, Faculty of Medicine and Health Sciences, Cape Town, South Africa

[5]University of California Davis, Davis, CA, USA

Corresponding Author:

Anishka Ramadhar

anishkaramadhar@gmail.com
0027 82 454 1732

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Declarations

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Keywords

1. Gastric cancer
2. Adenocarcinoma
3. Sub-Saharan Africa
4. Systematic review
5. Incidence
6. Epidemiology

Abstract

Introduction: Gastric cancer (GC) is the third leading cause of global cancer related mortality. Despite the shifting burden of GC to low-and middle-income countries, the data regarding incidence, treatment, and outcomes in these settings are sparse. The primary aim of this systematic review was to aggregate all available data on GC in sub-Saharan Africa (SSA) to describe the variability in incidence across the region.

Methods: Studies reporting population-based primary data on gastric cancer in SSA were considered. The inclusion was limited to primary studies published between January 1995 and March 2022 which comprised of adult patients in SSA with GC. Studies without accessible full text in either French or English language were excluded. Unadjusted GC incidence rates with their standard errors for each study were recalculated from the crude numerators and denominators provided in individual studies.

Results: A total of 5,626 articles were identified in the initial search, of which, 69 studies were retained. Reported incidence rates ranged from a high of 5.56 GC cases per 100,000 in Greater Meru Kenya to a low of 0.04 GC cases per 100,000 people in Benin City Nigeria. The overall crude pooled incidence was 1.20 GC cases per 100, 000 (95%CI 1.15-1.26) with a variability of 99.83% (I^2 $p<0.001$). From the 29 high-quality population-based registry studies the crude pooled incidence was 1.71 GC cases per 100,000 people (95%CI 1.56-21.88) with a variability of 99.60%.

Conclusions: This systemic review demonstrates that GC incidence is highly variable across SSA. The limited data on GC treatment, mortality, and survival presents a significant challenge to providing a complete epidemiologic description of the burden of GC in SSA. There is a need for further robust data collection, exploration, and research studies on cancer care in SSA, with continued assessment of primary data availability.

Strengths and limitations of this Study

Limitations:

- The employed search strategy is open to the biases of the search engines available to authors, potentially missing non-indexed reports published in regional journals.
- Calculations in the study were limited by the availability of regional and population-based estimates that were truly reflective of a given study's sample population.
- Sparse gastric cancer data available for the sub-Saharan African countries.
- Histological confirmation was reported in less than 50% of the studies which may have positively skewed the GC incidence. Histological confirmation is needed for accurate data reporting and scarcity of histological information could affect the epidemiology findings for GC incidence.

Strengths:

- This systematic review included studies which comprised of only primary data.
- This study is the only systematic review on gastric cancer in sub-Saharan Africa.
- This study provides the most stringent review of high-quality data available to date to better inform efforts to bolster regional data collection.

Introduction

Globally gastric cancer (GC) is the fifth most common malignancy with over 1,250,000 new cases diagnosed annually. GC causes over 950,000 deaths each year and ranks as the third leading contributor to global cancer related mortality [2]. While historically, the burden of GC has been attributed to higher income countries, the shifting burden of non-communicable disease now attributes over 80% of GC related deaths to low- and middle-income countries (LMICs) [2,3]. The World Health Organisation (WHO) 2020 report on cancer estimated 22,992 incident GC cases within Sub-Saharan Africa (SSA), amounting to over 20,000 deaths per year [4].

Current epidemiologic data on the burden of GC in LMICs is sparse [5]. GC is a multifactorial disease, impacted by genetic and environmental factors that result in wide epidemiologic variation. Up to 20-fold differences in incidence rates have been reported between different geographic regions[8]. Accurate epidemiologic data has historically been dependent on population-based registries. In the absence of high-quality data, cancer incidence and mortality have been reported by relying on mathematical estimates, which may not appreciate the regional heterogenicity of GC rates or may under-represent GC incidence [9]. This is especially true for SSA, where only 10% of the population are included in population-based cancer registry data collection [10]. Further knowledge of GC incidence, treatment, and outcome is necessary for adequate treatment and public health planning.

The primary aim of this systematic review is to aggregate all available data on GC in SSA to describe the incidence rates and rate variability of GC in adults in SSA countries. Secondary aims include describing treatment and mortality of gastric cancer in adults from SSA. The hypothesis is that GC is highly variable across the SSA region and this analysis has used primary studies to demonstrate this. The importance of GC variability indicates that the flow of risk factors to disease outcome differs by location. This is critical for public health planning which indicates that treatment and management approaches need to be customised to the variable GC situation at each location. This analysis will allow for a better understanding of the GC disease burden in SSA.

Methods

Eligibility Criteria

Studies reporting population based primary data on in SSA were considered. Country inclusion was in accordance with The World Bank definition of SSA. Primary data published between January 1995 and March 2022 which included adult patients in SSA with GC were included. Studies without accessible full text in either French or English language were excluded. All attempts to access texts and data were made, including contacting corresponding authors of publications. There was no involvement from any patients or the public in this systematic review.

Information sources, search strategy, and study selection

The terms ‘gastric cancer’ OR ‘stomach cancer’ OR ‘gastric carcinoma’ OR ‘cancer of the stomach’ OR ‘stomach adenocarcinoma’ were queried when they appeared in the title, abstract or keyword of studies. The names of the SSA countries were applied without language restrictions. A full search strategy is included in Appendix 1. Published studies were identified through a comprehensive search of the following electronic databases; Web of Science, Embase, PubMed and Google Scholar. Duplicate studies were identified and removed. Abstracts were then screened by three authors (AR, PM, CG) to assess eligibility using the predetermined inclusion criteria. Full text articles were then accessed and reviewed in detail to confirm appropriate inclusion and to extract relevant data. Additional citations were culled and included from the references of articles identified in the initial search. Citations were tracked using Zotero (6.0.8).

Publication bias and heterogeneity

Risk of bias was limited by maintaining a wide search criterion across multiple high quality electronic databases with a diversity of indexed articles.

Data Extraction

Data collection included the following variables: surname of primary author, publication year, the country where the study was conducted, the study design, diagnostic method, the age group (age rages including >18 years old), sample size, the number of gastric cancer reported, the overall cancer case number for study population, the overall population size, regional or national population, differences by age or gender, treatment type, and the case fatality rate of gastric cancer in the study. Unadjusted gastric cancer incidence rates with their standard errors

for each study were recalculated from the crude numerators and denominators provided in individual studies. Where denominators were not available regional and national population sizes were identified using a variety of sources such as macrotends.net, worldbank.org and countryeconomy.com [22,23,24]. The lowest population size value was used after verifying the values between various sources. Sub-group break downs (age, gender, race/ethnicity) were included. Age standardized rates were recorded without attempts to calculate backwards. Overall mortality and treatment strategies were recorded in crude numbers and percentages. To achieve a high level of reliability, the study lead (AR) and the two reviewers (PM, CG) assessed the same articles and reconciled differences before adopting a final and complete data collection document.

Quality criteria

The Strengthening Reporting of Observational Studies in Epidemiology (STROBE) checklist was used to assess the quality of the included studies. The final studies included in this systematic review were assessed using the STROBE checklist and ranked on the following criteria: (1) Inclusion of study in Cancer in Five Continents according to the International Agency for Research on Cancer (IARC) or the data was from a population-based registry [25] (2) 100% histologic confirmation of cancer from a regional registry or national registry (3) >80% histologic confirmation of cancer from a hospital registry (4) histologic confirmation of cancer from any type of registry. The highest rank went to papers included in "Cancer in Five Continents" and regional registries. The second highest rank included regionally or nationally representative studies that were >80% histologically confirmed. The third ranking category included hospital or pathology registries that showed histological confirmation. The final ranking category included registries that were not histologically confirmed. The quality of studies was given a rank from one to four.

Data synthesis and analysis

Unadjusted incidence with their standard errors for each study was recalculated based on the information of crude numerators and either denominators provided by individual studies or the regional population sizes. Regional and national population sizes were identified within the paper and when not reported, they were identified using online sources such as macrotends.net, worldbank.org and countryeconomy.com. Incidence rate patterns of gastric cancer across the various nations in SSA after recalculation was summarised. Descriptive analysis was done for the GC treatment and mortality studies. All data was stored in excel (Microsoft Inc, Redmond,

WA, USA) analyses were conducted using StataSE (version 15.1, College Station, Texas, USA).

Results

The database search returned a total of 5,626 articles including primary studies, case reports and reviews. Papers were collected from PubMed (694), Web of Science (4,887), and Google Scholar (45). After duplicates were removed there were 667 unique article titles left. Once the initial screening for titles including incidence of cancer in SSA was complete, 132 studies remained. From the 132 remaining studies, 14 papers were excluded by abstract alone, and the remaining 123 full text articles were assessed for eligibility. References were searched but did not reveal additional relevant titles. After applying the selection criteria, 69 studies were finally retained in this review (Fig. 1).

From the 69 retained studies, we identified that the data collection was conducted across 50 unique study sites (regions or cities) and 23 countries. Most studies were conducted in East Africa (32) with Uganda appearing nine times across six unique locations, Zimbabwe appearing six times in both Harare and Bulawayo and Malawi appearing five times in Blantyre and Lilongwe (Fig. 2). West Africa had the second most studies (25); Nigeria produced a total of nine studies across seven separate locations. East Africa and West Africa contributed 43% and 34% of the included studies respectively. North Africa provided studies from Sudan and South Africa provided four studies from Durban and the Eastern Cape (Table 1). Namibia, Botswana, South Sudan, Central African Republic, Chad, Niger, and Mauritania are the SSA countries with missing primary GC data (Fig. 2).

Data was primarily extracted from regional registries, which accounted for 42% (N=31) of the study sites, followed by retrospective reviews of hospital records (40%, N=29). The remaining data were recorded from national registries (9%, N=7) or retrospective reviews of pathology department data (8%, N=6). Of the studies reviewed, 32% (N=24) contained >90% histologically confirmed GC cases. A grading system was implemented to assess the quality of included studies: only 8% (N=6) were from national registries and therefore ranked as the highest quality studies. Most studies (56%, N=42) were from regional or national registries with <80% of the GC cases being histologically confirmed (Table 1).

From the 69 registry-based primary data sets, the overall crude pooled incidence was 1.20 GC cases per 100 000 people (CI 1.15-1.26). The variability between incidence calculation was

99.83% (I^2 p<0.001) (Fig. 3). From the 29 high-quality population-based registry studies the crude pooled incidence was 1.71 GC cases per 100 000 people (95%CI 1.56-21.88) and the variability between studies was 99.60% (Fig. 4). The GC incidence variability for West Africa I^2= 99.62 (p=0.00), Southern Africa I^2= 99.82 (p=0.00) and East Africa I^2= 99.88 (p=0.00) indicates significant inter- and intra-regional variability within SSA (Fig. 3). The study site with the highest incidence was Greater Meru in Kenya with an incidence of 5.56 GC cases per 100 000 people. The study site with the lowest incidence was 0.04 GC cases per 100 000 people in Benin City of Nigeria (Fig. 3).

Twelve (16%) of the studies included treatment information and were primarily from Nigeria (N=3) and Rwanda (N=2). The majority describe either palliation or curative resection (N=11) and a few described adjuncts like chemotherapy (N=4), in Rwanda, South Africa, Tanzania and Cameroon. In Nigeria, between 47% and 86% of patients had surgery with at least half described as palliative.

Twelve (16%) of studies included survival data, with the described time periods ranging from 1991-2018 across nine different countries. Median survivals were provided by approximately 33.3% of the studies (N=3), and five studies described absolute survival in five years. The median survival periods reported ranged from 4.7-13.6 (Table 3).

Discussion:

This systematic review (SR) is the first pooled analysis for GC incidence using primary data from SSA countries. While the pooled analysis shows an average incidence rate of 1.20 GC cases per 100,000 people (CI 1.15-1.26) in SSA, we demonstrate a significant incident variability between individual SSA countries and regions. Most data included in these studies were obtained from hospital registries or hospital data, with <10% included in national cancer registries and <50% containing histological confirmation. Analysis of pooled data limited to high quality studies reported a similar low incidence rate (2.12 cases/100000 people) but retained significant variability. Less than 20% of studies reported treatment or mortality data.

The methodology used in this analysis is similar to other systematic reviews and meta-analyses to estimate cancer incidence in SSA [10,11], where reliance on population and hospital-based registries leads to similar incidence rate heterogeneity [10, 11]. We found significant heterogenicity (I^2>99%, P<0.001) among the entire cohort and within geographic regional groups. This finding was maintained when analysis was limited to only the highest quality data,

as identified with the incidence of two East African nations, Ethiopia, and Rwanda with a GC incidence of 11.2 and 0.47 cases per 100 000 people respectively. The GC incidence rates in SSA are comparable to North America and Europe but far lower than Asia. The GLOBOCAN 2020 data shows the GC incidence rates were 5.7 in Northern America, 5.9 in Northern Europe, 4.6 in Western Europe, 8.5 in Western Europe and 22.4 in Eastern Asia where exposure to *H. pylori* is high and extensive genomic analysis have demonstrated genetic predisposition (31,39).The regional variation of GC is well established, attributed to different risk factors, genetic predisposition, dietary practices, environmental exposures and access to healthcare (3, 4). Helicobacter pylori is a key risk factor for GC and some SSA countries have a known high prevalence of this dependent on multiple factors including geographic elevation, water sources, and sanitation infrastructure (27). Mozambique and Zimbabwe have a high consumption of smoked, salted, and pickled foods, which are known risk factors for GC (28). Tobacco consumption is widespread in Ethiopia and Tanzania which may contribute to increased GC among involved populations (29). Our findings of high incidence variability highlight the importance of local data to better understand the true incidence rate and specific risk factor for any given community.

Namibia, Botswana, South Sudan, Central African Republic, Chad, Niger, and Mauritania has missing GC data, the North African and Southern African region provided limited GC data, whilst West and East Africa provided the bulk of the data used in this analysis. Nigeria, Malawi, Zimbabwe, and Uganda provided most of the data. This speaks to the long standing, high quality successful cancer registries in SSA, including the Harare, Kampala, and Eastern Cape population-based registries (13,16,17). The large gap from missing data contributes to the true incidence of GC in SSA remaining unknown. A dire need for these registries to be replicated in other African countries remain, highlighted by the geographic variability in cancer epidemiology and existing gaps in gastric cancer diagnosis and care in SSA. The data quality is vastly different among SSA countries, closing the data gap and standardising the quality of data collection will minimise incidence bias that is currently present for GC in SSA (38).

This SR incident results are similar to rates previously reported by modelling estimates (1). The 2020 International Agency for Research on Cancer (GLOBOCAN) estimated a SSA GC incidence rate of 2.1 cases per 100,000 people (7,8). Likewise, Institute for Health Metrics and Evaluation's (IHME) Global Burden of Disease estimates a crude incidence rate of 3.21 cases per 100,000(21). The overall reported incidence rates are similar to these modelled, validating

the accuracy of the average over the studies included. GLOBOCAN and IHME used different model to produce estimates of GC rates as a means to overcome the known limitations in primary data availability and quality on GC in SSA. However, these modelling methodologies are limited by the validity of assumptions regarding disease incidence and may not reflect the true disease burden in the population [26]. The GLOBOCAN methodology derived incidence rates from available registry information or from the average of rates from neighbouring countries, extrapolated over the known population of an entire country[8]. Only 12% of the countries in SSA had national data for these estimates, with 36% of countries incident rates relying on neighbouring country data [9]. The IHME rate was produced by estimating mortality rates for GC through registry information then dividing by modelled mortality-to-incidence ratios. While this methodology maximizes data coverage, it is based on reported case fatality rates, which may overestimate incidence in areas with worse than expected mortality. The methodology utilised in this SR was stringent as only primary data were included in the analysis and regional and national population sizes were verified with global population databases [22-24]. While our results are comparable to the modelled estimates over SSA as a whole, they have the added benefit of improved GC incidence characterization within subregions as evident by the high heterogenicity of reported rates [26]. These metrics may provide a more precise understanding of localized disease trends upon which disease prevention and management approaches may be planned.

In most SSA nations, access to healthcare is limited with decreased treatment capacity leading to increased mortality from GC [30]. Less than 20% of all the studies provide information for treatment or survival. From the available data, most surgeries reported were palliative. This is possibly a result of poor surveillance, late-stage presentation, and lack of treatment options upon presentation [5]. Late-stage GC diagnosis, healthcare costs, inadequate diagnostic tools and limited healthcare workers all contribute to restricted GC treatment in SSA [5-6]. The African enigma which hypothesizes the disassociation between GC and *H. pylori* infection is important to consider in further research [115]. The scarcity of robust data for GC in SSA, and the association between *H. pylori* and GC in SSA not being widely researched may indicate the African enigma is not as convincing as prior belief [115, 116]. Despite these limitations, treatment data are essential to establishing context relevant treatment guidelines [33]. Future data collection could focus on the current standard of GC care in SSA and available palliative services.

Population-based GC disease registries such as the successful Harare, Eastern Cape, and Kampala registries identifies demographic and geographic discrepancies in incidence and mortality rates which is valuable for improving cancer care and developing population specific control measures (34, 37). Granular data collected from hospitals, clinics and laboratories will give better clarity of the epidemiology and risk factors that shape the local epidemiology of GC. This information on GC in SSA is vital to achieve better understanding of the local and regional disease landscape and demonstrate the impact of local public health improvements accounting for the high regional variability of GC in SSA (35). Establishing and maintaining population-based registries at local levels pose a challenge to most SSA regions due to limited healthcare infrastructure, shortage of trained data collectors, high costs, time involvement, and accuracy needed for proper data collection (36). Disease registry success may be possible by focussing on local-level data collection that are aligned with and monitored by national data collection guidelines to ensure adherence to high quality standards. Regional and national health systems will benefit from investing in GC surveillance programmes, national control programmes, and training of health workers for accurate data collection (34, 40).

