The epidemiology of colorectal cancer: Global implications for measuring incidence, with a focus on trends, risk factors, and screening uptake in Saudi Arabia

Norah Mohammed Alsadhan

Submitted in accordance with the requirements for the degree of

Doctor of Philosophy

The University of Leeds

School of Medicine

January 2025

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I, Norah Mohammed Alsadhan, confirm that the work submitted is my own, except where work which has formed part of jointly authored publications has been included. My contribution and the other authors to this work has been explicitly indicated below. I confirm that appropriate credit has been given within the thesis where reference has been made to the work of others.

Chapter Two (Study One publication):

Alsadhan N, Almaiman A, Pujades-Rodriguez M, Brennan C, Shuweihdi F, Alhurishi SA, West RM. A systematic review of methods to estimate colorectal cancer incidence using population-based cancer registries. BMC Med Res Methodology. 2022;22(1):144. https://doi.org/10.1186/s12874-022-01632-7

Author's contribution to Study One:

I (NA) conceived the idea and research questions for the review with support from my supervisors (MPR, RW, CB, and FS). I developed the search strategy in consultation with an information specialist from the Academic Unit of Health Economics, University of Leeds. I created the data extraction forms, which were reviewed and approved by three supervisors (MPR, RW, SA). Another author (AA) and I screened all titles, abstracts, and full-text articles against the inclusion-exclusion criteria, with discrepancies resolved by a third reviewer (SA). I extracted the study data and assessed the quality of all included studies, while another supervisor (SA) crosschecked data extraction for 25 % of the studies. I conducted data analysis and wrote the first manuscript draft, which all authors reviewed. I submitted the manuscript for publication. Following peer review, I edited and reviewed the manuscript, and all authors read and approved the final version before re-submission.

Chapter Three (Study Two publication):

Alsadhan N, Almaiman A, Pujades-Rodriguez M, Brennan C, Shuweihdi F, Alhurishi SA, West RM. Statistical methods for measuring trends in colorectal cancer incidence in registries: A systematic review. Frontiers in Oncology. 2022;12:1049486. https://doi.org/10.3389/fonc.2022.1049486

Author's contribution to Study Two:

The authors' contributions are the same as in Study One, as this review was conducted in parallel.

Chapter Four (Study Three publication):

Alsadhan N, Pujades-Rodriguez M, Alhurishi SA, Shuweihdi F, Brennan C, West RM. Temporal trends in age and stage-specific incidence of colorectal cancer in Saudi Arabia: a registry-based cohort study between 1997 and 2017. Cancer Epidemiol. 2024;93:102699. https://doi.org/10.1016/j.canep.2024.102699

Author's contribution to Study Three:

I (NA) conceptualized the idea and developed the study methodology with support from my supervisor and one co-author (RW and MPR). I conducted the analysis with the support of two supervisors (RW and FS). I wrote the original manuscript draft, which all authors reviewed. I submitted the manuscript for publication. Following peer review, I edited and reviewed the manuscript, and all authors read and approved the final version before re-submission.

Chapter Five (Study Four publication):

Alsadhan N, Alhurishi SA, Pujades-Rodriguez M, Shuweihdi F, Brennan C, West RM. Demographic and clinical characteristics associated with advanced stage colorectal cancer: a registry-based cohort study in Saudi Arabia. BMC Cancer. 2024;24(1):533. https://doi.org/10.1186/s12885-024-12270-1

Author's contribution to Study Four:

I (NA) conceived the idea and research question and developed the study methodology with support from my supervisors and one co-author (RW, FS, SA, CB, and MPR). I conducted the analysis with support from two supervisors (RW and FS). I wrote the original manuscript draft, which all authors reviewed. I submitted the manuscript for publication. Following peer review, I edited and reviewed the manuscript, and all authors read and approved the final version before re-submission.

Chapter Six (Study Five publication):

Alsadhan N, Brennan C, Alhurishi SA, Shuweihdi F, West RM. Factors influencing colorectal cancer screening decisions among Saudi women: A qualitative study. PLoS One. 2025;20(4):e0321086.

https://doi.org/10.1371/journal.pone.0321086

Author's contribution to Study Five:

I (NA) conceptualized the idea and developed the study methodology with support from my supervisors (RW and CB). I recruited and interviewed all participants. I analyzed and coded all

transcripts with one author (SA), double-coding a proportion of transcripts. I developed the study's themes with support from my supervisors (CB and SA). I wrote the original manuscript draft, which all authors reviewed. I submitted the manuscript for publication.

Conference abstracts

Study Four publication:

- Accepted for a poster presentation at the 18th KFMC Annual Research Conference 2023.
- Accepted for an oral presentation at the Waey Association for Community Health Conference (online) 2023.

Thesis structure

This thesis is structured as an alternative style doctoral thesis. Based on the University guidance for this format, published or submitted materials are included as individual chapters without being rewritten, each with its list of references. However, the formatting of references, tables, figures, and appendices has been amended to ensure a consistent and coherent presentation of the thesis. The first chapter is an introduction, setting the context for the thesis, followed by the publication chapters. There is a final discussion chapter at the end, summarizing findings and highlighting key implications and future directions. All studies have been published.

The Graduate Board at the University of Leeds encourages students to publish their research findings. Therefore, the candidate planned from the outset to structure and organize their research as journal articles, which will aid in the timely dissemination of their work. The candidate's supervisors supported and approved this alternative style format, as it aligned with the candidate's objectives and the university's focus on encouraging publication.

Acknowledgments

I want to express my gratitude to my supervisors, Professor Robert West, Dr Cathy Brennan, and Dr Farag Shuweihdi. Thank you for your continued support and guidance throughout my PhD journey. Your expertise and insights have been valuable in shaping and developing my research skills. Thank you for your emotional support during stressful times and for always encouraging me. A special thank you to Robert for a supervisory experience that taught me how to lead my thesis and provided guidance that enhanced my analytical skills. I wish I had time to explore additional analytical approaches under your supervision. Observing your supervision approach has been a learning experience, and I feel honoured to call myself one of your students. I hope to continue learning from your expertise.