This review was limited by several factors. The employed search strategy is open to the biases of the search engines available to authors, potentially missing non-indexed reports published in regional journals. Additionally, our calculations were limited by the availability of regional and population- based estimates that were truly reflective of a given study's sample population. Despite these limitations, we provide the most stringent review of high-quality data available to date to better inform efforts to bolster regional data collection. Moreover, we likely underestimate the true burden of gastric cancer disease in SSA as the studies that do exist are limited by selection bias for those who receive care for GC.

Conclusion

This study demonstrates the high variability of GC incidence across SSA, independent of data quality. We calculated an overall rate of 1.20 cases per 100 000 people, similar to modelled estimated but highlighting the large regions devoid of primary data. The variable GC incidence rates from the contributing studies of this SR highlight the need for further development of population-based cancer registries (19, 20).

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Gastric cancer systematic review

Methods – extended search strategy and analysis

Articles applicable to this GC systematic review were identified by a PubMed, Google Scholar and Web of Science search between 1st January 1995 and 1st June 2022. Gastric cancer related search terms comprising "gastric cancer," "stomach neoplasm," "gastric neoplasm," "cancer of the stomach", "gastric cancer" and "stomach cancer" were applied to the search. The sub-Saharan African country name and the SSA regional was applied with no language restriction.

The final search terms used was *"(Cancer OR mass OR malignancy OR adenocarcinoma OR carcinoma OR neoplasm OR tumour) AND (Gastric OR stomach) AND (Botswana OR Burkina Faso OR Burundi OR Cabo Verde OR Cameroon OR central African republic OR Chad OR Comoros OR Democratic Republic of the Congo OR Congo OR Cote D'Ivoire OR Djibouti OR Equatorial Guinea OR Eritrea OR Swaziland OR Ethiopia OR Gabon OR Gambia OR Ghana OR Guinea OR Guinea Bissau OR Kenya OR Lesotho OR Liberia OR Madagascar OR Malawi OR Mali OR Mauritania OR Mauritius OR Mozambique OR Namibia OR Niger OR Nigeria OR Rwanda OR Sao Tome OR Senegal OR Seychelles OR Sierra Leone OR Somalia OR South Africa OR Sudan OR Tanzania OR Togo OR Uganda OR Zambia OR Zimbabwe OR sub-Saharan Africa OR Africa)"*

The participants included will be from primary gastric cancer studies from 1st january1995 to 1st June 2022 comprising of adult patients above the age of 18 years in SSA who have or had gastric cancer. Randomised control trials, cohort studies, case-control studies, and cross-sectional primary data studies of adult gastric cancer patients in SSA were included in this analysis. The primary exposure is gastric cancer. The primary outcomes of interest are incidence, treatment, and mortality. Studies that describe treatment interventions for gastric cancer including both surgery and chemoradiation were included. Gastric cancer studies conducted outside of SSA or inclusive of non-African countries, paediatric cancer studies, benign gastric tumours, and gastric lymphoma were excluded. Letters to the editor, case reports, case series, narrative reviews, commentaries, perspectives, literature reviews, meta-analyses, medical reports, and non-peer reviewed publications were excluded from the analysis.

All references identified after deployment of the search strategy were exported using Zotero software. All records obtained from the various databases were combined in a single Zotero

folder and all duplicates removed. The final search results underwent a title review to assess if the abstracts may contain relevant information for the study. After elimination of non-relevant titles, an abstract review was done prior to a full text review of pertinent studies. A data extraction form was employed on Microsoft Excel to record information on; the surname of primary author, year of publication, country of study, diagnostic method, registry type, study design, age group (age rages including >18 years old), sample size, gastric cancer case numbers, overall cancer case number for study population, overall population size, age or gender stratification, treatment type and numbers, and the case fatality rate of gastric cancer in the study. References of all relevant articles for additional data sources missed during our search was scanned and included where full texts were retrieved. References of pertinent reviews were also scanned.

5558 records were identified with the online database search. An initial record screening and removal of duplicated records resulted in 667 studies remaining. Five hundred and thirty-five records were excluded after title screening and 132 study abstracts were screened. After the abstract screening 14 studies were excluded and 123 studies were assessed for eligibility by full text reading and reference reviewal. A total of 85 studies were included in this systematic review after 38 full text articles were excluded due to outcomes of interest not being reported.

Two reviewers (CG and PM) independently evaluated the titles of studies obtained from the searches. The study lead (AR) and two reviewers (CG, PM) reviewed abstracts of papers obtained, after which the full texts of potentially eligible papers were retrieved. The three authors independently reviewed the full text of each potentially eligible study, compared their results, and resolved any discrepancies by discussion. For duplicate studies published in more than one report, the study reporting the largest sample size was considered. Studies with inaccessible full text either online or from the corresponding author was excluded. Methodological quality and risk of bias of included studies were assessed using the STROBE checklist. https://www.strobe-statement.org/

A systematic review with descriptive analysis was performed after the final data collection. A meta-analysis on the crude data was performed to determine the overall incidence of GC in SSA and subgroup analysis on the various regions in SSA as well as countries with the highest quality data. To determine the incidence of gastric cancer, the crude gastric cancer case numbers (numerators), the regional population and the population of people with diagnosis of cancer (denominators) were considered. Overall mortality and treatment strategies are reported

in crude numbers and percentages. Incidence patterns of gastric cancer across the various nations in SSA are summarised after the recalculation of incidence was done.

Summaries on the findings were created and stored based on incidence, mortality, treatment, population group and outliers. The PRISMA 27-item checklist was used for the study inclusion criteria. The articles were graded from 1 to 4 according to the data quality defined by the data source and the histology confirmation. One was the rank provide to articles containing the highest quality data and four was the rank provided to articles with the lowest data quality. A meta-analysis from the crude data was performed to determine the overall GC incidence in the whole of SSA, subgroup analysis by region and by countries with the highest quality data.

A narrative summary of findings regarding overall mortality and treatment strategies are reported due to the heterogeneity and paucity of data. All data analyses were conducted using StataSE (version 15.1, College Station, Texas, USA).

Tables and Figures

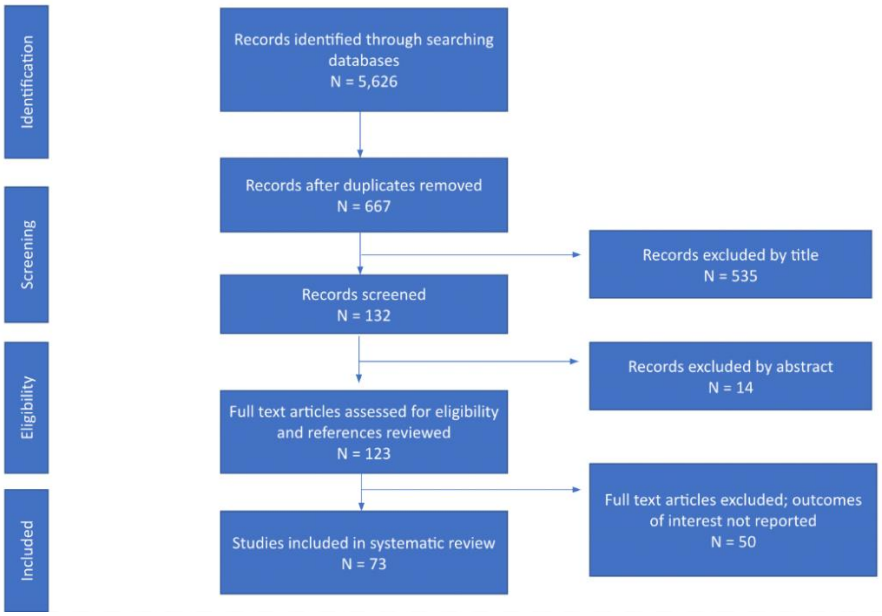
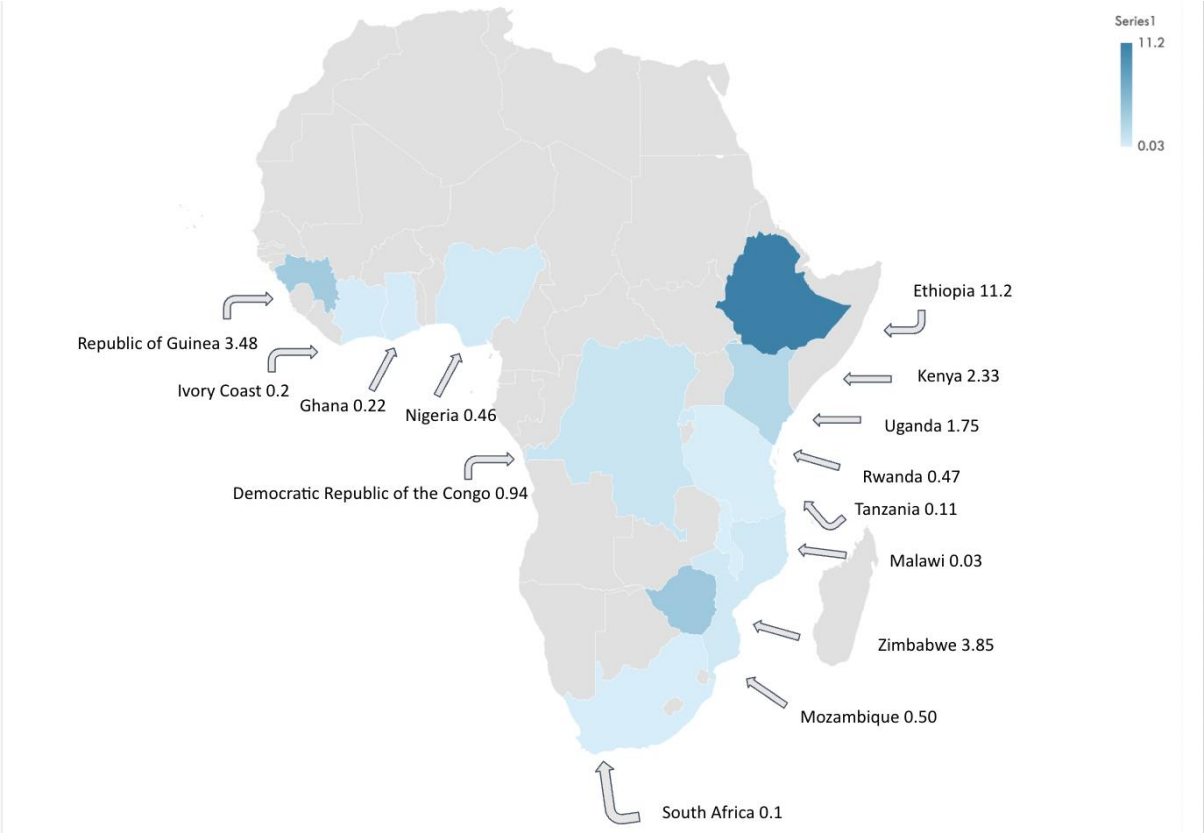


Figure 1: PRISMA flowchart diagram of the study selection



[1]Estimated size incidence cases per 100,000 described here. Data selected from the most recently published high-quality population-based registry reports.

Figure 2: Gastric Incidence Map with Case Incidence per 100,000 people

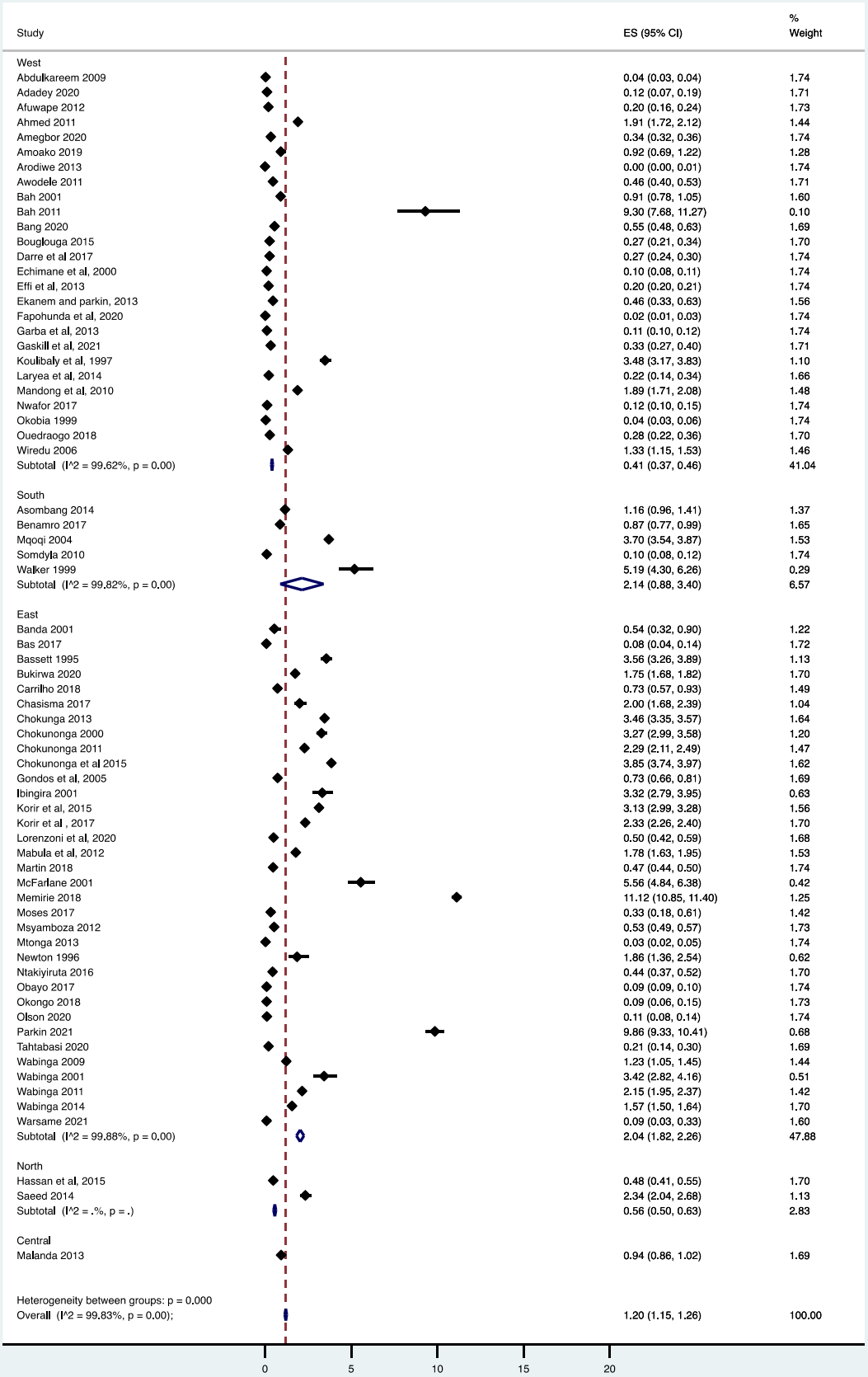


Figure 3: Crude Incidence for all Data Sets Describing Gastric cancer in Sub-Saharan Africa (N= 69)

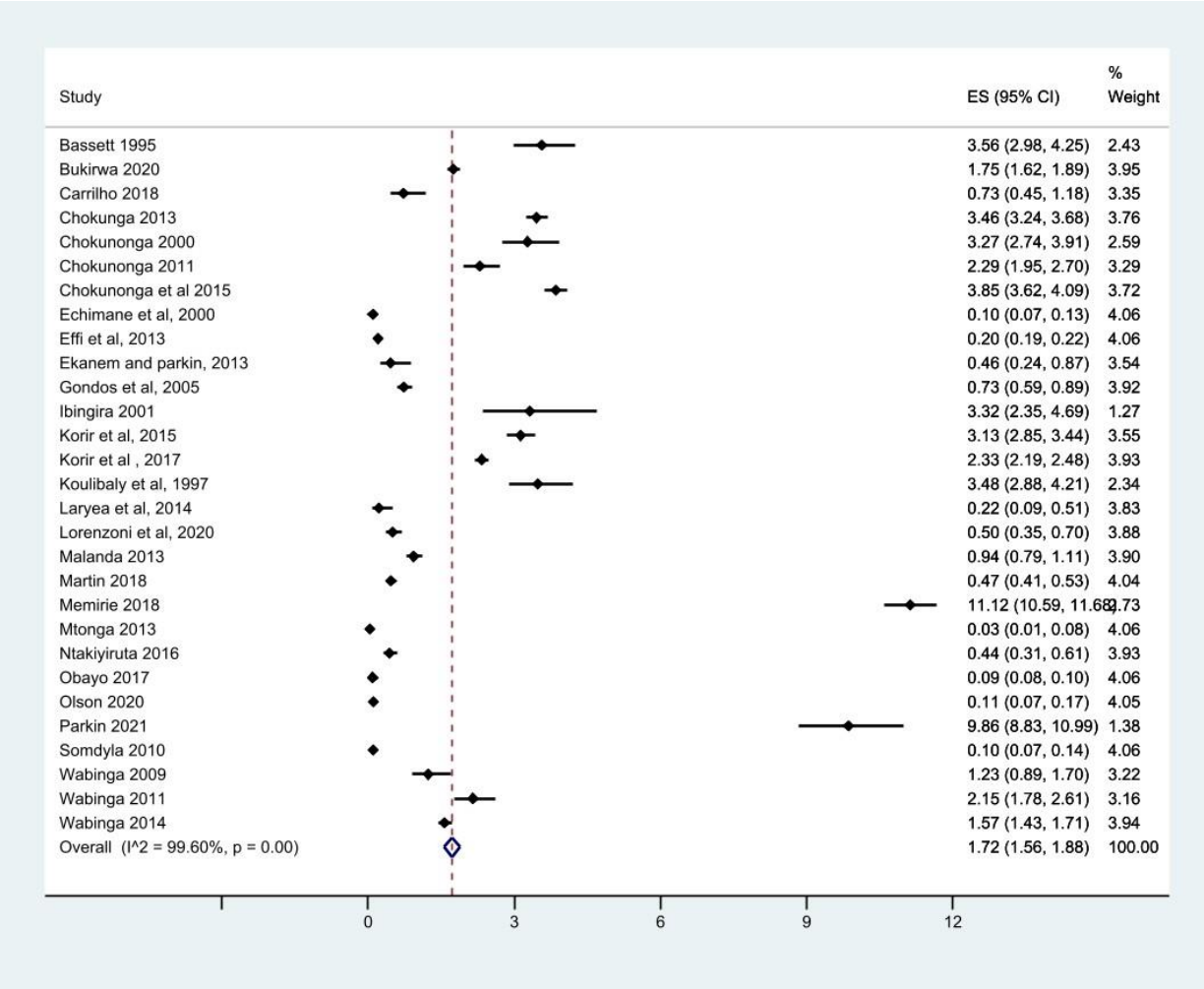


Figure 4: Crude Incidence from the High-Quality Population-Based Registry Studies Describing Gastric cancer in sub-Saharan Africa