I extend my gratitude to my internal supervisor at King Saud University, Dr. Sultana Alhurishi, for your support and encouragement during my thesis. Thank you as well to my former supervisor at Leeds, Dr Mar Rodriguez. It has been an absolute honour to have you as my supervisor, although for a short period. I'm grateful for your guidance and support during the early stages of my PhD, which helped me in shaping the scope of this thesis. I would also like to thank Dr. Rebecca Beeken, the LIHS PGR studies lead, for your exceptional support of all postgraduate researchers. Your prompt guidance and commitment to creating a safe and supportive environment are greatly appreciated.

To my parents, words cannot fully express my gratitude for your love, support, encouragement, and endless prayers. To my spouse, Abdullah, your unwavering support has been a cornerstone of my journey. To my children, Ghaliah and Khalid, the joy and pride of my life, I am grateful that you were by my side as I pursued my PhD. Despite your young age, you have been wonderfully supportive and understanding. Thank you for accompanying me on my work trips to Leeds and for taking pride in my academic endeavours. I'm grateful for all our memories together and hope to have demonstrated the value of pursuing one's dreams with hard work and dedication.

Thank you to all my fellow students in Leeds for your kind support and friendship. My visits to Leeds would not have been as enjoyable without you. The discussions we had and the good times we shared have enriched my experience and are memories I will always cherish. I would also like to thank all my friends back home and everyone who supported me in any way; Thank you for everything.

Abstract

Colorectal cancer (CRC) is a global public health concern, imposing considerable health and economic burdens. While population-based studies worldwide closely monitor CRC incidence, variations in incidence methods hinder reliable interpretation and comparisons of rates. A description of variations in incidence calculation and the quality of reporting incidence methods is lacking. In Saudi Arabia, CRC is the second most common cancer; about one-third of cases present with a late-stage disease, resulting in poor prognosis. A comprehensive analysis of CRC rates, trends, and factors associated with late-stage diagnosis is currently lacking. The Ministry of Health recently launched a national CRC screening program, yet the public's perceptions and acceptance of screening remain limited. This thesis aims to address the identified gaps by conducting five studies. Study One is a systematic review describing variations in the methods used in CRC incidence and the quality of their reporting. Variations in incidence calculation were identified, and recommendations were provided to enhance the reliability and reporting of incidence estimations. Study Two describes methods for estimating CRC incidence trends, highlighting the most common methods and the need for clarity and transparency in their reporting. Insights from studies One and Two informed methodological and reporting decisions in subsequent quantitative studies. Study Three is a retrospective analysis examining CRC incidence rates and trends in Saudi Arabia. Over time, CRC incidence rates increased across all age groups and stages at diagnosis, highlighting the critical need for cancer control policies and strategies. Study Four examines risk factors associated with late-stage CRC diagnosis in Saudi patients. Women under 50 had an increased risk, emphasizing the need for targeted preventive efforts. Study Five is a qualitative exploration of Saudi women's perceptions and attitudes towards CRC screening. The interviews revealed multifaceted factors influencing screening uptake, underscoring the need for tailored health promotion interventions.

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List of abbreviations

AAPC: Average annual percentage change

ACS: American Cancer Society

AGR: Annual growth rate

APC: Annual percentage changes

APCM: Age-period-cohort modelling

ASIR: Age-specific incidence rate

ASR: Age-standardized incidence rate

AXIS: Appraisal Tool for Cross-Sectional Studies

BE: Behavioral Economics

BMI: Body mass index

BRFSS: Behavioral Risk Factor Surveillance Systems

cAPC: Conventional annual percentage change

CI: Confidence interval

COREQ: Consolidated Criteria for Reporting Qualitative Studies

CR: Crude rate

CRC: Colorectal cancer

CRCS: CRC screening

DALYs: Disability-adjusted life years

DCO: Death certificate only

EO-CRC: Early-onset colorectal cancer

EQUATOR: Enhancing the Quality and Transparency of Health Research

E-TNM: Essential TNM

FAP: Familial adenomatous polyposis

FFT: Fast and Frugal Trees

FIT: Fecal immunochemical test

GASTAT: General Authority of Statistics

GATHER: Guidelines for Accurate and Transparent Health Estimates Reporting

GBD: Global Burden of Disease

GCC: Gulf Cooperation Council

GCO: Global Cancer Observatory

gFOBT: Guaiac-based Faecal Occult Blood Test

GLM: Generalized linear models

HDI: Human Development Index

HDL: High-density lipoprotein

HNPCC: Hereditary nonpolyposis colorectal cancer

HSTP: Health Sector Transformation Program

IACR: International Association of Cancer Registries

IARC: International Agency for Research on Cancer

IBD: Inflammatory bowel disease

ICD: International Statistical Classification of Diseases and Related Health Problems

ICD-O: International Classification of Disease for Oncology

IQR: Interquartile range

IRR: Incidence rate ratio

MAR: Missing at random

MD: Missing data

MetS: Metabolic syndrome

M/I: Mortality to incidence ratio

MICE: Multiple imputation by chained equations

MOC: Model of care

MOH: Ministry of Health

MV: Morphologically verified

N: Number

NA: Not applicable

NCI: National Cancer Institute

NOS: Not otherwise specified

NR: Not reported

NSAID: Non-steroidal anti-inflammatory drug

OR: Odds ratio

PAF: Population-attributable fraction

PBCR: Population-based cancer registry

PC: Percentage of change

PHC: Primary healthcare centers

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

QoL: Quality of life

RTA: Reflexive Thematic Analysis

sAPC: Segmented annual percentage change

SAS: Statistical Analysis System

SCR: Saudi Cancer Registry

SD: Standard deviation

SEER: Surveillance Epidemiology and End Results

SEM: Social Ecological Model

SNIH: Saudi National Institute for Health

SPSS: Statistical Package for the Social Sciences

TNM: Tumor-Nodes-Metastasis

US: United States; USA: United States of America

USPSTF: US Preventive Services Taskforce

WHO: World Health Organization

Chapter 1: Introduction

1.1 Chapter summary

This chapter sets the context for the thesis by describing the global and regional burden of colorectal cancer (CRC), including incidence trends, etiology, risk factors, management, and consequences. It reviews existing literature on CRC screening methods, guidelines, and programs, focusing on the Saudi healthcare system and local CRC screening efforts. The chapter also explains global and Saudi cancer registration systems and discusses CRC incidence measures derived from registry data and variations in the methods used to measure incidence. Finally, the chapter concludes by highlighting gaps in the Saudi CRC epidemiology literature, outlining the thesis's aims and objectives, and providing an overview of the thesis design and structure.

1.2 Colorectal cancer: definition

Cancer occurs when body cells begin to grow uncontrollably, forming tumors. These tumors can be benign—remaining confined to their original organ site— or malignant, which means they are cancerous and can spread to nearby tissues or distant parts of the body. CRC is a type of cancer that starts in the colon or rectum, which are parts of the gastrointestinal system. Colon cancer and rectal cancer are often grouped together as CRC due to their similarities. Both cancers originate in the large intestine, are composed of similar types of cells, and perform functions related to the processing and excretion of waste (1). Cancer stage refers to how much the disease has spread or progressed at the time of diagnosis. In its early stages, cancer is usually confined to the organ where it first developed. As it grows, it can spread to nearby tissues and ultimately to other body parts. The more the cancer has spread, the more advanced the stage, which is often associated with poor outcomes and requires more complex and advanced treatment (2, 3).

1.3 Colorectal cancer: global trends

Globally, CRC is the third most prevalent cancer and the second leading cause of cancer-related mortality. In 2022, CRC accounted for nearly 10% of all cancer cases and deaths, with approximately 1.9 million new cases and 904,000 deaths (4). In 2019, CRC accounted for around 24.3 million disability-adjusted life years (DALYs) worldwide, with each DALY representing one year of healthy life lost, a figure that has doubled since 1990 (5). CRC incidence rates are 44% higher in men (23.4 per 100,000 person-years) compared to women (16.2 per 100,000 person-

years) (6). Rates also vary across countries, and the disease has been considered a marker of socioeconomic development. Countries with the highest incidence rates are mainly high-income Western nations (4). In 2020, Northern America reported an age-standardized incidence rate (ASR) of 26.2 per 100,000 person-years. Similarly, ASRs in Australia, New Zealand, and several European countries exceeded 30 per 100,000 person-years. In contrast, lower incidence ASRs are observed in Africa, ranging from 6.7 to 13.7 per 100,000, and in South and Central Asia, where the rate is about 5.5 per 100,000 person-years (7).

Analysis of data from the Global Burden of Disease (GBD) Study 2019 revealed that CRC cases more than doubled from 1999 to 2019, accompanied by an increase in the global ASR from 22.2 to 26.7 per 100,000 person-years (5). However, global CRC incidence patterns highlight growing disparities in CRC burden across regions. Over recent decades, analysis of the annual percentage changes (APC) in CRC ASR revealed that trends have been stabilizing or slightly declining in high-income countries, including the United States (US), Canada, and Australia (8). Recent US data indicate that Between 2010 and 2019, the average annual percentage change (AAPC) in CRC incidence was 0.1 for individuals aged 50 to 64 years and -3.4 for those aged 65 and above (9). These trends have been attributed to the implementation of CRC screening measures targeting average-risk populations (9).

Conversely, CRC rates among those over 50 continued to rise in low and middle-income countries undergoing major social and economic transitions (8). The increasing incidence in these regions has been attributed to adopting Western lifestyles and the rising prevalence of several CRC risk factors (10). According to GLOBOCAN 2022 projections, the global CRC burden will continue to grow, with the number of new cases rising from 1.96 million in 2022 to 3.6 million by 2050. The greatest case increase is expected in the Eastern Mediterranean region (137%) and Africa (148%) (11).

Although there has been a decline in CRC incidence for adults aged 50 or older over the last two decades across some regions, several reports indicated an alarming global increase in early-onset CRC (EO-CRC) (8, 12-14). According to the GBD 2019 report, global CRC rates have increased more rapidly in younger adults, at 1.6% annually, compared with a 0.6% annual increase in adults aged 50–74 (15). In most epidemiological publications, EO-CRC is defined as CRC diagnosed before age 50. This age threshold was chosen because it marks the usual onset of routine CRC screening, in which incidence rates are expected to rise (16). EO-CRC tends to arise in the distal colon and rectum, often presenting with an advanced disease stage at diagnosis (17, 18).

The Gulf Cooperation Council (GCC) countries—a governmental union of six neighboring countries: Oman, Qatar, Bahrain, Kuwait, Saudi Arabia, and the United Arab Emirates—are considered a low-incidence area for CRC. Yet, the rates of all cancers, including CRC, have been steadily increasing in these regions during the last decades (19). Between 1990 and 2019, Saudi Arabia recorded the highest ASR increase in CRC among GCC countries (20). In 2020, CRC was the second most prevalent cancer in Saudi Arabia after breast cancer, accounting for 12.3% of all malignancies. CRC was the most common cancer in men and the third among women, with an ASR of 12.4 and 9.6 per 100,000 person-years, respectively. The disease affected more males (55.9%) than females (44.1%). The median age of diagnosis was 60 for males and 58 for females. Concerning cancer stage at diagnosis, 36% of cases were localized, 32% were regional, and about one-third presented with an advanced stage (21).

In examining global CRC trends, it is crucial to consider that although the Global Burden of Disease (GBD) Study and GLOBOCAN offer important insights into the global CRC incidence estimates, figures from these sources should be interpreted with caution.

GLOBOCAN, developed by the International Agency for Research on Cancer (IARC), a branch of the World Health Organization (WHO), provides estimates of cancer incidence, mortality, and prevalence for 185 countries in 2022. These estimates are available through the Global Cancer Observatory (GCO), which enables users to visualize, explore, and extract data by region, sex, and cancer type. Estimation methods in GLOBOCAN vary depending on the availability and quality of national data. Incidence figures are usually based on data from population-based cancer registries (PBCRs) and mortality estimates are derived using data from vital registration systems. However, in some low- and middle-income countries, such registry systems often have poor data quality, limited population coverage, missing information, or are lacking altogether, undermining the reliability of the estimates representing these populations. In some cases, estimates are generated through modeling, often using data from neighboring countries. This reliance on proxy data sources and statistical modeling raises concerns about the validity of the generated figures. The reliability of mortality data is also a concern, particularly in settings where death registration systems are absent, cause-of-death reporting is of low quality, or where autopsy rates are declining—which is the case in some high-income countries. Moreover, comparisons between estimates from different GLOBOCAN releases should be interpreted cautiously, as observed changes in figures may reflect improvements in data quality and availability rather than actual shifts in cancer risk (22-25).