Table 1: Characteristics of Included Studies Describing Gastric Cancer Incidence in Sub-Saharan Africa

Reference number	Author	Country	Region/City	Study period	Regional population	Study cancer population	Gastric cancer cases	% Histologically confirmed GC cases	Registry type	Age group	Quality rank
41	Abdulkareem et al 2009	Nigeria		1995-2006	220000000	713	78	100	regional	all	2
42	Adadey *et al* 2020	Ghana	Volta	2012-2014	6900000	567	8	0	regional	all	3
43	Amegbor *et al* 2020	Togo		1984-2008	112000000	5251	379	100	pathology	all	3
44	Afuwape *et al* 2012	Nigeria		2004-2009	25000000		49	89	hospital	adults	3
45	Ahmed *et al* 2011	Nigeria	Zaria	1995-2009	9375000		179	100	hospital	adults	2
46	Amoako *et al* 2019	Ghana		2015	2616000	736	24	0	regional	all	3
47	Arodiwe *et al* 2013	Nigeria		1995-2010	158000000	335	4	0	hospital	adults	4
48	Asombang *et al* 2014	Zambia	Lusaka	2010-2012	4384000		51	100	hospital	all	3
49	Awodele *et al* 2011	Nigeria	lagos, Oyo	2005-2009	48000000	5094	221	0	hospital	all	4
50	Bah *et al* 2001	Gambia		1988-1997	10152000	2957	92	21	national	all	3
51	Bah *et al* 2011	Gambia		1993-1997	559000		52	19	national	all	3
52	Banda *et al* 2001	Malawi	Blantyre	1994-1998	2600000	2259	14	39	regional	all	4
53	Bang *et al* 2020	Cameroon		2013-2018	19000000	1105	105	100	hospital	all	3
54	Bas 2017	Somalia		2016-2017	14190000	403	11	0	regional	adults	4
55	Bassett *et al* 1995	Zimbabwe	Harare	1990-1992	3400000	2716	121	50	regional	all	1
56	Benamro *et al* 2017	South Africa	Durban	2009-2014	15000000		131	100	hospital	all	3
58	Bouglouga *et al* 2015	Togo	Lome	2005-2012	11200000	250	30	100	hospital	all	3
59	Bukirwa *et al* 2020	Uganda,	Kampala	1991-2015	38007000	31357	665	0	regional	all	1

60	Carrilho *et al* 2018	Mozambique	Maputo	2015-2016	2200000	1705	16	76	regional	all	1
61	Chasisma *et al* 2017	Malawi	Blantyre	2008-2010	2046000	3711	41	100	regional	all	2
62	Chokunga *et al* 2013	Zimbabwe	Harare	1991-2010	27000000	28319	933	0	regional	all	1
63	Chokunonga *et al* 2000	Zimbabwe	Harare	1993-1995	3696000	3571	121	59	regional	all	1
64	Chokunonga *et al* 2011	Zimbabwe,	Harare	1993-1997	6278000	2300	144	67,4	regional	all	1
65	Chokunonga et al 2015	Zimbabwe	Harare	1991-2010	27000000	37787	1040	0	regional	all	1
66	Darre et al 2017	Togo	Lome	2009-2016	54968097	1738	147	100	hospital	all	3
67	Echimane et al, 2000	Ivory Coast	Abidjan	1995-1997	38007000	2815	37	0	regional	all	1
68	Effi et al, 2013	Ivory Coast	Abidjan	1984-2009	384000000	12841	782	100	regional	all	1
69	Ekanem and parkin, 2013	Nigeria	Calabar	2009-2013	1967000	719	9	100	regional	all	1
72	Fapohunda *et al* et al, 2020	Nigeria	Lagos	2015	50800000	548	9	0	hospital	all	4
73	Garba et al, 2013	Niger		1992-2009	212000000	7031	236	42	national	all	3
74	Gaskill et al, 2021	Ghana		2014-2015	30000000	2562	98	0	hospital	adults	4
75	Gondos et al, 2005	Uganda	Kampala	1993-1997 (2002 follow-up)	12500000	1831	91	48	regional	adults	1
76	Hassan et al, 2015	Sudan	Khartoum	2000-2004	18450000	1958	88	100	hospital	adults	3
77	Ibingira 2001	Uganda	Kampala	1995	964000		32	100	hospital	adults	1
78	Korir et al, 2015	Kenya	Nairobi	2004-2008	13922000	8982	436	83	regional	all	1
79	Korir et al , 2017	Kenya	Nairobi	2000-2014	43700000		1019	0	regional	all	1
80	Koulibaly et al, 1997	Guinea	Conakry	1992-1995	3043300	2064	106	0	national	all	1
81	Laryea et al, 2014	Ghana	Kumasi,	2012	2300000	253	5	74	regional	all	1

82	Lorenzoni et al, 2020	Mozambique	Beira and Maputo	2014-2017	6629000	4373	33	70	regional	all	1
83	Mabula et al, 2012	Tanzania	Mabula	2006 - 2011	13000000	5134	232	100	hospital	adults	3
84	Malanda 2013	Congo	Brazaville	1998-2009	14428000		135	0	regional	all	1
85	Mandong et al, 2010	Nigeria	Plataeu State	1985-2004	10862000	5705	205	100	hospital	all	3
86	Martin et al, 2018	Rwanda		2012-2016	51000000		229	100	hospital	all	1
87	McFarlane *et al* 2001	Kenya	Greater Meru	1991-1993	3600000		200	0	hospital	adults	4
88	Memirie *et al* 2018	Ethiopia	Addis Ababa	2012-2015	14539000	64285	1617	89	regional	all	1
90	Moses *et al* 2017	Malawi	Lilongwe	2009-2012	3000000	1453	10	0	hospital	adults	4
91	Msyamboza *et al* 2012	Malawi		2007-2010	56400000	18946	299	0	national	all	4
92	Mtonga *et al* 2013	Malawi	Blantyre	2010 - 2010	15000000	244	5	100	hospital	all	3
93	Mqoqi *et al* 2004	South Africa		1998-1999		60908	1999	0	national	all	1
94	Newton *et al* 1996	Rwanda	Butare	1991 - 1993	2100000	455	39	0	regional	all	4
95	Ntakiyiruta *et al* 2016	Rwanda		2006-2007	8000000		35	57	hospital	all	1
96	Nwafor *et al* 2017	Nigeria	Akwa Ibom	2007-2015	36391420	1186	45	100	hospital	all	3
97	Obayo *et al* 2017	Uganda	5 regional hospitals	2002-2011	292000000		270	100	hospital	all	1
98	Okobia *et al* 1999	Nigeria	Benin City	1989-1998	104500000	816	44	36	hospital	all	4
99	Okongo *et al* 2018	Uganda	Acholi	2013-2016	18000000	1627	17	0	regional	all	4
100	Olson *et al* 2020	Tanzania	Lake Zone	2008-2016	15000000	2772	16	0	hospital	all	1
101	Ouedraogo *et al* 2018	Burkina Faso	North-east	2013-2017	22000000	352	61	0	hospital	all	4
102	Parkin *et al* 2021	Zimbabwe	Bulawayo	2011-2015	3257000	4105	321	100	regional	all	1
103	Saeed *et al* 2014	Sudan	Khartoum	2009-2010	8900000	6771	208	0	regional	all	4

105	Somdyla *et al* 2010	South Africa	Eastern Cape	1998-2002	33000000	2501	33	0	regional	all	1
106	Tahtabas *et al* i 2020	Somalia	Mogadishu	2017-2019	6300000	1306	13	100	hospital	all	3
107	Wabinga *et al* 2009	Uganda	Kyadondo	1995-1997	3000000	1290	37	0	regional	all	1
108	Wabinga *et al* 2001	Uganda	Mbarara	1995-1999	1460000	585	50	0	hospital	all	3
109	Wabinga *et al* 2011	Uganda	Kampala	1993-1997	4833000	2523	104	0	regional	all	1
110	Wabinga *et al* 2014	Uganda	Kyadondo	1991-2010	31529670	22494	494	0	regional	all	1
111	Walker *et al* 1999	South Africa	Durban	1995	2100000	3823	109	0	hospital	all	4
112	Warsame *et al* 2021	Somalia	Mogadishu	2019	2180000	126	2	0	hospital	adults	4
113	Wiredu *et al* 2006	Ghana	Accra	1991-2000	14000000	3659	186	0	hospital	all	4

! = stratified by age and sex

Table 2: Treatment Data Reported in Available Studies on Gastric cancer from Sub-Saharan Africa

Study Reference number	Author	Country	Region/City	Study period	Regional population	Study cancer population	GC cases	Treatment		
								Chemotherapy	Surgery	Radiation
44	Afuwape 2012	Nigeria		2004-2009	25000000		49		Curative = 10 Palliative = 13	
45	Ahmed 2011	Nigeria	Zaria	1995-2009	9375000		179	57	Total = 155 (D1 = 37 and D2 = 50) Curative = 38 Palliative = 68	
48	Asombang 2014	Zambia	Lusaka	2010-2012	4384000		51	6	Palliative = 12	6
53	Bang 2020	Cameroon		2013-2018	19000000	1105	105	Curative = 30 Palliative = 77	Curative =32 Palliative = 16	
56	Benamro 2017	South Africa	Durban	2009-2014	15000000		131	Curative = 21 Palliative = 40	Curative = 36 Curative = 1 Palliative = 12	17
74	Gaskill et al, 2021	Ghana		2014-2015	30000000	2562	98			
77	Ibingira 2001	Uganda	Kampala	1995	964000		32		Curative = 2 Palliative = 15 Diagnostic/Biopsy = 18	
83	Mabula et al, 2012	Tanzania	Mabula	2006 - 2011	13000000	5134	232	Curative = 53	Curative = 53 (Total =1 and Partial =52) Palliative =120 Biopsy = 50	
86	Martin et al, 2018	Rwanda		2012- 2016	51000000		229	Curative = 15 Palliative = 13	Curative = 30 Palliative = 87	
95	Ntakiyiruta 2016	Rwanda		2006-2007	8000000		35		Curative = 1 Palliative = 34	
98	Okobia 1999	Nigeria	Benin City	1989-1998	104500000	816	44			

Table 3: Mortality Data Reported in Available Studies on Gastric cancer from Sub-Saharan Africa

Reference number	Author	Country	Region/City	Study period	GC cases	Outcomes		
						Post-operative complications	Mortality rate (%)	Survival
42	Adadey 2020	Ghana	Volta	2012-2014	8		90 all ages = 0.09 60-69=1.21 >70=0.96	
45	Ahmed 2011	Nigeria	Zaria	1995-2009	179	47% (post resection: 1 during index hospitalization)		Median 13.6 months
48	Asombang 2014	Zambia	Lusaka	2010-2012	51			Median 4.6 months
50	Bah 2011	Gambia		1993-1997	52			4.5% 1 year: 17.8% 3 year: 17.8% 5 year: 4.5%
53	Bang 2020	Cameroon		2013-2018	105		Mean =5.91 months 85 dead	5 year: 19.0%
64	Chokunonga 2011	Zimbabwe	Harare	1993-1997	144		82 1 year: 37.5% 3-year: 19.0% 5-year: 18.1%	
75	Gondos et al, 2005	Uganda	Kampala	1993-1997	91			0%
83	Mabula et al, 2012	Tanzania	Mabula	2006 - 2011	232	86	82	5 year survival rate: 6.9% 76 patients followed up 156 lost to follow up
86	Martin et al, 2018	Rwanda		2012- 2016	229	31		
98	Okobia 1999	Nigeria	Benin City	1989-1998	44		50 (N=26) 7 died within 30 days of hospitalisation	
109	Wabinga 2011	Uganda	Kampala	1993-1997	104		100 1 year: 39.1 3 year: 7.5 5 year: 0	Median survival 4.2 months
13	Wiredu 2006	Ghana	Accra	1991-2000	186		100	

Chapter 4: Gastric Cancer in South Africa – Incidence and Mortality Trends

Anishka Ramadhar[1], Mazvita Muchengeti MBChB MSc PhD [1,2,3], Sizeka Mashele[1], Phoebe N Miller MS MD[4], Cameron Gaskill MD MPH[5], Juliana Kagura MSc PhD[1]

[1] Division of Epidemiology and Biostatistics, School of Public Health, University of the Witwatersrand, Johannesburg, South Africa

[2] National Cancer Registry, National Health Laboratory Service, Johannesburg, South Africa

[3]DSI-NRF South African Centre of Excellence in Epidemiological Modelling and Analysis (SACEMA), Stellenbosch University, Stellenbosch, South Africa

[4] University of California San Francisco, San Francisco, CA

[5]University of California Davis, Davis, CA

Corresponding Author:

Anishka Ramadhar
anishkaramadhar@gmail.com

Abstract

Objective

Globally, gastric adenocarcinoma (GAC), in this study referred to as gastric cancer (GC) is the fifth most common cancer and cause of the fifth highest cancer related mortality. The aim of this study was to determine the ethnic, sex-specific incidence and mortality for GC in the South African (SA) adult population.

Methods

This epidemiologic cross -sectional study used GC incidence data from the SA National Cancer Registry (NCR) and GC mortality data from Statistics South Africa (STATS SA). Male and female SA adult patients diagnosed with GC between the years 2002 and 2020 were included in study. Incidence, mortality trends and average annual percentage changes (AAPC) were calculated using the Joinpoint Regression software.

Results

There were 22 391 GC cases and 20 212 GC deaths over the 18-year study period, with GC incidence increasing in the SA population from the age of 40 years, and the highest incidence in the 60-64-year age group. Men had more than twice the GC age standardised incidence rate (ASIR) than females at 0.46 and 0.16 GAC cases per 100 000 people respectively in 2002; and 0.39 and 0.15 GC cases per 100 000 people respectively, in 2020. Men had more than twice the GC age standardised mortality rate (ASMR) than females at 0.40 and 0.19 GAC deaths per 100 000 people respectively, in 2002; and 0.31 and 0.14 GC deaths per 100 000 people respectively, in 2018. The overall AAPC for ASIR (-0.8) and ASMR (-1.55) in the SA GC population was decreasing without statistical significance.

Conclusion

Overall, there is a decline GC ASIR and ASMR in the SA population, and an increase in GC incidence above the age of 40 years with a greater burden in males than females. The GC ASIR and ASMR were higher in males than females. The SA Coloured males and Asian females have the highest GC incidence, and Coloured males, Coloured females, and Asian females have the highest GC mortality. Differential exposure to risk factors such as red meat, chilli, alcohol, and tobacco may explain the differences observed by population. Identifying the burden of GC in SA is crucial for public health policies and GC control measures.

Introduction

Globally, gastric adenocarcinoma (GAC), in this paper will be referred to as gastric cancer (GC) is the fifth most common cancer and the fifth highest cause of cancer related mortality (1). A global report of 195 countries from 1990 to 2017 reported an excess of 1.22 (95% CI 1·19–1·25) million incident GC cases with 865 000 (95% CI 848 000–885 000) GC deaths, accounting for 19.1 million disability adjusted life years (DALYS) (2). A 2020 global population-based cohort study observed a decrease in GC mortality in 39 of 49 countries from 1980 to 2018, 25 of these countries were in Europe and the rest were from Asia, the Americas and Australia (31). Gastric cancer prognosis is generally poor however early detection, and modern treatment may reduce the mortality rate as seen in the European and Asian countries where strict public health measures for gastric cancer control are implemented (5).

The 2019 South African National Cancer registry (NCR) report indicated that in South Africa (SA), GC makes up 1.19% of all cancers in females and 2% of all cancers in males (6), ranking as the 15th and 10th most common malignancy in females and males respectively, but the 5th most common cause of cancer related mortality in SA (17).

The burden of GC in SA is higher among certain populations, including SA males and individuals living in urban areas, who may experience easier access to care, diagnosis, and treatment. Time to diagnosis and treatment is variable and many patients are only diagnosed in the late stages of GC (9). Known risk factors for GC in SA include a high salt diet, smoked and pickled foods, *Helicobacter pylori (H. pylori)* infection, tobacco use, alcohol consumption, gastrointestinal reflux disease, obesity, and a family history of GC (10).

Given the increasing availability of effective therapies and the limitations of existing literature for South African GC epidemiology, a contemporary analysis of trends in GC incidence and mortality is warranted. The aim of this study was to determine the incidence and mortality rates for GC in the South African adult population.

Methods

Study design and study population

This epidemiologic study analysed cross-sectional GC incidence data from the South African NCR and GC mortality data from Statistics South Africa (STATS SA). The SA NCR is a department within the National Health Laboratory Services (NHLS). Since 1986 the NCR

serves as SAs primary repository of national cancer incidence data that has been diagnosed via histology, cytology and bone marrow aspirate (35). South Africa is a middle-income country with a population of 60.14 million. Approximately 51% of the population are female and 49% are male with a life expectancy of 65 for females and 59 for males (28). The population of SA is officially classified into 4 major race groups according to STATS SA; Black (80.7%), Coloured (8.8%), White (7.9%) and Asian (2.6%). The Coloured race refers to the multiracial ethnic community in SA who may have ancestry from more than one population group inhabiting the region, including African, European, and Asian (29). The study population is the SA population since the NCR and STATS SA are national cancer and death registries respectively. The NCR incidence data used in this study includes the years 2002 to 2020 and the STATS SA mortality data ranges from the years 2002 to 2018 inclusive.

Eligibility Criteria

South African male and female adult patients who were histologically diagnosed with GC between the years 2002 and 2020, under the ICD 10 code C16.0 to C16.9, and who were reported to have died from GC between the years 2002 and 2018, were included in the study. Patients who presented with gastrointestinal tumours that did not include gastric adenocarcinoma histology were excluded from the analysis, including gastrointestinal stromal, neuroendocrine, and lymphomas.

Data collection

Person-level, anonymised, routinely collected data for GC incidence was provided by the SA NCR. Diagnosis for GC at the NCR is confirmed by pathology-based surveillance from histology and cytology reports (6). The variables in the data set included age, year of diagnosis, gender, race group and geographical area for the years 2002 to 2020. STATS-SA provided GC mortality data from 2002 to 2018. The variables in the mortality data set included age, year of death, gender, race group and geographical area.

Statistical analysis

Trends and AAPC for both GC incidence and mortality were calculated using age-standardized GC rates and then stratified by gender and race. Age-standardisation for GC was utilized for the benefit of comparability of GC incidence and mortality across different populations adjusting for differences in age structure. The incidence trends were evaluated using the

Joinpoint Regression method. Joinpoint regression methods are used to summarize cancer incidence and mortality trends over a period of time [36]. SEER programme of the USA Surveillance Research Program (SRP) in the National Cancer Institutes' (NCI) Division of Cancer Control and Population Sciences (DCCPS) was used to make Joinpoint Regression calculations and Stata 15 (version 15.1, College Station, Texas, USA) statistical software package was utilised for all data cleaning, management, and generating of age-standardised incidence rates for GC incidence and mortality.

Results

Overall, there were 22 391 CG incidence cases and 20 212 GAC deaths during the study period. Males had a higher GC incidence (14296/22391, 63.85% vs 8095/22391, 36.15%) and mortality (11970/20212, 59.22% vs 8242/20212, 40.78%) burden than females (Fig. 1). Gastric cancer incidence and mortality in the SA adult population increased from the age of 40 years, with the highest incidence in the 60-64-year age group (Fig. 2, Fig. 3). The mortality to incidence ratio for GC is high in SA males and females from 2002 (males 0.87, females 1.19) to 2018 (males 0.8, females 0.8).

Amongst male patients the GC ASIR was twice that of female patients in both 2002 (0.46 [95% CI 0.43-0.50] ASIR males, 0.16 [95% CI 0.14-0.18] ASIR females) and 2020 (0.39 [95% CI 0.36-0.42] ASIR males, 0.15 [95% CI 0.14-0.17] ASIR females) (Fig. 6). Among the SA adult females, the Asian ethnicity had the highest GC ASIR at the beginning and end of the study period (0.52 [95% CI 0.35-0.89] GAC cases per 100 000 people) when compared to Coloured and White females (0.37 [95% CI 0.28-0.49] and 0.30 [95% CI 0.24-0.40] GC cases per 100 000 people). Black females in SA had the lowest GC ASIR at the beginning of the study period at 0.08 (95% CI 0.07-0.10) GC cases per 100 000 people. Overall, GC ASIR in the SA female population decreased over the 18-year study period except amongst the Black females where the GC ASIR increased from 0.08 (95% CI 0.07-0.10) to 0.11 (95% CI 0.09-0.13) GC cases per 100 000 people. However, in 2020, overall Black females had the lowest ASIR compared to Coloured, Asian, and White women (0.28 (95% CI 0.22-0.37), 0.27 (95% CI 0.18-0.60), and 0.25 (95% CI 0.20-0.36) GC cases per 100 000 people) (Fig. 4).

Among the SA adult males, the Coloured male population had the highest GC ASIR both at the beginning and end of the incidence study period (1.02 [95% CI 0.83-0.24] and 0.74 [95% CI 0.62-0.89] GC cases per 100 000) (Fig. 5). Black males had the lowest ASIR at the beginning and end of the incidence study period at 0.27 (95% CI 0.24-0.31) and 0.24 (95% CI 0.21-0.27)

GC incident cases per 100 000 people. The overall GC ASIR amongst SA males decreased during the study period. (Fig. 5)

Men had more than twice the GC ASMR than women throughout the mortality study period from 2002 (0.40 [95% CI 0.36-0.43] and 0.19 [95% CI 0.17-0.21] GC deaths per 100 000 people) until 2018 (0.31 [95% CI 0.28-0.33] and 0.14 [95% CI 0.12-0.15] GC deaths per 100 000 people) (Fig.9). Among the SA females, the Asian females had the highest GC ASMR and Black females had the lowest GC ASMR (0.54 [95% CI 0.35-0.92] and 0.15 [95% CI 0.13-0.17] GC deaths per 100 000 people) at the beginning of the mortality study period (Fig. 6). The GC ASMR decreased for all females at the end of the study period, Coloured females had the highest GC ASMR and Black females had the lowest GC ASMR (0.37 [95% CI 0.30-0.47] and 0.11 [95% CI 0.09-0.12] GC deaths per 100 000 people) (Fig. 7). Among SA males, the Coloured population had the highest GC ASMR from 2002 to 2018 (1.42 [95% CI 0.20-0.69] and 0.92 [95% CI 0.78-1.09] GC deaths per 100 000 people) (Fig. 6), and the Black population had the lowest GC ASMR from 2002 to 2018 (0.30 [95% CI 0.26-0.34] and 0.22 [95% CI 0.19-0.25] GC deaths per 100 000 people) (Fig. 8).

The overall AAPC for GC ASIR (-0.1, p=0.70) decreased in the SA GC population but is not statistically significant (supplementary table 1). The AAPC for Asian (-1, p<0.1), Coloured (-1.7, p<0.1) and White (-0.1, p=1) females decreased with no statistical significance (p> 0.05) (supplementary table 1). The AAPC for the Black female population increased at 2.5 (p<0.1) for GC ASIR and this is also not a statistically significant AAPC. The AAPC for GC ASIR for all the male population groups (Asian -1.4, Black -0.3, Coloured -1.5, White -0.8 (p<0.1)) decreased without any statistical significance (supplementary table 1). The AAPC for the entire SA male and female GC ASIR are -0.8 (p<0.1) and 0 (p=1), also not statistically significant.

The overall AAPC for GC ASMR (-0.1, p=1) decreased with no statistical significance (supplementary table 2). The ASMR AAPC are -2.4 (p<0.1) for the Black and White female population, -1.7 (p<0.1) and -1.3 (p<0.1) for the Asian and Coloured females respectively, -2.2 (p<0.1) for Black and Coloured males, -1.4 (p<0.1) and -1.9 (p<0.1) for Asian and White males respectively, and -1.3 (p<0.1) and -1.8 (p<0.1) for the total female and male GC population (supplementary table 2).

Discussion

This study is the first to explore national SA GC incidence and mortality trends over an 18-year period using primary data analysis. The results show that from the beginning to end of the

study period, there is a decline in the ASIR and ASMR for GC in the SA adult population. Overall, we report an increase in GC incidence above the age of 40 years with a greater burden in SA males than females. The ASIR and ASMR for all race groups were higher in males than females. The SA Coloured males and Asian female have the highest GC incidence, and Coloured males, females and Asian females have the highest GC mortality.

There are many strengths in this study including this being the first study in SA to link GC incidence and mortality across all population groups using NCR data for incidence rates and STATS SA data for mortality rates. The presentation of the epidemiological data is from high quality data bases containing histologically confirmed GC cases (SA NCR) and national records of mortality cases (STATS SA) by age, sex and race. The limitations of this study are that the incidence period is 2 years longer than the mortality period as STATS SA were unable to provide data from 2019 to 2020. The secondary data used for this study analysis was limited to age, sex and race for analysing GC trends. Additionally, the mortality data is not histologically confirmed, and reports are taken from hospital records and death certificates.

The ASIR and ASMR were higher in SA males than females across all ethnic groups, which correlates with GC ASIR and ASMR findings in China, USA, and Europe. Studies have shown that this may be due to males being more susceptible to GC due to increased exposure to alcohol, smoking and obesity focussed on visceral fat, and females being protected by oestrogen for most of their adult life (13,14) The 50-year trend of GC globally shows a steady decline in incidence and mortality rates (11), which aligns with the findings from this study (12).

This study shows that GC incidence increases from the age of 40 with the highest incidence and mortality in the 60–70-year age group, this aligns with global GC epidemiology findings where GC incidence below the age of 50 is a rare occurrence and the average age of diagnosis in between the ages of 60-70 years (15). The average age of GC incidence correlates with the mortality age due to patients being diagnosed late and not surviving very long after diagnosis (9).

Globally, the decline in GC incidence and mortality rates may be due to improved diet, less consumption of tobacco and alcohol, improved food preservation methods such as the increased use of refrigerators, reduction in *H. pylori* infection, and earlier screening and detection of GC which may lead to better treatment options (12). In SA the slight decline in GC incidence and mortality may be attributed to decreased *H. pylori* infection (27) and positive lifestyle changes in the SA population. However, there exists continued challenges from

delayed patient presentation, lack of GC data collection, under reporting of GC cases, and poor hospital follow-up (19).

The SA Coloured males had the highest incidence of GC followed by Asian males. Risk factors for GC include tobacco smoking, chilli consumption, alcohol consumption, high consumption of red meat and pickled vegetables (38-40). Most of the older Black patients may not have access to GC diagnosis and is as such biased by underreporting (20). The proportion of the SA Black population that live in rural areas, and that live in low socio-economic conditions are greater than the other population groups in SA (44), resulting in more SA Blacks having limited access to red meat, processed food, spicy food, alcohol, and tobacco compared to SA Asians and Coloureds (41,42). Research shows that the SA Coloured and Asian male population are exposed to GC risk factors such as spicy food, sedentary lifestyle, high sugar, and fat consumption in greater quantity and more frequently than the black population (41,42). The SA Coloured population has the highest prevalence for tobacco smoking compared to the other population groups (43). The SA Coloured males had the highest GC mortality followed by Asian males which is consistent with the GC incidence pattern.

South African Asian women had the highest GC incidence and mortality, followed by SA Coloured women for both incidence and mortality which may be due to their high chilli, salt and fat diet. and sedentary lifestyle (18, 20). This diet and lifestyle pattern leads to conditions such as gastritis, gastric ulcers, and obesity, which are also risk factors for GC (22). The GC patterns for SA females are consistent with the male counterparts of the same population groups for GC incidence and mortality.

This study reveals that SA has a high GC mortality to incidence (M: I) ratio from 2002 (males 0.87, females 1.19) to 2018 (males 0.8, females 0.8) which is indicative of the high fatality of GC and the poor treatment and management outcomes (32). Countries with a high human development index (HDI) have a low M:I ratio indicating better patient outcomes. South Africa compares to Eastern, Middle and Western African regions where they have a high M:I ratio for GAC in both males (M: I 0.9) and females (M: I 0.8) (33). North America (GC M: I 0.4), Western Europe (GC M: I 0.6) and Australia-New Zealand (GC M:I 0.5) are countries with a high HDI and have low GC M:I ratio (33).

The ASMR over 16 years is almost equal to the ASIR over 18 years which indicates that GC mortality may be better recorded that GC incidence due to a comprehensive reporting of

deceased patients as part of the SA governments National Population Register (24). The GC ASMR being almost equal to the ASIR indicates that GC remains nearly completely fatal in SA which aligns with the global literature reporting high case-fatality rates among GC, especially in men (34). Gastric cancer has a high mortality rate and risk reduction may be essential in the control of GC because once patients are diagnosed their chances of dying are very high (2, 39). Gastric cancer risk reduction includes maintaining a diet rich in fresh fruit and vegetable, healthy body weight and physical activity, and reducing consumption of tobacco, alcohol, chilli, red meat, and pickled food (38, 39). The AAPC for GC ASIR and ASMR over the study period shows a decline but this was not statistically significant.

Identifying the burden of GC in SA is crucial for public health policies and GC control measures (25). The incidence and mortality trends for GC in SA will impact public health by encouraging the promotion of GC screening, reporting and prevention mechanisms. Establishing a GC database from hospital records and registries that allows for tracking of patients' diagnosis, treatment, and management results, and undertaking prospective longitudinal hospital-based registry studies will improve patient prognosis and outcomes. Once a GC data registry or reporting process is established the priority for GC risk reduction may be implemented at a national public health level (26).

In conclusion, incidence and mortality trends for GC capture distinct phases of a dynamic, time-reliant disease journey. Incidence and mortality patterns are similar for the SA population groups despite the data being sourced from 2 unrelated databases, which may infer that the risk factors such as diet and lifestyle are influencing the incidence and mortality of GC in SA. It is a necessity to reduce the GC risk factors especially excessive alcohol, chilli, red meat and tobacco consumption for improved GC control. Exploration of these GC trends is crucial to obtain a thorough understanding of the regression or progression in effective GC control in SA.