Similarly, the GBD Study, launched in 1991, provides annual estimates for 371 diseases and injuries in 204 countries, enabling comparisons across time and populations. Its estimates are based on diverse data sources, including registries, surveys, administrative records, and cohort studies. Nevertheless, like GLOBOCAN, the GBD estimates are limited due to data availability and quality variability, particularly in resource-limited settings. One limitation is the generalization of associations between risk factors and health outcomes across diverse populations. Most evidence is derived from cohort data in high-income countries, and assuming that relative risks are consistent across populations may mask regional or cultural variations in exposure. Despite GBD's efforts to employ various estimation methods and maintain transparency, its estimates' uncertainties must be acknowledged (26).

GLOBOCAN and GBD databases are crucial for shaping health policies and research. Yet, it is imperative that countries invest in strengthening their own national data systems to improve data quality. Given the highlighted limitations in estimates from global databases, conducting independent analyses of available data from local sources can yield more accurate assessments of disease burden and support the development of more effective public health strategies and policies.

1.4 Etiology and risk factors

Although the underlying causes of CRC remain elusive, it is well-established that a series of gene mutations contribute to its development (27). CRC develops through a process called the adenoma-carcinoma sequence. This process begins when colon or rectum cells experience changes in their DNA, causing them to grow and multiply faster than usual and form benign growths called adenomas or precancerous polyps. Over a period of time, which can take up to 18 years, adenomas may turn into malignant cancers that can invade nearby tissue or spread to distant body parts (28).

Most CRC cases (60-65%) are sporadic, occurring in individuals with average risk who do not have a family history or genetic predisposition to the disease. Approximately 25% of cases have familial CRC, defined as having two or more first-degree relatives affected by CRC (29). A smaller proportion, around 5%, of cases are linked to hereditary cancer syndromes such as familial adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal cancer (HNPCC), also known as Lynch Syndrome (30).

Several risk factors are associated with CRC development. Non-modifiable risk factors include age, sex, and hereditary factors (31). Having a gastrointestinal condition, such as inflammatory bowel disease (IBD), including both ulcerative colitis and Crohn's disease, increases the risk of developing CRC by 2-3-fold, with the risk accumulating over time (32). Additionally, existing evidence indicates that diabetes may increase the risk of CRC due to metabolic dysregulation leading to inflammation and oxidative stress, which can promote cancer growth (33). However, most CRC cases are attributed to modifiable environmental and lifestyle factors that characterize Westernization. Several studies have highlighted a direct association between overweight and obesity and the development of CRC (34). Obesity stimulates metabolic changes such as insulin resistance and chronic inflammation, leading to cancer development (28). A meta-analysis of 23 studies reported a 10% increase in CRC risk for every 8 kg/m^2 rise in body mass index (BMI) (35).

Additionally, the 2018 revised summary report by the World Cancer Research Fund and the American Institute of Cancer Research identified several lifestyle risk factors for cancer, such as physical inactivity, smoking, excessive alcohol consumption, and diets high in red/processed meats but low in fiber (36). Recent studies have also highlighted gut microbiome dysbiosis— a condition characterized by functional and compositional abnormalities in the microbiota—as a critical factor in the pathogenesis of CRC and in influencing patient prognosis and treatment outcomes (37, 38). Although the exact mechanisms through which gut flora may affect CRC are not fully elucidated, it is hypothesized that they may involve inflammation and DNA damage in intestinal cells (39).

Factors associated with EO-CRC have been heavily discussed in the literature. Although hereditary or genetic factors and conditions like IBD may predispose individuals to EO-CRC, most cases occur sporadically. The underlying mechanisms for these sporadic cases remain elusive. Early-life exposures (during childhood and adolescence) to Westernized diets and lifestyles may induce changes in the gut microbiota and immune response and cause genetic alterations in intestinal cells, contributing to EO-CRC (30, 40, 41). A growing body of literature also underscores the rising obesity prevalence among children as a risk factor for EO-CRC (42, 43). The Nurses' Health Study, a prospective, ongoing study of US females aged 18-42, reported that a BMI ≥23 at age 18 years was associated with 63% increased relative risk for EO-CRC (44). Childhood or adolescent obesity may lead to an earlier manifestation of metabolic disorders such as type 2 diabetes mellitus, independently elevating CRC risk (45). A systematic analysis of the global burden of disease study in 2019 found that diets low in milk and calcium were main factors associated with EO-CRC (46). In GCC countries, a recent study found that high BMI and diets low in milk were the highest attributable risk factors for male and female EO-CRC, respectively (47).

Several factors have been identified for their protective effects against CRC, including increased consumption of dairy products and dietary fibers (48). A recent meta-analysis of 12 studies from four diverse populations reported a significant 25% reduction in CRC risk associated with dietary fiber intake (49). Additionally, research over the last two decades has highlighted the chemopreventive potentials of non-steroidal anti-inflammatory drugs (NSAIDs), such as aspirin, against CRC development (50). These drugs primarily inhibit pro-inflammatory signals that facilitate cellular proliferation (51).

1.5 Symptoms, presentation, and management

CRC usually presents with symptoms related to the lower gastrointestinal system, such as rectal bleeding, abdominal pain or mass, changes in bowel habits, unexplained weight loss, and iron-deficiency anemia (52). Asymptomatic patients often have a better prognosis than those presenting with symptoms (53-56). Brenner et al. found that asymptomatic CRC patients diagnosed through screening had better overall and CRC-specific survival rates than those diagnosed with symptoms. This association remained even after adjusting for cancer stage and other prognostic markers (57).

Treatment strategies for CRC are influenced by many factors, including cancer stage at diagnosis, patient's age, and comorbidities (58). Patients may only require minimally invasive procedures in early stages, such as a polypectomy. In more advanced stages, however, surgical resection may be necessary and is often combined with adjuvant chemotherapy to reduce the risk of recurrence (59). For metastatic CRC, treatment usually includes a combination of chemotherapy, radiation, targeted therapy, and surgery (60). Palliative care is often provided for incurable cancer patients to improve their symptoms and quality of life (61).

1.5.1 Cancer staging

CRC stage at diagnosis influences patient outcomes, with more advanced stages associated with poorer prognosis (2). When detected early, the five-year survival rate for CRC can exceed 90%, but this rate drops sharply as the cancer advances to more severe stages (3). This emphasizes the critical role of early detection public health efforts, such as routine CRC screening, in improving survival rates by catching the disease early, when treatment is most effective (62). Additionally, continuous monitoring of stage-specific cancer survival is essential for evaluating healthcare systems, early detection efforts, and cancer control programs (63).