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Tables and Figures

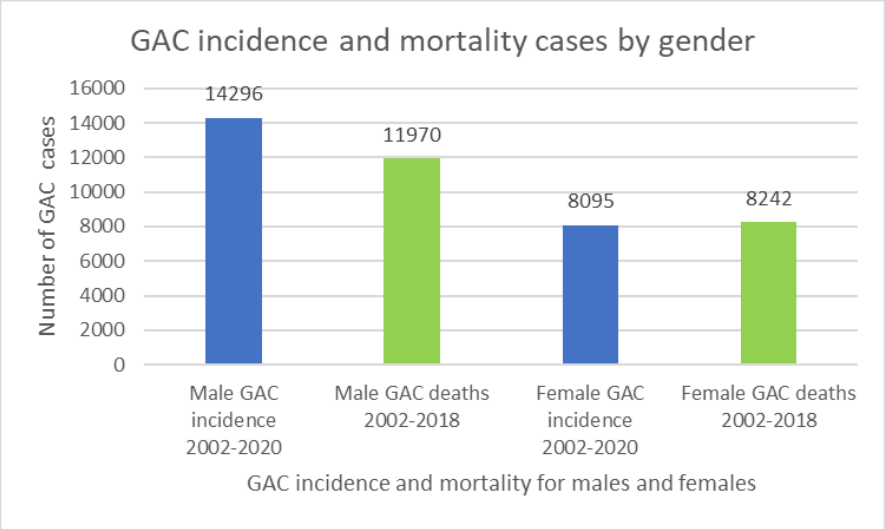


Figure 1: Gastric adenocarcinoma cases and mortality by gender

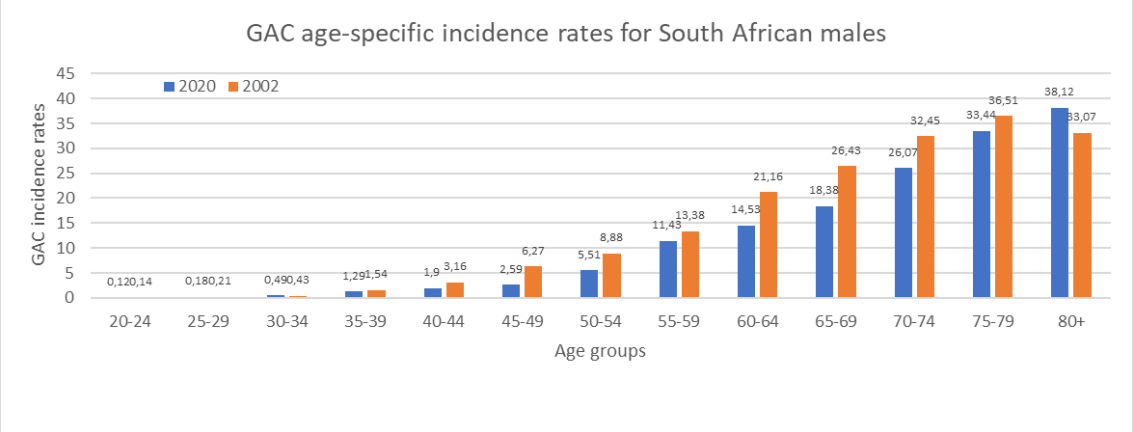


Figure 2: Gastric adenocarcinoma age-specific incidence rates for SA males

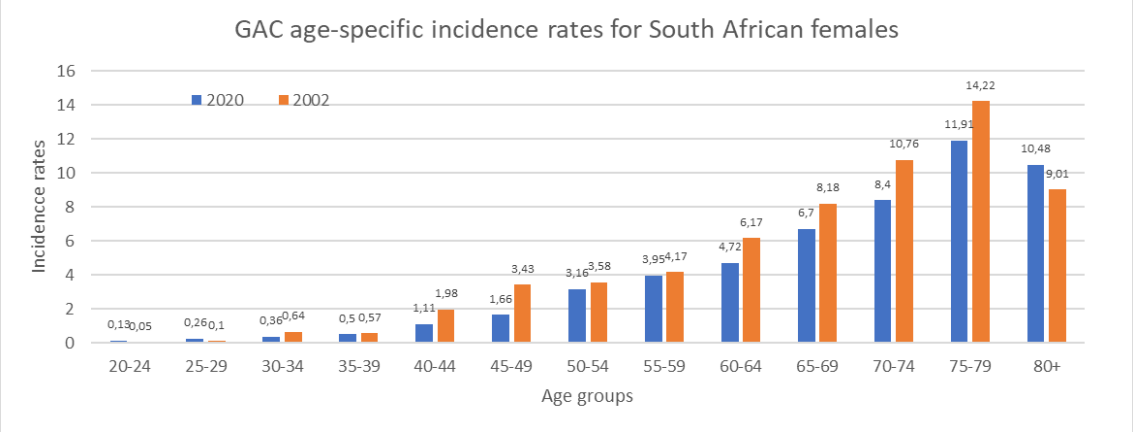


Figure 3: Gastric adenocarcinoma age-specific incidence rates for SA females

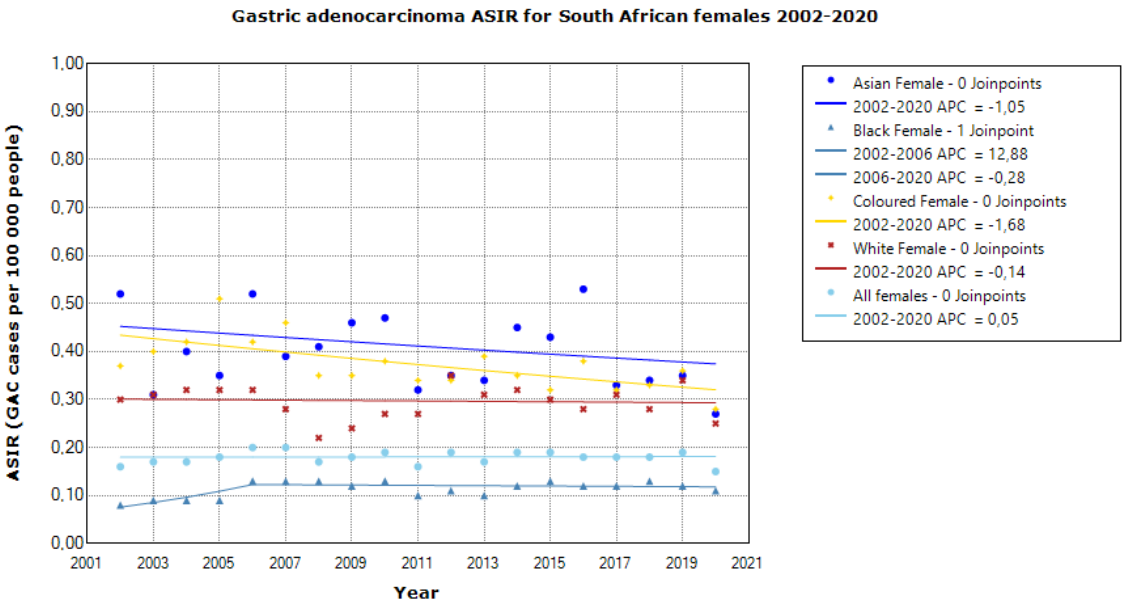


Figure 4: Gastric adenocarcinoma ASIR with APC for SA females

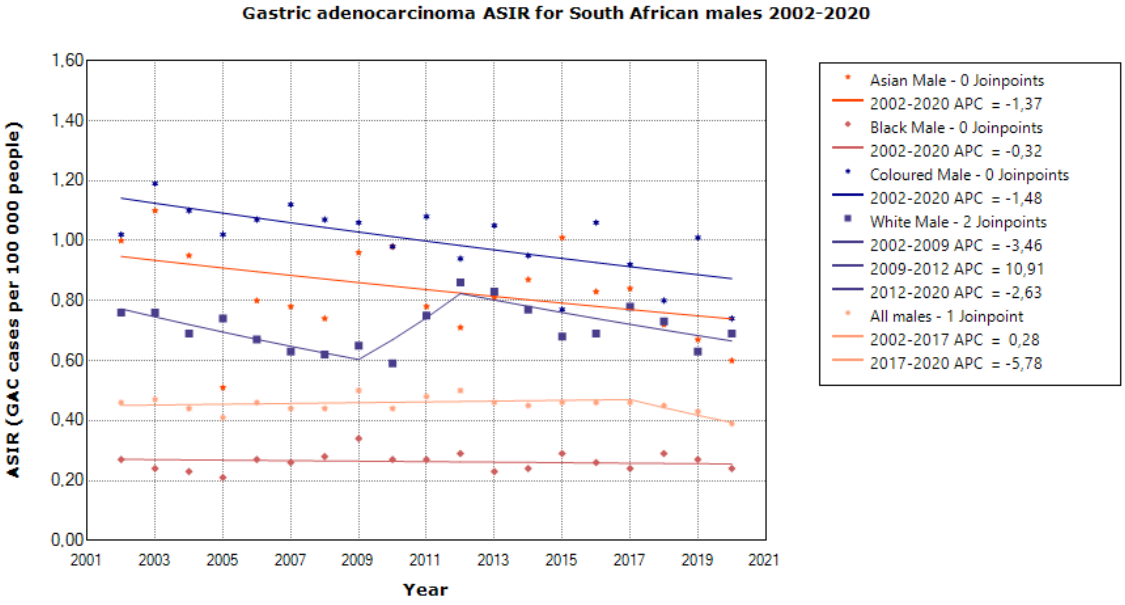


Figure 5: Gastric adenocarcinoma ASIR with APC for SA males

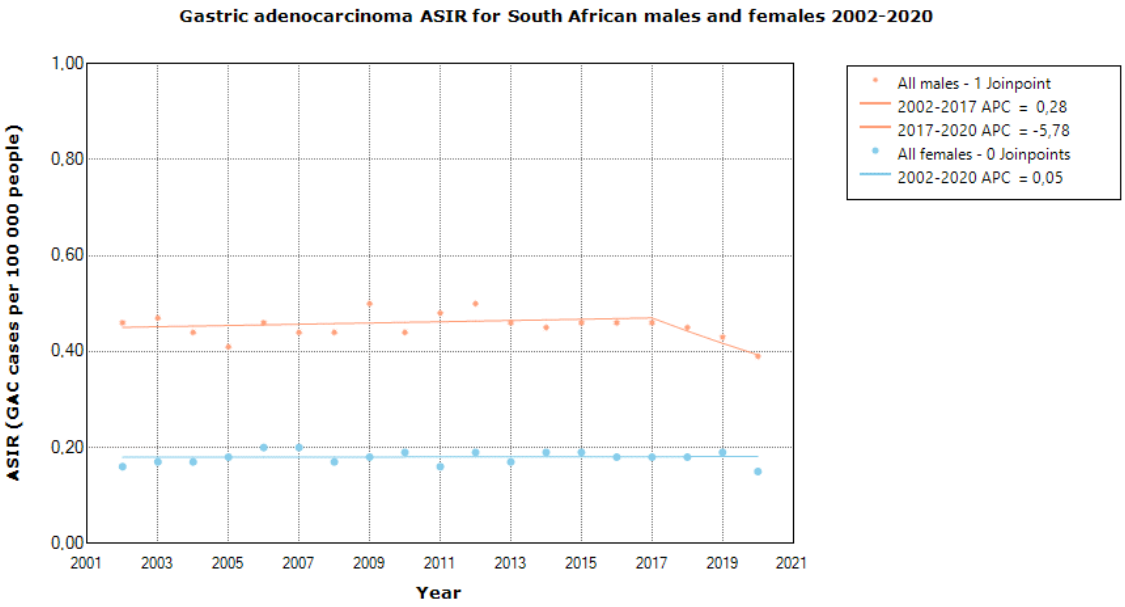


Figure 6: Gastric adenocarcinoma ASIR with APC for SA males and females

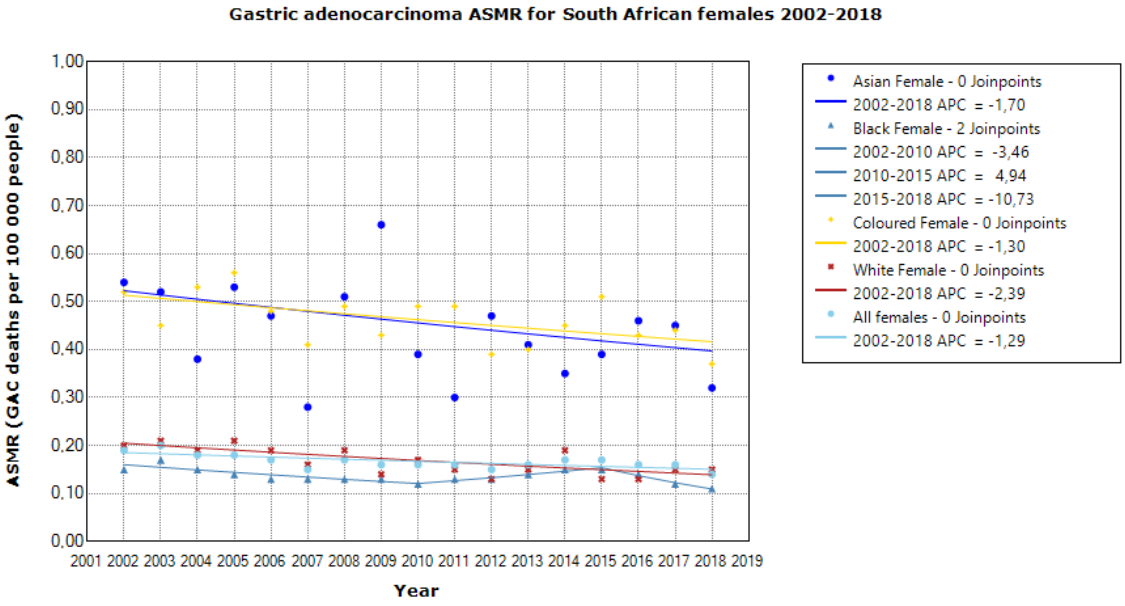


Figure 7: Gastric adenocarcinoma ASMR with APC for SA females

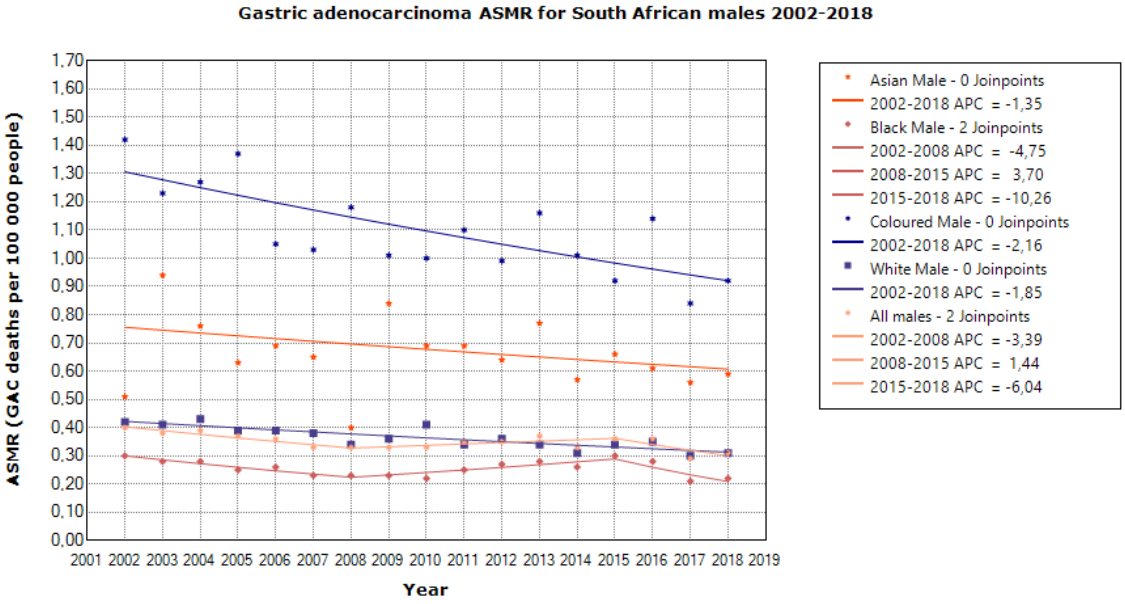


Figure 8: Gastric adenocarcinoma ASMR with APC for SA males

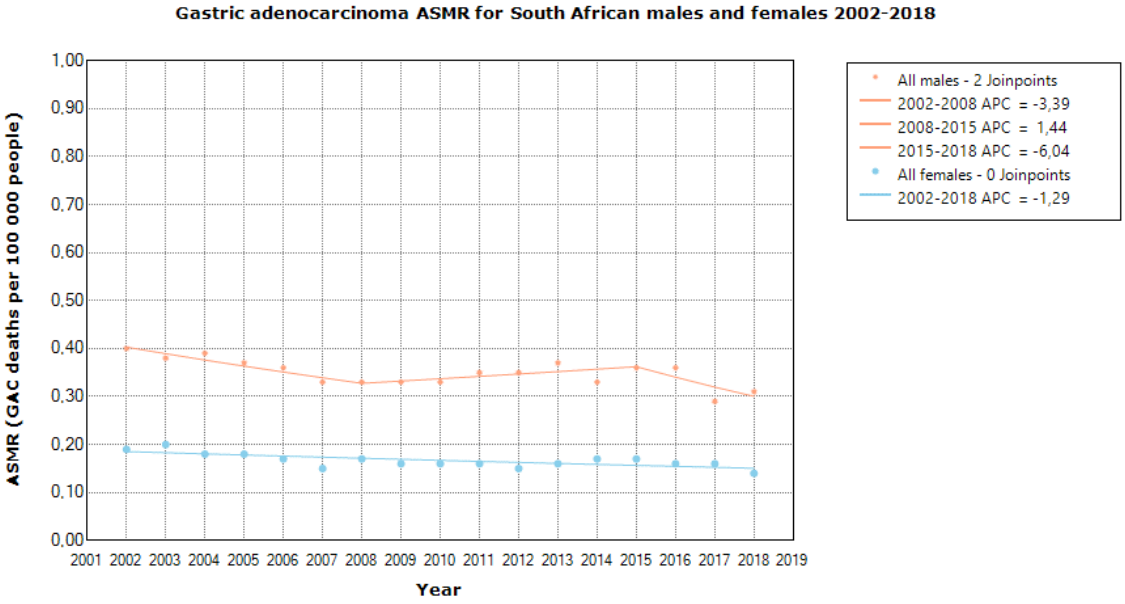


Figure 9: Gastric adenocarcinoma ASMR with APC for SA males and females

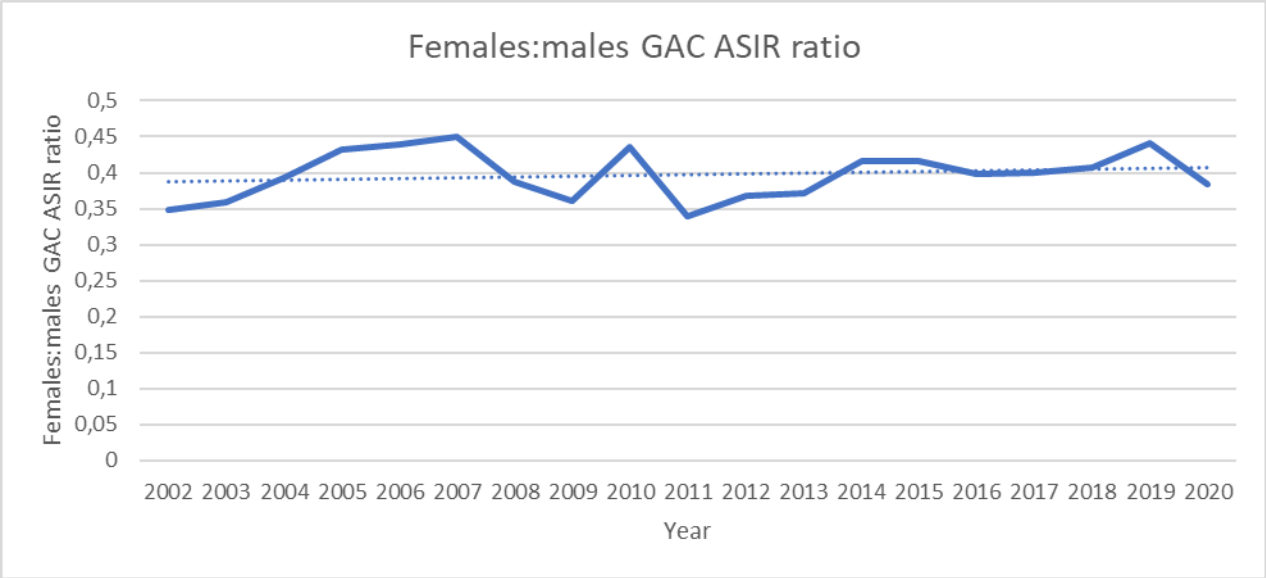
Supplementary tables and figures

Paper 2: Gastric Cancer in South Africa – Incidence and Mortality Trends

Table 1: GAC ASIR APC all population groups							
Cohort	**Segment**	**Lower Endpoint**	**Upper Endpoint**	**APC**	**Lower CI**	**Upper CI**	**Prob > |t|**
Asian Female - 0 Joinpoints	1	2002	2020	-1	inf	-100	0,214
Black Female - 1 Joinpoint	1	2002	2006	12,9	inf	-100	0,035
Black Female - 1 Joinpoint	2	2006	2020	-0,3	inf	-100	0,605
Coloured Female - 0 Joinpoints	1	2002	2020	-1,7	inf	-100	0,001
White Female - 0 Joinpoints	1	2002	2020	-0,1	inf	-100	0,77
Asian Male - 0 Joinpoints	1	2002	2020	-1,4	inf	-100	0,067
Black Male - 0 Joinpoints	1	2002	2020	-0,3	inf	-100	0,497
Coloured Male - 0 Joinpoints	1	2002	2020	-1,5	inf	-100	0,002
White Male - 2 Joinpoints	1	2002	2009	-3,5	inf	-100	0,008
White Male - 2 Joinpoints	2	2009	2012	10,9	inf	-100	0,242
White Male - 2 Joinpoints	3	2012	2020	-2,6	inf	-100	0,013
All males - 1 Joinpoint	1	2002	2017	0,3	inf	-100	0,365
All males - 1 Joinpoint	2	2017	2020	-5,8	inf	-100	0,057
All females - 0 Joinpoints	1	2002	2020	0	inf	-100	0,892
GAC ASIR AAPC all population groups							
Cohort	**Range**	**Lower Endpoint**	**Upper Endpoint**	**AAPC**	**Lower CI**	**Upper CI**	**P-Value~**
Asian Female - 0 Joinpoints	full	2002	2020	-1	inf	-100	< 0,1
Black Female - 1 Joinpoint	full	2002	2020	2,5	inf	-100	< 0,1
Coloured Female - 0 Joinpoints	full	2002	2020	-1,7	inf	-100	< 0,1
White Female - 0 Joinpoints	full	2002	2020	-0,1	inf	-100	1
Asian Male - 0 Joinpoints	full	2002	2020	-1,4	inf	-100	< 0,1
Black Male - 0 Joinpoints	full	2002	2020	-0,3	inf	-100	< 0,1
Coloured Male - 0 Joinpoints	full	2002	2020	-1,5	inf	-100	< 0,1
White Male - 2 Joinpoints	full	2002	2020	-0,8	inf	-100	1
All males - 1 Joinpoint	full	2002	2020	-0,8	inf	-100	< 0,1
All females - 0 Joinpoints	full	2002	2020	0	inf	-100	1
Entire Cohort	full	2002	2020	-0,1	inf	-100	1