Globally, various systems are used for staging CRC, including the Surveillance, Epidemiology, and End Results (SEER), the TNM (Tumor-Nodes-Metastasis) staging system proposed by the American Joint Committee on Cancer, and the Dukes' classification, which is specific to CRC. Among these, the TNM system is the most widely used in clinical practice worldwide as it provides detailed anatomical information, which is pivotal in diagnosing and developing treatment plans. In the TNM system, the T category indicates the size of the primary tumor, the N category refers to the number of regional lymph nodes involved with cancer, and the M category denotes whether the cancer has spread to distant body parts. These categories are subsequently grouped into stages from I to IV. Healthcare professionals use data from various sources, including clinical and pathological reports, to determine the final TNM stage that best reflects the patient's condition (63).

PBCRs are crucial for cancer surveillance and informing public health strategies for cancer control. However, accurately capturing detailed staging information from medical records can be challenging, particularly as cancer registrars often lack medical training. This limitation can result in incomplete or missing TNM data within registries. To address this issue, simplified staging systems like the SEER Summary Stage System, developed and maintained by the National Cancer Institute (NCI) and mainly used in the US, have been introduced (63).

Although many European registries continue to use the TNM system, the SEER system offers a simpler, consistent methodology applicable across all cancer types (63). It classifies CRC based on how far the tumor has spread from its origin into five stages: 1- In situ, in which malignant cells are confined within the epithelial layer of the organ without penetrating the basement membrane; 2-Localized cancer remains within the site of origin without invading adjacent structures or lymph nodes; 3-Regional cancer has spread beyond the primary site to nearby organs or lymph nodes; 4-Distant cancer has metastasized to remote body parts, forming new tumors at these locations; and 5-Unstaged, where data is insufficient to determine the stage (64). The simplicity of the SEER system has contributed to improved completion rates for staging data in certain cancers, such as breast and cervical cancers in the US, where it reached 90% (63). An analysis of SEER data from the US shows that the five-year survival rates for CRC patients are 91% for localized stages, 73% for regional stages, and 13% for those with distant-stage disease (3). These figures highlight the importance of recording stage data to determine disease prognosis and guide cancer control strategies, especially for cancers amenable to early detection like CRC.

Despite its simplicity and broad applicability to all cancer types, SEER staging is rarely used outside of cancer registries. It lacks detailed stage information and does not align well with TNM stages commonly used in clinical care and other registries (63, 65). Thus, reliance on the SEER system may hinder effective clinical decision-making and restrict comparability with global data that does not employ the same system. Walters et al. highlighted that variations in classification systems for recording the cancer stage could limit international comparisons of cancer survival outcomes. They stressed the need for a simplified, globally applicable cancer staging system to enhance data quality and facilitate comparative research (65).

In response to the challenges in collecting complete and standardized staging data across various regions, a working group comprising representatives from IARC introduced the Essential TNM (E-TNM) system in 2017. E-TNM simplifies the standard TNM categories, facilitating assessments of cancer extent when complete TNM information is missing from patient records. This system is designed to facilitate the data extraction process for registrars and encourage the transition toward global TNM usage. The stage groups (I-IV) derived from E-TNM align and correspond well with those from the standard TNM system (63). The IARC has developed and published a user's guide and flowcharts to aid in abstracting stage data using E-TNM (66). However, to the best of the researcher’s knowledge, the extent of E-TNM's adoption across registries remains unclear. A 2022 study investigating staging practices in PBCRs in the Middle East and Northern Africa region reported a growing awareness and interest in E-TNM, although no registries were currently implementing it (67). As variability persists in the staging systems used, promoting the global adoption of tools like E-TNM is crucial for enhancing the validity and comparability of cancer surveillance data.

1.6 Colorectal cancer consequences

The economic burden of CRC is substantial, with the costs of diagnosis, treatment, and rehabilitation placing a considerable strain on healthcare systems, patients, and their families. The costs associated with CRC vary by factors such as stage of diagnosis and treatment modalities. In the US, CRC’s annual medical costs were estimated at $24.3 billion in 2020, representing 12.6% of all cancer treatment expenditures (68). In Saudi Arabia, direct medical costs for treating 1,908 CRC patients in 2019 were estimated at $111 million, with the highest costs documented for younger patients and those at more advanced disease stages (69).

CRC also leads to substantial indirect costs, often equal to or exceeding medical care expenses. These costs are mainly due to lost productivity from morbidity (such as job loss, sick leave, and

early retirement), premature mortality, and caregiver productivity losses (68, 70). In Europe, the total economic burden of colon cancer, encompassing both direct and indirect costs, reaches about 12.2 billion EUR annually, the highest among digestive system cancers (71). The global CRC economic impact is expected to increase, with projections suggesting a cumulative cost of 2,760 billion international dollars from 2020 to 2050, accounting for 0.06% of global GDP (72).

Additionally, CRC can negatively impact a patient's psychological and emotional health. A substantial proportion of CRC patients suffer from anxiety (19%), depression (13-14%), and distress throughout their illness (73). Compared with the general population, CRC patients are 3.7 times more likely to be diagnosed with a mental disorder within the first two years after their diagnosis (74). These psychological effects can also persist among long-term CRC survivors, who continue to face ongoing distress, including post-traumatic stress disorder, fear of cancer recurrence, and other cancer-related concerns (73). As a result, physical and mental quality of life (QoL) scores for CRC patients are lower than those of the general population. CRC patients had a mean score of 41.3 for physical health and 51.0 for mental health, compared to 42.7 and 51.7 in individuals without cancer (75). A recent cross-sectional assessment of psychological well-being and QoL among Saudi CRC survivors indicated a substantial level of depression (55%) and anxiety (31%) among patients, with mean QoL scores (56.9) lower than mean regional (64.5, 79.7) and global (62.8) figures. Impaired physical functioning, financial difficulties, and fatigue were frequently reported factors impacting QoL scores (76). A recent systematic review highlighted that the CRC impact on QoL is particularly pronounced in younger adults as the disease affects vital aspects of their lives, such as fertility, body image perceptions, and financial security. Of the six studies in the review that compared the degree of emotional distress between younger and older patients, four reported increased anxiety among younger individuals (77). Additionally, informal caregivers, such as family members or friends, may experience financial, occupational, physical, or emotional strains, such as anxiety (16-56%) and depression (10-53%), that negatively impact their psychological and overall health (78-80). A systematic review of caregivers' QoL has shown that long-term caregiving is linked with increased stress and behavioral health issues, decreasing caregivers' QoL (81).