Table 2: GAC ASMR APC All Population Groups							
Cohort	**Segment**	**Lower Endpoint**	**Upper Endpoint**	**APC**	**Lower CI**	**Upper CI**	**Prob > |t|**
Asian Female - 0 Joinpoints	1	2002	2018	-1,7	inf	-100	0,109
Black Female - 2 Joinpoints	1	2002	2010	-3,5	inf	-100	0,002
Black Female - 2 Joinpoints	2	2010	2015	4,9	inf	-100	0,083
Black Female - 2 Joinpoints	3	2015	2018	-10,7	inf	-100	0,03
Coloured Female - 0 Joinpoints	1	2002	2018	-1,3	inf	-100	0,019
White Female - 0 Joinpoints	1	2002	2018	-2,4	inf	-100	0,001
Asian Male - 0 Joinpoints	1	2002	2018	-1,4	inf	-100	0,141
Black Male - 2 Joinpoints	1	2002	2008	-4,7	inf	-100	0,032
Black Male - 2 Joinpoints	2	2008	2015	3,7	inf	-100	0,114
Black Male - 2 Joinpoints	3	2015	2018	-10,3	inf	-100	0,034
Coloured Male - 0 Joinpoints	1	2002	2018	-2,2	inf	-100	< 0,001
White Male - 0 Joinpoints	1	2002	2018	-1,9	inf	-100	< 0,001
All males - 2 Joinpoints	1	2002	2008	-3,4	inf	-100	0,068
All males - 2 Joinpoints	2	2008	2015	1,4	inf	-100	0,259
All males - 2 Joinpoints	3	2015	2018	-6	inf	-100	0,112

All females - 0 Joinpoints	1	2002	2018	-1,3	inf	-100	0,001
GAC ASMR AAPC All Population Groups							
Cohort	**Range**	**Lower Endpoint**	**Upper Endpoint**	**AAPC**	**Lower CI**	**Upper CI**	**P-Value~**
Asian Female - 0 Joinpoints	Full	2002	2018	-1,7	inf	-100	< 0,1
Black Female - 2 Joinpoints	Full	2002	2018	-2,4	inf	-100	< 0,1
Coloured Female - 0 Joinpoints	Full	2002	2018	-1,3	inf	-100	< 0,1
White Female - 0 Joinpoints	Full	2002	2018	-2,4	inf	-100	< 0,1
Asian Male - 0 Joinpoints	Full	2002	2018	-1,4	inf	-100	< 0,1
Black Male - 2 Joinpoints	Full	2002	2018	-2,2	inf	-100	< 0,1
Coloured Male - 0 Joinpoints	Full	2002	2018	-2,2	inf	-100	< 0,1
White Male - 0 Joinpoints	Full	2002	2018	-1,9	inf	-100	< 0,1
All males - 2 Joinpoints	Full	2002	2018	-1,8	inf	-100	< 0,1
All females - 0 Joinpoints	Full	2002	2018	-1,3	inf	-100	< 0,1
Entire cohort	Full	2002	2018	-0,1	inf	-99	< 0,2



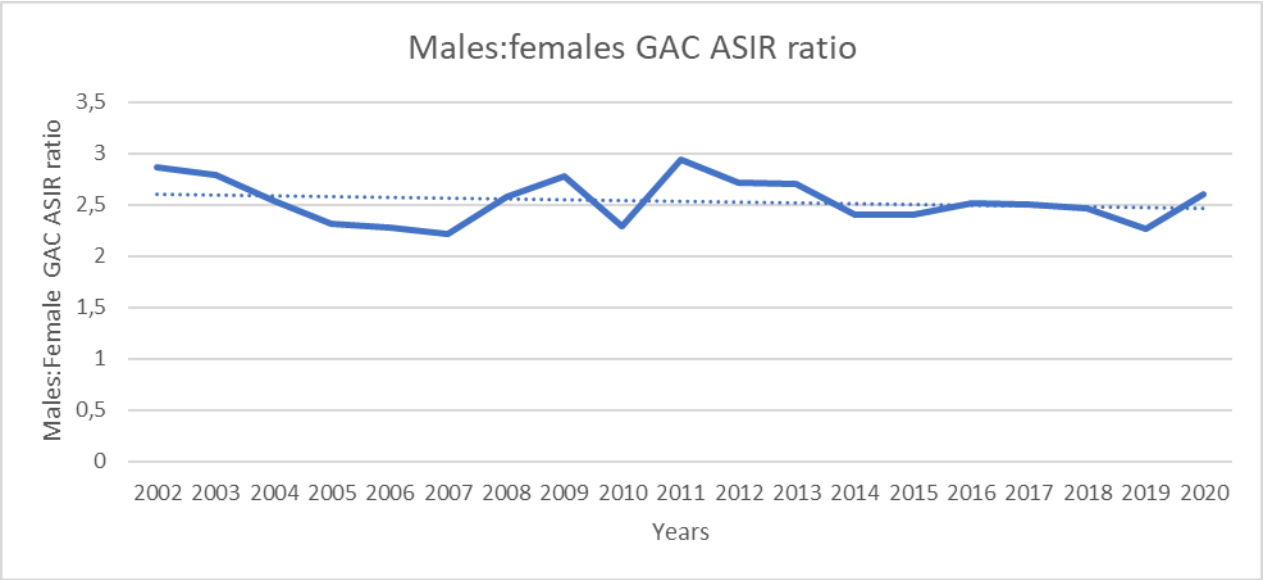


Figure10: Females: Males and Males: Females GAC ASIR ratio

Chapter 5: Exploring the Gastric Cancer Care Pathway in South Africa

Anishka Ramadhar[1], Juliana Kagura MSc PhD[1], Mazvita Muchengeti MBChB MSc PhD [1,2,3], Cameron Gaskill MD MPH[4], Natasha Khamisa PhD[5]

[1] Division of Epidemiology and Biostatistics, School of Public Health, University of the Witwatersrand, Johannesburg, South Africa

[2] National Cancer Registry, National Health Laboratory Service, Johannesburg, South Africa

[3]DSI-NRF South African Centre of Excellence in Epidemiological Modelling and Analysis (SACEMA), Stellenbosch University, Stellenbosch, South Africa

[4] University of California San Francisco, San Francisco, CA

[5] Division of Health and Society, School of Public Health, University of the Witwatersrand, Johannesburg, South Africa

Corresponding Author:

Anishka Ramadhar
anishkaramadhar@gmail.com

Abstract

Background

Data on gastric cancer (GC) diagnosis and care in South Africa (SA) is sparse, and SA has a high GC mortality rate. Mapping the GC care pathway is needed to explore the pathway efficacy in association with the SA GC burden and mortality.

Aim

The aim of this study is to map the SA GC care pathway from diagnosis to various healthcare professionals (HCPs) and explore the barriers and facilitators to the effective flow of the GC care pathway.

Setting

Analysis for this paper was done from SA HCP interviews. The GP was the first contact point with chain-referral sampling used to source other clinicians.

Methods

Interviews were conducted via Microsoft Teams (MS Teams) and Google Meet with qualitative analyses via MAXQDA.

Results

Themes identified were GC care pathway coordination processes, public versus private healthcare system differences, and GC care pathway challenges. Multidisciplinary team (MDT) care is practiced for GC in SA. Care starts with the GP or nurse followed by the gastroenterologist (GI), surgeon, pathologist and back to the surgeon and oncologist. Thereafter the nurse, dietician and palliative care specialist are involved. Healthcare sector differences are time to diagnosis, GC staging, and waiting periods for HCPs and treatment. Challenges include low GC index of suspicion by primary care clinicians (PCC) and *Helicobacter pylori (H. pylori)* detection.

Conclusion

A MDT approach for optimal treatment and patient care may be the best method for prolonged life. A SA national consensus for GC care via a MDT, with emphasis on early diagnosis to aid in a robust treatment plan for improved patient outcomes is warranted.

Introduction

Gastric cancer (GC) is a substantial public health problem worldwide. In 2022 it was reported that GC was the 5th most common cancer and 5th leading cause of cancer-related mortality globally (11). The 5-year survival rate for GC is estimated to be below 20%, with males having double the frequency of GC than females (4, 5). Gastric cancer incidence varies vastly between countries and regions, and this may be due to many factors such as infectious agents, genetics, environmental toxins, and diet (5). Over 50% of new GC cases are identified in developing countries compared to developed countries (5).

The 2022 South African National Cancer registry (NCR) report indicated that in SA, GC makes up 1.92% of all cancers in males and 1.13% of all cancers in females (6), ranking as the 10th (804 cases) and 14th (518 cases) most common malignancy in males and females respectively. The latest Statistics SA report (2018) shows GC is the 7th and 10th most common cause of cancer deaths in SA males and females respectively (7). Delayed time to diagnosis results in many patients being diagnosed in the late stages of GC resulting in limited treatment options (8). Risk factors for GC in SA include a high salt diet, excessive alcohol and red meat consumption, *Helicobacter pylori (H. pylori)* infection, tobacco use, gastrointestinal reflux disease, obesity, and a family history of GC (9).

Care pathways for various conditions are used to strategize and implement a standardised patient centric care approach from diagnosis to post treatment phases (1). The goals of care pathways are clear communication between healthcare professionals (HCPs) and patients, thorough diagnostic workup, and synchronisation with all members of the care team for optimal treatment tailored to each patient (2). Effective care pathways facilitate standardised flow of care processes while also keeping the individual patient in focus. This enables the pathway to guide each unique patient journey (3). Literature indicates that the essential components of a care pathway include (i) the care plan; (ii) pathway development and implementation by multidisciplinary teams (doctors, nurses, dieticians); and (iii) its application to various facets of care (investigation, diagnosis, treatment) (10). Mapping the SA GC pathway will influence SA healthcare practices to enhance GC quality of care, increased patient safety and satisfaction, and optimal use of resources (13). Health policy may be influenced by leveraging the GC care pathway to inform national GC care guidelines for the unique SA ethnic and environmental

diversity. These health policy changes may improve GC healthcare quality and patient outcomes (14).

In SA, data regarding GC diagnosis and care is sparse, yet GC is a dire condition with a substantial age standardised mortality rate of 0.31 per 100 000 people in males and 0.14 per 100 000 people in females (12). Further research is needed to understand the GC pathway considering the GC burden, incidence and mortality rates in SA. The aim of this study is to map the SA GC care pathway from diagnosis to various HCPs involved in the GC patient journey and to explore the barriers and facilitators to the effective flow of the GC care pathway.

Methodology

Study design

This research article follows a qualitative study design using in-depth HCP interviews.

Setting

Participants in this study are HCPs from the public and private healthcare sectors in South Africa. The participants are HCPs that diagnose, treat or manage GC.

Study population and sampling strategy

The interview participants included general practitioners (GP), gastroenterologists (GI), surgeons, oncologists, nurses, pathologists, dieticians, and palliative care specialists in the private and public healthcare sectors from the 3 most populated provinces in South Africa - Gauteng, KwaZulu Natal and Western Cape. The GP was the first point of contact and chain-referral (snowball) sampling was used to source other clinicians involved in the diagnosis, care and treatment of GC. The GPs were sourced by their likelihood of encountering cancer patients based on the size of their practice and geographical location. The interview guides were piloted by a GP, oncologist, and surgeon to increase the accuracy and relevance of the questions for further dissemination to HCPs.

Data collection

Primary data was collected from 30 HCPs using qualitative in-depth interviews via telephone call, and online meeting platforms (Google meet and Microsoft Teams) which were recorded for accurate transcription. The duration of the interviews ranged from 20 to 40 minutes per HCP over a 5-month period. Informed consent was received by all interview participants for participation and recording. There were eight sets of interview transcripts unique to the eight

disciplines of HCPs. After the interviews were conducted, they were transcribed manually and precisely on Microsoft (MS) word, followed by cleaning, formatting, and processing of transcripts in MS Word. Files were cleaned to remove any duplicate text elements such as repeated questions, responses, or words, to ensure accuracy and clarity of the transcriptions.

Data analysis

Computer-assisted qualitative data analysis software (CAQDAS) MAXQDA was used to analyse the processed and formatted interview transcripts. A MAXQDA project was created to organize, analyse, and visualize qualitative data efficiently, for efficient data management and comprehensive qualitative insights. MAXQDA streamlined the data analysis to maintain consistency and improve the rigour of the qualitative research.

Inductive qualitative analysis was employed to eliminate preconceived ideas and patterns. The transcript data analysed inductively allowed for the unbiased generation of concepts and themes. The first phase of the analysis for the generation of initial codes employed open coding in MAXQDA, which distinctly partitions the qualitative data to identify similarities and differences. Labels were assigned to different data segments that represent significant concepts. This step generated a large number of codes, displaying the thorough and distinct nature of the qualitative data. After open-phase coding in MAXQDA, similar codes were identified and merged to eliminate overlaps, ensuring each code represents only one concept for clarity of the data analysis.

The Consolidated criteria for reporting qualitative research (COREQ) guideline was used for this qualitative analysis. the COREQ guideline consists of a 32-item checklist for participant interviews and analysis of the insights.

After code finalization, homogeneous codes were grouped together into sub-themes to classify the data for further analysis to obtain insights. Homogeneous sub-themes were further grouped into broader categories called themes, to capture overarching concepts of the data and to summarize the findings. Common patterns across the sub-themes were identified and organized into higher-level themes that represent the vital aspects of the data. After the analysis a report was generated in MS Word.

Ethical considerations

Ethics approval for this study was issued by the University of the Witwatersrand Human Research Ethics Committee (Medical), certificate number M220752.

Results

The 8 disciplines of 30 HPCs comprising 5 GPs, 4 GIs, 4 surgeons, 5 oncologists, 2 pathologists, 5 nurses, 3 dieticians and 2 palliative care specialists all had more than 10 years of experience treating cancer patients from both the public and private health sectors in SA. The HCPs comprised of an equal number of men and women distributed equally across the 3 most densely populated provinces.

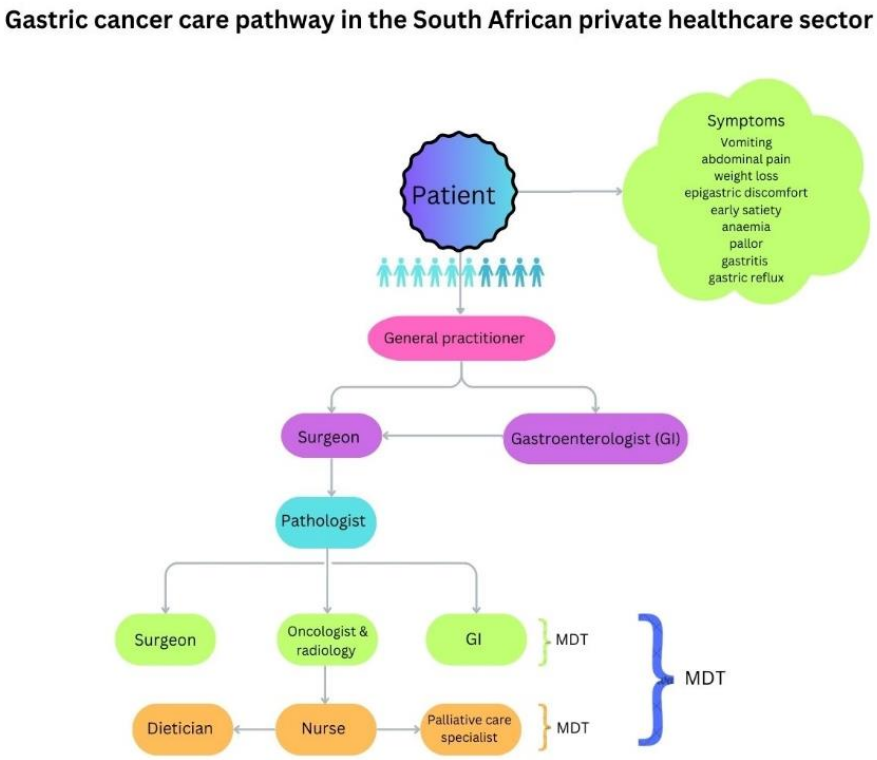


Figure 1 Gastric cancer care pathway in the South African private health sector

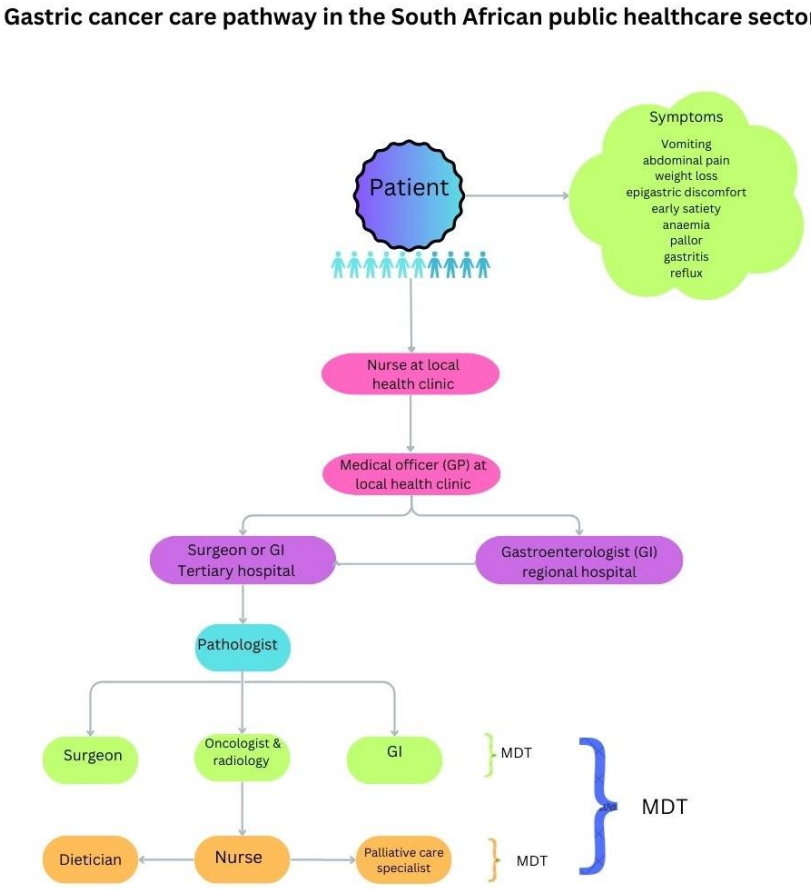


Figure 2 Gastric cancer care pathway in the South African public health sector

The private and public healthcare sectors in SA follow a similar GC care pathway - with slightly more linearity in the public sector - regarding HCPs selection in the referral process and the diagnostic, staging and treatment regimens (figures 1 and 2). The generic flow of care from the initial consultation starts with the GP or nurse at a local public clinic followed by the GI, surgeon and pathologist. After pathology the flow reverts to the surgeon and the introduction of the oncologist, and thereafter the supportive functions by the nurse, dietician and palliative care specialist. The nurse is usually introduced into the pathway upon diagnosis of GC. The dietician and palliative care specialists are also introduced at the diagnosis step, but this differs between the private and public sectors. The stark differences between the 2 healthcare sectors are the time to diagnosis, staging of GC, and the waiting periods for consultation with the various clinicians and GC treatment at each step.