1.7 Colorectal cancer screening

Given the myriad negative impacts of CRC, it is essential to develop effective prevention and management strategies to mitigate the expected future rise in cases. CRC is among the few cancers for which secondary prevention through screening is well-established (62). Because of the disease's long preclinical and asymptomatic phase, there is a potential opportunity for early

detection and intervention through screening. Removing adenomas can disrupt the adenoma-carcinoma sequence, preventing the progression to CRC and reducing its overall incidence (82). Furthermore, detecting and managing early cancerous lesions can lead to a better prognosis (62). A recent study indicated that CRC screening resulted in a more favorable distribution of cancer stages than clinically identified cases (83). Evidence from randomized trials and observational studies has shown that screening methods such as fecal occult blood tests, flexible sigmoidoscopy, and colonoscopy can substantially lower CRC incidence and mortality (84-86). Patients referred through screening also had better survival rates, regardless of pathological and patient factors influencing prognosis (87).

CRC screening and early management are more cost-effective than treating advanced cases with surgery and chemotherapy. A recent systematic review of 48 studies evaluating the cost-effectiveness of various CRC screening methods in average-risk populations found that all screening strategies were more cost-effective than not screening (88).

1.8 Methods for CRC screening

Cancer control strategies aim for cancer prevention and early detection. Various screening modalities are employed for this purpose. Stool-based tests are designed to detect CRC while patients are asymptomatic, and treatment is more effective. In contrast, advanced visual techniques can prevent CRC by identifying and removing precancerous polyps before they become malignant (89). Below is a description of the most common screening modalities.

1.8.1 Non-invasive screening methods

1.8.1.1 Guaiac-based Faecal Occult Blood Test (gFOBT)

The gFOBT was the first screening tool shown to reduce mortality in randomized controlled trials. This test is inexpensive, simple, quick, and can be done at home. It works by detecting blood in the stool. A positive result indicates the presence of occult blood, which may suggest the existence of precancerous polyps or malignant lesions in the colon or rectum. The gFOBT requires three stool samples for every screening session. Dietary restrictions and avoidance of vitamin C and NSAIDs before the test are needed to avoid incorrect results (89, 90).

1.8.1.2 Faecal Immunochemical Test (FIT)

The FIT uses antibodies to detect human blood in stool, thus improving its specificity and eliminating the need for dietary or medication restrictions before testing. A meta-analysis of 19 studies showed improved performance characteristics for FIT, with pooled sensitivity and specificity for CRC reported at 79% and 95%, respectively (91). Additionally, the sampling procedure of FIT—requiring only one stool sample—has been associated with increased screening participation and adherence compared with gFOBT. Due to its ease of use and high overall diagnostic accuracy, screening with FIT generally replaced gFOBT (89, 92, 93).

1.8.2 Invasive screening methods

1.8.2.1 Flexible Sigmoidoscopy

Flexible sigmoidoscopy enables visualization of the distal sections of the colorectum. This screening method is essential for the early detection of cancerous lesions or for preventing CRC by removing premalignant polyps. The procedure is generally performed without sedation; minimal bowel preparation is required compared with a colonoscopy (89). Screening with flexible sigmoidoscopy reduced CRC incidence and mortality rates in randomized controlled trials (94).

1.8.2.2 Colonoscopy

Colonoscopy is used to thoroughly examine the colon and rectum and confirm the diagnosis through tissue biopsy. Colonoscopy is the definitive procedure for all abnormal fecal-based screening tests; it facilitates the removal of premalignant polyps and the diagnosis of CRC at early stages (89). The positive effects of colonoscopy screening on CRC risk and mortality have been well-reported in the literature (94, 95). A colonoscopy requires sedation and complete bowel preparation. While the procedure is generally safe, there is a low but potential risk of complications, such as bleeding or bowel perforation (96).

1.9 CRC screening guidelines

Most global CRC screening guidelines recommend screening average-risk individuals aged 50 to 75 using either flexible sigmoidoscopy every five years, colonoscopy every ten years, or stool blood testing—particularly the FIT—either annually or biennially. The latest recommendations from the American Cancer Society (ACS) and the US Preventive Services Task Force (USPSTF) advocate for initiating screening at age 45 for average-risk individuals. This recommendation was driven by

epidemiological evidence of a significant rise in EO-CRC and microsimulation analyses confirming the cost-effectiveness of starting at 45 or even 40 in specific scenarios (97-100). Most CRC guidelines recommend an upper screening age limit between 70 and 75, as the harms may outweigh the benefits beyond this age. However, screening decisions for elderly individuals should be based on their overall health, screening history, comorbidities, and personal preference (101). For individuals at high risk, such as those with a family history, specific recommendations often advocate for screening at age 40 or 10 years earlier than the age at which a first-degree relative was diagnosed (52, 102).

In 2015, the Saudi Centre for Evidence-Based Healthcare convened a group of experts representing various official organizations and associations to establish national CRC screening guidelines in Saudi Arabia. The panel recommended screening for average-risk asymptomatic individuals aged 45 to 70 and advised against screening for those over 70. The screening modalities suggested are in line with the USPSTF (102, 103). The panel, however, highlighted the need for further research to validate the recommended threshold age for screening within the Saudi context (103).

Over the past decades, Saudi Arabia has undergone an epidemiological transition from infectious diseases to chronic conditions (104). This shift was accompanied by advancements in public health measures such as vaccination, alongside socioeconomic changes that have led to the adoption of Westernized lifestyles. Consequently, there has been a rise in lifestyle-related risk factors for chronic diseases, such as smoking, poor dietary habits, and lack of physical activity across all age groups in Saudi Arabia (105-107). These factors are known contributors to CRC development (36), as well as E0-CRC (30, 40, 41), and may have contributed to increased incidence rates among the Saudi population. Additionally, the demographic composition of Saudi Arabia is currently skewed towards the young, with approximately 88% of the population under the age of 50 (108). This demographic structure necessitates consideration when evaluating the current age threshold for CRC screening.

Given these factors, further research is needed to determine whether younger age groups might be at increased risk and might benefit from screening at a younger age. Such exploration is vital to ensure that national screening guidelines are tailored to the epidemiological, health behavior, and demographic trends in Saudi Arabia, which may differ from those in Western nations.

1.10 CRC screening programs

Numerous screening programs have been implemented globally in response to the evidence supporting CRC screening. The decline in CRC incidence and mortality in high-income countries was attributed to the widespread adoption of population-based screening programs (92, 109, 110). Globally, most CRC screening programs use the FIT as the primary non-invasive screening method, conducted annually or biennially, with colonoscopy used as a follow-up for individuals who receive positive results (111). The effectiveness of screening programs in curbing the CRC burden is well-documented (110-112). Lee et al. showed that implementing a nationwide FIT-based screening program for individuals aged 50-69 in Taiwan, starting in 2004, significantly reduced CRC mortality. Screening coverage rates increased from 21.4% in 2009 to 63.8% by 2013. Consequently, there was a 7% decrease in CRC mortality among the screened population from 2004 to 2013 compared with the previous decade (113).

CRC screening can be conducted under either an organized or an opportunistic model. In organized screening, eligible individuals are systematically invited to participate in screening. This approach is characterized by a robust system continuously monitoring the program's implementation, attendance rates, and patient outcomes. Conversely, opportunistic screening relies on an individual's decision to seek screening based on a personal choice or a healthcare provider's recommendation (89, 114, 115). Opportunistic screening is still used in the US, whereas in European countries, organized screening programs have been adopted and implemented, enhancing the public's participation (96, 114).

CRC screening effectiveness depends on the public's uptake and adherence. Yet, screening rates remain low in many countries. While awareness of cancer and screening methods can influence an individual's decision to participate, merely increasing awareness is insufficient. To enhance participation, addressing social, financial, and structural barriers is imperative (115, 116). Additionally, physicians' involvement in advocating for CRC screening is vital (117).

1.11 Saudi Arabia: Country profile and health care system

The Kingdom of Saudi Arabia is located in the furthest part of southwestern Asia. It occupies most of the Arabian Peninsula, covering approximately two million square kilometers, and is considered the largest country in the Middle East (118). The country is divided into 13 administrative regions, with Riyadh as the capital and largest city. Arabic is the official language, and Islam is the main religion, shaping the country's culture. Saudi Arabia has one of the largest economies in the world,

driven mainly by the discovery of oil, leading to rapid socioeconomic development in recent decades (118, 119). As of 2022, the population is estimated to be around 32 million, of which 58% are Saudi nationals. Males and females each represent about half of the Saudi population. The country has a relatively young population, with 54% under 25, 34% between 25 and 49, and less than 4% over 65 (108).

During the past decades, healthcare services in Saudi Arabia have been funded, managed, and delivered by the Ministry of Health (MOH). The MOH provides approximately 60% of health services, while other governmental bodies and the private sector deliver the remaining 40%. The Saudi healthcare system is structured into primary, secondary, and tertiary care. Primary care is offered through primary healthcare centers (PHC), which deliver preventive and curative services, such as immunization, health education, and chronic disease management. PHCs also enable referrals to advanced and specialized care facilities when needed (119, 120). Although primary healthcare services have improved substantially over the years and resulted in noticeable reductions in infant mortality rates and infectious diseases (120), the healthcare system was criticized for being predominantly treatment-focused rather than prevention-oriented. It lacked a well-integrated system across primary, secondary, and specialized care levels. Moreover, there was a pressing need to develop electronic and remote healthcare services to facilitate patient's access to care (121).

The Saudi healthcare system has recently undergone major reforms to enhance its effectiveness and accessibility. In 2016, Saudi Arabia launched "Vision 2030", which aspires to establish the country as a global leader by creating a thriving economy, a vibrant society, and an ambitious nation. One of the vision realization programs is the "Health Sector Transformation Program (HSTP)", which seeks to restructure the healthcare system into an integrated framework that prioritizes patient care. The HSTP aims to improve access to healthcare services, raise the quality and efficiency of care, and reduce health risks. A new model of care (MOC) was introduced to reach these objectives. In this model, healthcare provision is organized into clusters—"groups of providers located near major medical cities or large hospitals"—allowing for the integration of primary, secondary, and specialized care. This approach intends to improve patient experiences and reduce service duplication (121, 122).

The HSTP and MOC include initiatives to reform and strengthen the primary health care system. Patients must seek care at PHCs for initial evaluations, with referrals to secondary care provided as necessary. The MOC also provides virtual healthcare services and uses digital technologies and e-

health facilities to refer and monitor patients, schedule appointments, and prescribe medication. The HSTP and MOC also developed a workforce strategy to ensure sufficient skilled healthcare professionals are optimally distributed across the country. The National Health Insurance Center funds the health clusters, ensuring that quality care is provided free of charge to all citizens. Currently, the MOH acts as a regulator, monitoring the healthcare sector to ensure that all needs are addressed and that high standards of care are met across all service providers (121).

Despite these advancements, oncology care in Saudi Arabia remains primarily concentrated in specialized centers in major urban areas, particularly central cities. The centralization of healthcare services can limit access to timely specialized care for residents in rural areas (119, 123). Attempting to address this issue, the MOH launched the “Ehalati” e-referral system in 2017 (123). This system is an electronic platform designed to enhance and expedite the referral process from primary to secondary or tertiary healthcare facilities. It improves the appointment scheduling process by integrating with a mobile application that enables patients to manage their appointments efficiently (124).

However, there is currently limited evidence of the system’s effectiveness and quality. Information regarding factors influencing the referral process to oncology care is also scarce. A recent Saudi cross-sectional analysis examining referral patterns from primary healthcare services to hospitals revealed a strong association between geographic proximity to hospitals and the likelihood of being referred to specialized care (124). For CRC screening, the E-referral system is crucial for patients transitioning from primary care to secondary or tertiary care facilities, where more advanced diagnostic procedures are available and necessary for confirming their diagnoses. Given the pivotal role of early detection in improving CRC prognosis, maintaining an efficient and quick referral process is crucial. Therefore, further investigation is needed to examine and address logistical and operational barriers affecting the referral process. It is also important to explore patients’ experiences navigating the healthcare system to identify potential areas for improvement.