The major themes that were identified in the qualitative analysis were:

1. Referral and coordination processes in the GC care pathway
    - Diagnostic processes
    - Role of HCPs in GC care pathway

- Multidisciplinary team care

2. Public versus private sector healthcare system differences
   - Disparities in diagnosis stage
   - Disparities in treatment access
   - Disparities in time and access to HCPs
3. Challenges and gaps experienced in the GC care pathway
   - Delays in the GC diagnosis
   - Low GC index of suspicion by primary care clinicians (PCC)
   - *H. pylori* detection

1. Referral and coordination processes in the GC care pathway

   Referral and coordination processes in the GC care pathway describe the route from initial consultation with the PCC which is a GP or nurse, to either a GI or surgeon for a gastric endoscopy depending on the symptoms such as gastric reflux, weight loss, nausea, dyspepsia, gastric disturbances, epigastric pain and anaemia that does not subside with treatment. The surgeon makes the GC diagnosis from the biopsy results provided by the pathologist. After a GC diagnosis, the oncologist is consulted, and a treatment regimen is decided upon by the surgeon and oncologist based on the GC stage. The nurse is introduced to the care pathway to assist the oncologist and surgeon with treatment administration, side effect management, patient counselling, and the patients' bedside care. The dietician is consulted for optimal nutritional intake to prepare the patient for treatment and ensure optimal recovery after treatment. Palliative care is usually introduced to GC patients in late-stage diagnosis for improved comfort and quality of life. The analysis revealed a multidisciplinary team (MDT) approach for optimal care of GC patients. The MDT at the initial level comprises of the GI, surgeon and oncologist and the second level includes the nurse, dietician and palliative care specialist. The nurse is involved in both levels of the MDT.

2. Public versus private sector healthcare system differences

   Healthcare system differences between the private and public sectors include GC staging disparities at diagnosis, endoscopy referral and scheduling, access to cancer specialists, timeliness and support for GC treatment, post-treatment management and follow-up in GC care. All the aspects of the public health sector are severely delayed compared to the private sector due to limited resources and inefficiencies in the public health sector.

3. Challenges and gaps experienced in the GC care pathway

Challenges and gaps experienced in the GC care pathway include H. pylori screening and detection in GC patients, and gaps in GC index of suspicion by PCC and GC diagnosis delays.

Table 1: Summary of themes, sub-themes, and quotes from healthcare professional interviews

Themes	Sub-themes	Quotations
Referral and Coordination Processes in GC Care Pathway	Diagnostic Processes in GC Care Pathway	*"If patient is over 40, losing weight, anaemic, not responding to proton pump inhibitors (PPI) then the patient is referred for a gastroscopy." (BI-Gastroenterologist)* *"GC is only confirmed with a scope. Biopsy of the lesion will be taken, and the confirmation will be made in the laboratory." (VGN-Gastroenterologist)*
	Role of Healthcare Providers in GC Care Pathway	*"Normally when the patient comes to the clinic, they would have already seen the surgeon, then they come in to see the oncologist and at that point they introduce the nurse as the chemo sister who will be doing the treatment plan. Nurse introduced at first consult after diagnosis." (AM-Nurse)* *"Epigastric pain or vomiting blood are symptoms that GC patients come in with, hence they are referred to surgeons for investigation into the abdominal pain or GI bleeding, and surgery and scoping can be done if needed on the investigation." (Dr LP-Surgeon)* *"Oncologist do not make diagnosis, the surgeon or GI specialist will diagnose the patient. Patients always referred to oncologist after diagnosis for treatment." (MN-Surgeon)* *"As palliative care nurse we are specialists and play a very active role, take history and assess patient. Diagnose pain, emotional state, spiritual state, psychosocial issues and refer to necessary people like social worker, spiritual healer." (KM-Palliative Care)*
	Multidisciplinary Team care	*"All members of the multidisciplinary team work well together and interact well with each other. All work together to provide good support to patient." (VR-Nurse)* *"HCPs in the multidisciplinary team are good with referring to the necessary healthcare professionals like the dietician or psychologist and have a good relationship with each other." (AM-Nurse)* *"Multidisciplinary team manage patient and all members consult with the patient. Surgeon and oncologist mostly manage the patient. GI will come in for further scopes if needed." (VGN-Gastroenterologist)*
Public Vs. Private Sector Healthcare System	disparities in diagnosis	*"Within 24 hours in private sector for gastric carcinoma in lancet."* *"In state it is highly variable and can possibly be a month to diagnose GC." (TP-Pathologist)* *"In state in patients where the HCP has a high index of suspicion then the scope can happen in 2 weeks provided the GI specialist is consulted and they understand the severity of the situation. If the GI is not consulted and an endoscopy is ordered, from first consult with the initial clinician to the endoscope can take 4 to 8 weeks." ." (VGN-Gastroenterologist)*
	disparities in treatment access	*"Capacity at the hospital, office space, financial issues for transport to hospital. In the hospital, when patients have chemotherapy, it is difficult to navigate to the chemotherapy ward. The government hospital does not employ navigators." (SB onco)* *"The actual treatment not being available is very common and this is a delay as well. Office space for radiation is too small so they have a high backlog for radiation." (NV Onco)* *"Delays with surgery are due to scheduling of patients in the theatre and you have to share theatre space to other cancers and other conditions." (MN Surgeon)*

	Disparities in time and access to Cancer Specialists	*"When patients are referred to state and regional hospital, they are not thoroughly looked at, not examined, and not investigated properly. It is an absolute travesty in state hospitals. Referral letters are not read. The issues are with the doctors and nursing staff." (PDR GP)* *"Huge discrepancy between private sector and state sector. In state, you must wait a long time for a scope, the patient has to wait to come back to the clinic for histology, then the referral to surgeon and there is a delay there and a further delay to see oncologist. All these delays cause the gastric cancer to spread before being treated." (BI-Gastroenterologist)* *"In state sector patients on average wait 6 months from one HCP consult to the next. There is no continuity in state and no commitment to the patient in state. The patient is just a number in state." (DP onco)*
Challenges and gaps experienced in the GC care pathway	Delays in the diagnosis, staging and treatment of GC	*"in state we very rarely see gastric cancer patients with early disease, most patients – 80% of patients - are in state are stage 3 or 4, and they are terminal and treatment will only improve survival." (NV-Oncologist)* *"In private sector there is no delay" (JR onco)* *"In state 20% are early stage. Locally advanced (stage 2 and 3) mostly about 50 – 60% of patients. Stage 4 cases are about 30 to 40%." (GD-Oncologist)* *"in private Only in advanced setting there is delay, in early in neo adjuvant and adjuvant setting there is no delay. In metastatic setting or locally advanced irresectable there may be delay in funding of trastuzumab if patient is HER2+." (GD-Oncologist)* *"in state it is late presentation 80%, early 20%, in private it is 50 -50 with early and late stage" (NV-Oncologist)*
	H. pylori detection	*"Stool and breath test sensitivity and specificity may not be accurate and may not distinguish between current and previous infection."* *"Does not know why clinicians order or do not order H. pylori testing but in the laboratory the specimen is always tested for H. pylori." (KF pathologist)* *"Pathologists will always look at biopsy samples for H. pylori. Chance of H. pylori in the tumour is rare because H. pylori does not like abnormal mucosa that result from malignancy, they like normal gastric mucosa." (TP pathologist)* *"If there is a large ulcerating lesion, then biopsy will be taken but H. pylori will not show cos H. pylori is not in the tumour itself but in other parts of the stomach, that's why it is missed. Cannot do biopsy in normal stomach at same time as tumour biopsy because the same forceps are used and the tumour cells may spread to healthy parts of the stomach." (EL Gastroenterologist)*

Table 2: Barriers and facilitators to the effective flow of the GC care pathway

Barriers to an effective GC care pathway	Facilitators to an effective GC care pathway
Public health care sector	Private healthcare sector
Large patient numbers	Small patient numbers
Delayed time to diagnosis	Patients living closer to hospitals
Delayed time to treatment	Timely diagnosis
Poor health-seeking behaviour	Health awareness from patients
Low index of suspicion at primary care level	High index of suspicion at primary care level
Medical insurance waiting period for treatment approval	Medical insurance covering all treatment in the guidelines
Treatment shortage	Multidisciplinary team care
Staff shortage	
H. pylori screening delays	
Community bias against chemotherapy	
Poor patient referral to specialists	

Discussion

The aim of this study is to map the SA GC care pathway from diagnosis to various healthcare professionals involved in the GC patient journey and to explore the barriers and facilitators to the effective flow of the GC care pathway. The GC care pathway indicates that the HCPs work in a MDT for optimal care of the GC patient in both the private and public health sectors. The findings from the study show that diagnostic process for GC involves the patient's clinical examination, endoscopic biopsy testing and radiology. There are disparities in GC diagnosis, access to treatment and access to cancer specialists in both the private and public health sectors. These disparities are due to medical insurance differences in the private sector, and limited resources and staff inefficiencies in the public sector. There are significant delays to GC diagnosis, treatment and staging in the public sector compared to the private sector. *H. pylori* detection is a challenge in GC patients due to primary health practitioners not screening early enough, and the absence of the bacteria in biopsy tissue.

The GC diagnostic process revealed in this study are aligned with literature where recently diagnosed GC patients presents with an epigastric endoscopy report for mild symptoms, including dyspepsia and reflux, but also for signs and symptoms indicative of advanced disease, such as gastrointestinal (GI) bleeding, anaemia, dysphagia, weight loss, and severe vomiting. Gastric endoscopy with a computed tomography (CT) scan and endoscopic ultrasound provides a GC diagnosis and clinical staging for GC. Positron emission tomography (PET) scans are required to detect advanced GC disease and peritoneal washing (15).

The 2022 National Comprehensive Cancer Network (NCCN) and the 2022 European Society for Medical Oncology (ESMO) guidelines recommend a MDT approach for GC treatment and patient care which supports the findings of this study (16, 17). The guidelines state that GC patient management requires a few disciplines comprising surgical oncology, medical oncology, radiation oncology, GI, radiology, and pathology (16, 17). Findings from this study reveals that the GC patient management in SA follows a similar structure comprising of the surgeon, clinical oncologist (includes medical and radiation oncology), GI, radiology and pathology. The guidelines mention the importance of supportive care provided by the nurses, palliative care specialist, nutritionists, and social workers which aligns with the findings of this study where the nurses, dieticians, palliative care specialists and GPs comprise of the supportive

MDT health workers (16, 17). In this study it is found that nurses form part of the primary MDT as well as the supportive MDT. Literature supports this finding as nurses are known as oncology "coordinators of care" or "navigators" and are integral in relaying physical and psychosocial patient information to the specialists in the MDT and administering specialist prescribed treatment to patients (29). Multidisciplinary team care for GC patients have been shown to reduce time to treatment, unnecessary staging tests and treatment inconsistencies (18). These factors improve quality of care, staging techniques like endoscopic ultrasounds, and consistent patient management (18).

A strong theme that emerged was the disparities in the private healthcare system compared to the public healthcare system especially with regards to diagnosis, treatment and access to cancer specialists. In SA 84.2% and 15.8% of the population uses public health services and private medical insurance, respectively (19). Majority of the population are dependent on the under-resourced public health sector and the wealthier minority use private healthcare services which are well resourced with a system that works seamlessly for both patients and HCPs (6). In this study finding that GC diagnosis is delayed in both the private and public sector, greater delays exist in the public health sector. Research shows that majority of patients using public health services have poor health seeking behaviour and financial constraints that limit them from accessing healthcare clinics and hospitals (20, 21). Private healthcare patients live closer to hospitals, have means to travel and funds to pay for diagnostic testing (21). Herein lies a plausible explanation for a greater proportion of public health users experiencing longer delays in their GC diagnosis as well as being diagnosed at a more advanced GC stage than private healthcare users.

In the private sector there are generally no delays to GC treatment and HCP access due to the patients being members of private medical insurance schemes which covers patient care at private hospitals (25). If patients experience delays, they are due to instances where the patient may need to pay a co-payment for their diagnostic endoscopy if their medical insurance plan does not cover the entire cost or if their medical insurance plan only covers the prescribed minimum benefit for GC, which is the equivalent of public sector treatment. In this case the patient must pay for any additional targeted therapy or immunotherapy for metastatic GC (25). If the medical insurer approves additional specialised treatment there is usually a waiting period of 5 to 30 working days for treatment approval. Targeted therapy and immunotherapy are not

available in public sector hospitals where only surgery, chemotherapy and radiation are available (11).

Research on public health services in SA show poor quality of care and poor patient outcomes owing mainly to ineffective leadership at hospitals and clinics (22). Public healthcare funds and budget are misused, and the clinics and hospitals have old and often broken infrastructure that are unable to accommodate the large number of patients (8). Medicinal and staff shortages are a challenge in the SA public health system and this issue is exacerbated by reduced staff capacity and competencies (23, 24). The shortage of medicines and medical staff, suboptimal infrastructure and staff competencies, and poor safety and working conditions in the public health (9, 10) sector align with the delayed time to GC diagnosis, delayed treatment access, limited treatment options and restricted nutritional and palliative care identified in this study.

Challenges and gaps identified in the GC care pathway exist in both the private and public health sectors and include a low index of suspicion for GC by the PCC, H. pylori screening delays and poor public health service. Early recognition and diagnosis of GC for timely treatment requires accessible, good quality health services coupled with optimal healthcare workers and resources (26). This is lacking in the SA public health sector which is responsible for the care of 84% of the population. Herein lies the low index of suspicion from PCC for GC which leads to delayed referral for diagnosis and limited treatment options. The implications of delayed diagnosis and limited treatment options range from increased anxiety of the patients and caregivers, presentation of advanced disease stage requiring multi-modality treatment, and poor prognosis and survival rates (30, 31).

Literature indicates that the leading risk factor for peptic ulcer disease and GC is *H. pylori* infection with a prevalence of over 80% in adults from developing countries (27). Recent data indicate 89% of the global GC prevalence may be attributed to *H. pylori* infection (27). This information differs to the findings of this study where pathologists reported that *H. pylori* was not present in the GC biopsy tissue. Surgeons' biopsy potentially malignant tissue for GC testing and this tissue does not test positive for *H. pylori* as the bacteria travels away from malignant tissue to areas of the GI tract with healthy gut mucosa (28). This is a challenge because GC in SA cannot be attributed to *H. pylori* infection due to *H. pylori* not being screened at the early stage of only peptic ulcer disease, and screening from malignant GC biopsy tissue is too late for *H. pylori* presence.

The limitation of this study notes the exclusion of patient participation and the lack of verification of the pathway from the patient perspective. Patient participation was not possible due to the public hospitals not providing permission and ethical clearance to interview the GC patients and there would be bias if only the private sector patients were interviewed. Barriers to the GC care pathway at a patient level was not identifiable due to exclusion of patient participation. The difference between the oncology and radiology practice structure between the Gauteng province and the rest of the SA is a limitation as the medical oncologist from Gauteng cannot practice radiology and thus cannot comment on this treatment modality. The reflexivity limitation of the primary investigator and interviewer was that the Western Cape and Gauteng provinces had superior treatment and care for gastric cancer patients due to the investigator living in KwaZulu Natal and witnessing poor healthcare from the KZN public sector hospitals. This bias was cleared up in the interview stage as participants reported similar insights from all 3 provinces.

The strengths of this study include it being the first study to explore the GC care pathway in South Africa, the participation of 8 different health worker disciplines, HCP participation from the 3 major provinces in SA, HCP participation from both the private and public health sectors. Insights gathered on other areas of GC treatment and care like nutrition, targeted therapy and staging of GC are also notable strengths.

Future research is necessary to address the gaps and limitations of this study. There is a need for further studies on *H. pylori* by collaborating with GPs and pathologists to explore the causal relationship between *H. pylori* and GC in SA (32). A study on the GC care pathway from a patients' perspective will allow for verification of this study's findings and an understanding of the patients' GC treatment and management journey. Research into the tolerability and efficacy of the available treatment and the subsequent quality of life of patients in the public and private health sectors will provide further insight into the outcomes of current practices in the different health sectors.

Recommendations from this research include the training of PCC by specialist HCPs to increase their GC index of suspicion (32), *H. pylori* screening earlier in the GC patient journey to decrease time to diagnosis and time to treatment (28). Exploring possible synergistic agreements between the private and public health sectors to expedite GC diagnosis in the public health setting by leveraging the high functioning private healthcare system (20, 21). The robust

cohort of study participants and their experience with treating GC have provided valuable insights which can aid in shaping practice of MDTs for GC and harmonise treatment and management decisions at all stages in the GC patient journey (33). An advisory board for a standardised approach to GC care in the private and public sector with a similar robust HCP cohort can influence GC healthcare policies at a national level (33).

Conclusion

In conclusion, this study findings suggest that thorough initial staging upon GC diagnosis provides a basis for a vigorous treatment plan, enhanced decision making on surgery and treatment administration. These steps will facilitate the effective flow of the GC care pathway and provide patients with a solid understanding of their disease and prognosis. An effective care pathway may assist in identifying a potential for cure or increased quality of life as early as possible in the patients' treatment plan (15). Guidelines encourage MDT decision-making to reduce and relieve suffering of GC patients and improve their quality of life irrespective of their GC stage by providing optimal treatment options. A MDT approach for optimal treatment and patient care is believed to be the best method for prolonged life (16). A SA national consensus for GC care via a MDT, with emphasis on early detection and diagnosis to aid in a robust treatment plan for improved patient outcomes is warranted. A national consensus will aid in public health strategies for a uniform and patient-specific approach for GC care in SA.

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Chapter 6: Integrated Discussion

6.1 Summary of study findings

The aim of this research was to determine the epidemiology of GC in SSA and SA, the incidence and mortality rates for GC in the SA adult population, and explore the care pathway of GC in SA, from available published literature, SA cancer and data registries, and primary data collection via interviews. The main findings included the high variability in GC incidence and scarcity of GC data in SSA, GC incidence and mortality in SA is the highest in the Coloured and Asian populations with men having higher GC incidence and mortality rates than women across all population groups, and the GC care pathway in SA comprising a MDT, with more diagnostic, treatment and resource challenges in the public health sector compared to the private health sector.

The SR demonstrated that GC incidence is highly variable across SSA. The meta-analysis calculation showed an overall pooled incidence rate of 1.20 GC cases per 100 000 people, similar to GLOBOCAN modelled estimates, but highlighting the large regions devoid of primary data (1). In SA, there is an overall decline in GC ASIR and ASMR, and an increase in GC incidence above the age of 40 years with a greater burden in males than females. The ASIR and ASMR were higher in males than females. The SA Coloured males and Asian females have the highest GC incidence, and Coloured males, Coloured females, and Asian females have the highest GC mortality. The SA GC findings align with the SR of GC in SSA with a similar GC incidence rate of 1.20 GC cases per 100 000 people, and the high incidence and mortality rate variability among the different population groups of SA. Differential exposure to risk factors such as red meat, chilli, alcohol, and tobacco may explain the differences observed by population groups (2-5).

Exploration of the SA GC care pathway in light of the GC incidence and mortality trends revealed a multidisciplinary team (MDT) approach for the diagnosis, treatment and management of GC patients in both the private and public healthcare sectors in SA. The 2022 NCCN and ESMO guidelines recommend a MDT approach for GC treatment and patient care for optimal patient outcomes (6, 7). Multidisciplinary team care for GC patients reduces time to treatment, unnecessary staging tests and treatment inconsistencies, and improves quality of care and consistent patient management (8). The private healthcare sector in SA is shown to be more efficient in GC care regarding time to diagnosis, access to HCPs and treatment and overall

patient management. The barriers and challenges expressed by the HCPs may explain the mortality rate being greater than the incidence rate and the continued burden of GC in SA. The stark differences in the private and public healthcare sectors highlighted the challenges in the public sector which include delayed time to diagnosis, delayed treatment, extended delays from initial HCP consultations to specialist consultations, delays with laboratory feedback for biopsy result and delays in the flow of care from one clinician to the next. The public sector does not have sufficient resources and infrastructure to manage GC patients timeously with optimal care which results in poor patient outcomes. Both in the private and public healthcare sectors, there is low index of suspicion for GC, and this hinders early diagnosis and early-stage diagnosis of GC.

6.3 Strengths

This sequential mixed methods thesis includes an abundance of strengths. The sequential methodology offered a logical order of data analysis and exploration, and linking initial findings to consecutive analysis for comparative purposes and verification of findings. The mixed methods design provided a rich and robust data set for this thesis that captures the diversity and intricacy of the research. The mixed methods research enabled the validation of the data analysis findings from the varied sources and analysis approaches to increase trustworthiness of the research. Mixed methods research designs address the limitations of one approach with the strengths of another approach, thereby refining the research rigor. Sequential mixed methods research can produce novel perspectives that can emerge from the data integration or results from either approach, hence continuing the contribution of the research.

6.2 Limitations

Sequential mixed methods have their share of limitations with the initial aspect of sequential in which data analysis must follow a certain order and analysis cannot be conducted on data unless the previous results have been revealed. Mixed method challenges also include additional time, resources and expertise to design, implement, and record findings. Ethical and theoretical considerations for data collection, analysis and integration needed more than one study reviewer to verify any issues.

Recommendations

The findings from this thesis provides a foundation for recommendations on clinical care, surveillance, future research, and health policy.

Clinical care

- Collaboration between GPs and specialists such as GIs and pathologists are necessary to educate the PCC on the role of *H. pylori* in GC and the importance of early investigation for GC in patients with GC symptoms.
- Training of PCC and nurses to recognise signs and symptoms of GC for early investigation.
- Gastric cancer education and awareness to patients for improved healthcare seeking behaviour, and HCPs to increase index of suspicion for GC.

Surveillance

- The variable GC incidence rates from the contributing studies of this SR highlight the need for further development of high-quality population-based cancer registries.
- Establishing GC hospital registries from hospital records that allows for tracking of patients' diagnosis, treatment, and management results, and undertaking prospective longitudinal hospital-based registry studies will improve patient prognosis and outcomes.
- Accurate and high-quality reporting of all GC cases to the SA NCR with addresses for geographical location that will offer insight into environmental risks.
- Accurate and high-quality reporting of cancer deaths to NCR from STATS SA for survival analysis and identifying disparities in age, race and geographical location.
- Allowing the SA national identification numbers in all data bases for completeness of reporting, to link individuals across databases for survival analysis.

Research

- Future data collection and research could focus on the current standard of GC care in SSA and SA and available palliative services.
- Further research into risk factors that contribute to GC in the various population groups is necessary to identify and reduce the risks most pertinent to certain population groups for a more targeted risk reduction approach.

- Research into the supportive functions of the GC pathway from the nurses, dieticians, palliative care specialists and psychologists will provide a layered understanding into the GC care pathway.
- A qualitative analysis on GC patients to understand their perspective of the GC care pathway will provide validity to the results gained from the HCP perspective analysis.

Policy

- The SA National Department of Health should standardise a care pathway in a national GC guideline that aligns with global guidelines and is also pertinent to the SA population.
- Allow reporting of identifiable GC deaths from STATS SA to NCR to track patients' mortality and survival-over-time.
- Implement the SA national identity number as heath identifier for linkage of the STATS SA and SA NCR database.
- Enforce compulsory MDT care to all GC patients and report on cases at each hospital to track progress and challenges for continued evolution of patient care.

6.5 Conclusion

There is a need for further robust data collection, exploration, and research studies on cancer care in SSA, with continued assessment of primary data availability. Enhancement of clinical care and surveillance for GC will benefit both the healthcare sector and GC patients in SA and health policy recommendations will provide long term GC control measures.

The incidence and mortality trends for GC in SA will impact public health by encouraging the promotion of GC screening, reporting and prevention mechanisms. Incidence and mortality patterns are similar for the SA population groups despite the data being sourced from 2 unrelated databases, which may infer that the risk factors are influencing the incidence and mortality of GC in SA. It is a necessity to reduce the GC risk factors especially excessive alcohol, chilli, red meat and tobacco consumption for improved GC control. A GC data registry or reporting process will assist in tracking the burden of GC in SA and the priority for GC risk reduction may be implemented at a national public health level for public health policies and GC control measures.

A proper staging regimen upon GC diagnosis provides a basis for a vigorous treatment plan to inform patients on their disease state, prognosis, and assist in identifying a potential for cure or increased quality of life. A MDT approach for optimal GC treatment and management is believed to be the best method for prolonged life and patient comfort. A SA national consensus for GC care via a MDT, with emphasis on early detection and diagnosis to aid in a robust treatment plan for improved patient outcomes is warranted.

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Appendices

Appendix 1:Prospero registration number

These are records that have either been published or rejected and are not currently being worked on.

ID	Title	Status	Last edited
CRD42022341498	The epidemiology of gastric cancer in Africa: a systemic review protocol To enable PROSPERO to focus on COVID-19 registrations during the 2020 pandemic, this registration record was automatically published exactly as submitted. The PROSPERO team has not checked eligibility.	Registered	03/07/2022

Appendix 2: Research Ethics certificate

Appendix 3: Ethical clearance certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Miss Anishka Ramadhar et al

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M220752

NAME: (Principal Investigator)	Miss Anishka Ramadhar et al
DEPARTMENT:	School of Public Health
PROJECT TITLE:	Understanding the epidemiology and pathways to care of gastric cancer in South Africa
DATE CONSIDERED:	29/07/2022
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Mazvita Muchengeti and Dr Juliana Kagura
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	24/10/2022

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions.Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report.** The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in **July** and will therefore be due in the month of **July** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature _____ Date _____

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix 4: University of the Witwatersrand Information sheet

WITS UNIVERSITY

STUDY INFORMATION DOCUMENT

Study title: Understanding the epidemiology and pathways to care of gastric cancer in South Africa

Greeting

Introduction:
I, Anishka Ramadhar, am doing research on gastric cancer in South Africa . Research is a process used in seeking new knowledge. In this study we want to learn about the trends of gastric cancer in the various South African populations and the care pathway for gastric cancer patients.

Invitation to Participate: We are inviting you to take part in this research study and all information will be kept confidential.

What is involved in the study. This could include but would not necessarily be limited to such features as:

1. Mixed methods study design where you will be required to answer a few questions on the gastric cancer care and management protocol.
2. The study will commence as soon as ethical clearance has been obtained.
3. The standard procedure is for the participant to answer the questions honestly and these answers will be analysed to track a care pathway for gastric cancer.
4. We will only require 60 minutes of your time, once off.
5. The questionnaire will be disseminated online via an interview process.
6. Open ended questions and multiple choice questions will be asked.

Risks of being involved in the study: There is no risk to the participant and at any point if the participant wants to stop the answering questions and withdraw from the questionnaire, they may do so.

Benefits of being in the study: There is no direct benefit to the participant. There may be potential future benefit once we analyse the gastric cancer trends and map the gastric cancer care pathway. This analysis may allow for earlier diagnosis and improved care to gastric cancer patients in future.

Alternative procedures or courses of treatment that might be advantageous to the subject.

The Participant will be given pertinent information on the study while involved in the project and after the results are available.

Participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the Participant is otherwise entitled, as, for example, a hospital patient; that the Participant may discontinue participation at any time without penalty, or loss of benefits to which the Participant is otherwise entitled; that there is no requirement to provide a reason for withdrawing

All participants should be offered a copy of the Participant Information Document to keep for their records.

Appendix 5: Informed Consent sheet

PhD Research
The University of the Witwatersrand
Faculty of Health Sciences
School of Public Health

Anishka Ramadhar - 2244064
PhD Candidate

Research title: **Understanding the epidemiology and pathways to care of gastric cancer in South Africa.**

Informed consent:

It is warranted that you provide informed consent to participate in this questionnaire.
By selecting "agree" below, you consent to the following:

- I am 18 years old or older

- I have read the information sheet and understand that my data will be anonymous.

• Agree

Appendix 6: Turnitin Report

turnitin

Digital Receipt

This receipt acknowledges that Turnitin received your paper. Below you will find the receipt information regarding your submission.

The first page of your submissions is displayed below.

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Assignment title:	Submit here for plagiarism report
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Word count:	20,092
Character count:	105,720
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Understanding the Epidemiology and Pathways to Care of Gastric Cancer in South Africa.

A THESIS

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Appendix 7: PhD Paper 3 HCP Interview Guide

Dietician Interview Guide

1. At what stage in the gastric cancer (GC) patients' journey do you become involved in the patient care and why?
2. How is nutrition a factor in treatment delay or progression?
3. What is an optimal gastric cancer diet that a patient can follow? (describe meal plan)
4. In your opinion, how is a persons' diet a risk factor for gastric cancer?
5. Please describe the diet a patient needs to follow before and after surgery and chemo.
6. How does the diet change as the GC stages progress or worsen (patient improves and worsens)
7. How do you know that the diet regimen is working?
8. Are you involved in tube or IV feeding?
9. Please provide any demographic information or patterns you notice in practice.

Gastroenterologist (GI) Interview Guide

1. Who refers the gastric cancer (GC) patient to you?
2. What makes you suspect that your patient has GC?
3. What limitations do you experience to a clinical diagnosis at a GI level?
4. What encourages you to send your patient for endoscopy?
5. How long does it take to work up the GC patient before endoscopy?
6. For a pt with suspected GC, what else is on differential?
7. What are there the delays or expeditions from the referring HCP?
8. At what point do you review the pathology with the patient?
9. Do you refer to back to GP for patient discussion or do you continue liaising with the patient on your own?
10. In the next step of the patient journey, which clinician do you refer the patient to?
11. What delays or expeditions happen for a patient that is going to see a cancer specialist or surgeon?
12. What delays or expeditions occur in the pathology report?
13. How do you manage the patient after they have been treated by the surgeon and oncologist?
14. What role does H. pylori investigation play in the diagnostic workup
15. Please provide any demographic information or patterns you notice in practice.

General Practitioner Interview Guide

1. What makes you suspect that the patient has gastric cancer (GC)?
2. Do you suspect GC immediately and when do you refer to other HCPs for further investigation?
3. What limitations do you experience to clinical diagnosis at a GP level?
4. At what stage does the patient come to you for a consult? what is the reason for the consult at this stage?
5. H. Pylori information and testing protocol?
6. Describe the process of sending the patient for an endoscopy?
7. What encourages you to send the patient for endoscopy?
8. How long does it take to work up the patient before endoscopy?
9. For a patient with suspected GC, what else is on differential? (what else could it be except GC)
10. What delays occur for endoscopy referral completion?
11. Who is the next HCP that you refer the patient to?
12. How do you manage the GC patient throughout the diagnosis and treatment pathway even though they are now treated by other HCPs?
13. Please provide any demographic information or patterns you notice in practice.

Nurse Interview Guide

1) At which point in the gastric cancer (GC) patients' journey is the role of the nurse introduced?
2) What delays or urgencies are seen in chemo, radiation, or targeted therapy?
3) At what stage do patients come to the cancer ward for treatment?
4) What proportion of patients go into remission or become terminal?
5) How long do these patients stay in hospital before they go into remission or pass away (Duration of visits)?
6) What is the role of the nurse in treating and caring for the GC patients?
7) Describe the rapport with all HCPs involved in the treatment and care of the patient?
8) Do you see the patient before or after surgery or before or after chemo or at all stages in the patients' treatment journey?
9) Please provide any demographic information or patterns you notice in practice.

Oncologist Interview Guide

1. What is the average time that it takes to stage the gastric cancer (GC) patient?
2. By the time a patient reaches you, at what stage are they in their GC journey?
3. What delays or processes occur before a patient has a consultation with the oncologist?
4. How quickly can a patient go from initial oncology consultation to chemotherapy? If not chemo, which is the next alternative?
5. What are the delays or expeditions to treatment?
6. What are the delays or expeditions for port placement?
7. Does the patient require medical aid approval? How long does that take?
8. Are patients delayed because of medical aids and the cost of treatment?
9. Who refers patients to you? Why do you feel the surgeon is contacted before the oncologist?
10. Are there any delays with treatment associated with surgery? If yes, why?
11. What type of chemotherapy or other treatment do you administer?
12. What is your experience with H. pylori and GC?
13. Please provide any demographic information or patterns you notice in practice.

Palliative care specialist Interview Guide

1. At what stage in the gastric cancer (GC) patients' journey do you get involved in patient care?
2. How long does it take for a patient to be referred to the palliative care nurse/unit/doctor?
3. Which type of palliative care patients still undergo treatment?
4. How often do you see the patient?
5. Describe your role in the patients' life?
6. How long does a patient spend in palliative care before they pass on?
7. How often do patients choose to just go home after a while or do they persevere with palliative care?
8. Are there any incidences where patients ever recover or improve/ get better?
9. Please provide any demographic information or patterns you notice in practice.

Pathologist Interview Guide

1. What is the Length of time taken for the pathology specimen to be diagnosed?
2. What details does the pathology report show?
3. What are the percentage frequencies for the different stages of gastric cancer?
4. What delays are there in pathology testing and result output processes?
5. Are you ever in contact with patients or is all information passed via the HCP, if so, which HCP?
6. Where do the specimens come from?
7. At what stage in the patients' journey are they screened for H. pylori? Which HCP do these requests come from?
8. What percentage of GC patients test positive for H. pylori?
9. Is there a reason why H. pylori is not routinely screened for by clinicians even in reflux or other GI conditions?
10. Please provide any demographic information or patterns you notice in practice.

Surgeon Interview Guide

1. What is the average time that it takes to stage a GC patient for surgery?
2. What delays and processes occur before a GC patient goes to a surgeon?
3. How quickly can a patient go from consulting with the surgeon to actually getting surgery?
4. What are the delays and processes for scheduling surgery with regards to theatre availability?
5. Who refers patients to you? GP, GI, or oncologist? Percentage from each?
6. Is there a reason that patients are referred to you before being referred to an oncologist?
7. When do you do diagnostic laparoscopy for staging?
8. Do you routinely refer back to GI for endoscopic ultrasound (EUS) or would this be done by you?
9. What are there any delays or processes with treatment associated with preoperative chemo?
10. How does H. pylori investigation fit into your stage of GC diagnosis?
11. Please provide any demographic information or patterns you notice in practice.