Saudi citizens have several options when seeking healthcare. While some choose to visit public PHCs, others may prefer to access health services provided by governmental agencies with which they are affiliated. Citizens with medical insurance—usually through their employers—can seek care at private hospitals or clinics. Some people without insurance may choose to pay out of pocket for private health services. Some citizens may choose to use private services due to the ease of appointment scheduling and access to specialized care.

1.11.1 CRC screening in Saudi Arabia

Under the HSTP prevention initiatives, various public health strategies were developed, targeting communicable and non-communicable diseases. For cancer control, breast and CRC screening initiatives have been prioritized for implementation under the leadership of the MOH. In 2017, the MOH launched the “colorectal cancer early detection program” to reduce the incidence and mortality of CRC through early diagnosis and treatment of lesions. The program’s services are available exclusively through public PHCs across the kingdom’s 13 administrative regions. The FIT is recommended for average-risk individuals aged 45 to 75, followed by colonoscopy for patients with positive FIT results or those at increased risk for CRC due to hereditary factors or specific health conditions. Information on participating screening centers and their locations is available on the Ministry’s website (125).

Despite this initiative, up to the researcher's knowledge, no studies have evaluated the Saudi public’s awareness, uptake, or perceptions of the program. Furthermore, no published reports from the screening program on attendance rates or patient outcomes exist. Previous survey-based studies have explored the Saudi population’s awareness of CRC and its screening modalities, with most indicating insufficient knowledge (126, 127). In 2018, Khoja et al. investigated the use of CRC screening services in Saudi Arabia among 2,946 participants in the Saudi National Survey for Elderly Health. Their findings revealed a low CRC screening uptake (5.64%), with less than 1% of participants undergoing colonoscopy (128).

Additionally, a survey of 130 family physicians revealed that, despite recognizing the effectiveness of screening, 56% of physicians reported low implementation of screening in their practice (129). An in-depth exploration is needed to understand the public’s knowledge and perceptions of CRC screening provided by the national early detection program. Such insights will inform and enhance the MOH’s screening efforts, ultimately improving the program’s effectiveness and reach.

1.12 Cancer registration

The primary objective of a cancer registry is to systematically collect, code, analyze, interpret, and disseminate reports on cancer data. The information provided by cancer registries is integral for measuring cancer occurrence and burden in a population (130). Cancer registries can be either hospital-based or population-based registries. The purpose of hospital-based registries is to record patient information about cancer treatment and its outcomes in a health institution. Because these data lack a well-defined catchment population, their relevance in understanding cancer

epidemiology is limited, thus mainly used for administrative purposes and clinical outcome monitoring (130-132).

Conversely, a population-based cancer registry (PBCR) systematically collects data on new cancer cases within a geographically defined population. This data is vital for national cancer planning and surveillance, facilitating the analysis of incidence, prevalence, and survival rates across various demographic groups and regions (131). PBCRs have become essential for monitoring and predicting cancer trends, generating hypotheses about causes, evaluating public health interventions, and informing cancer-control strategies and policies (132-135).

Efforts to estimate the number of new cancer cases in a population date back to the 1900s, primarily in European countries. In 1926, the first PBCR was established in Hamburg, Germany. In the following decades, more countries have set their PBCR (131). The most recent cancer report by the International Agency for Research on Cancer (IARC) included data from 460 registries across 65 countries, covering about 19% of the world's population (136). The International Association of Cancer Registries (IACR) was established in 1966 to standardize collection methods across registries. It is also a membership organization for cancer registries and works with the IARC in producing scientific publications concerning cancer registration and epidemiology (130). The Global Initiative for Cancer Registry Development, a global partnership led by the IARC, was established to assist socioeconomically transitioning countries in establishing cancer registries and using data for cancer control planning. Under this initiative, regional hubs were established to provide further support and guidance, enhancing these countries' ability to maintain high-quality registries (137).

According to the IACR, PBCR data should be collected by qualified, trained registrars from various sources, including treatment facilities such as hospitals and diagnostic departments such as laboratories (130). The personal or clinical information collected in a registry will depend on data availability. However, when collecting cancer data, the IARC emphasizes quality over quantity (131). Personal identification information such as names, sex, and date of birth are required for record linking and to avoid registration duplication. It's also important to collect details like the patient's address, ethnicity, clinical characteristics of the tumor, and how the diagnosis was confirmed. When possible, death certificates are also obtained from death registry systems. However, in many countries, reliable cause-specific death data are unavailable. In relation to the classification and coding of neoplasms, the IARC recommends using the International Classification

of Disease for Oncology (ICD-O) to code the topography (anatomical location) and morphology (histological appearance) of cancer (130, 131).

The availability and quality of cancer registry data vary considerably across countries. According to the Global Initiative for Cancer Registry Development, only about one-third of countries can provide high-quality cancer data (137). The value of a PBCR and its ability to provide reliable estimates of the cancer burden depends on data quality and the effectiveness of the registry's quality control measures (138-140). The IACR recommends that each registry maintain an internal quality control checking process that regularly assesses data quality (138). The four main data quality dimensions in cancer registration are comparability, completeness, validity, and timeliness. Comparability refers to how closely classification and coding procedures, as well as definitions of incidence, adhere to standardized international guidelines. Completeness is defined as the degree to which all cancer incidents in a population are captured and included in the registry. Validity is concerned with the degree of accuracy in coding and identifying cases, while timeliness pertains to the rapidity in collecting and reporting reliable cancer data. Quantitative and qualitative methods are used for each dimension to evaluate several quality indicators (139, 140).

1.12.1 The Saudi Cancer Registry

The Saudi Cancer Registry (SCR) was established in 1992 by the MOH and began registering cases in 1994. In 2014, the management of the SCR was transferred to the Saudi Health Council, under which it now operates. The registry collects cancer data from governmental and private health institutions nationwide. To ensure comprehensive coverage, the SCR's main office in Riyadh manages and coordinates data collection efforts through five regional offices located in the Central, Eastern, Western, Southern, Madinah, and Northern regions (21, 141).

Cancer registrars at oncology centers document and register cancer cases. The data collected includes identifiable patient information (names, ID numbers, addresses, and contact information), demographic characteristics (age, sex, marital status, and nationality), and tumor-specific information (date of diagnosis, primary site, histology, grade, behavior, stage, and diagnostic method). The registry does not collect data on hereditary disorders or CRC risk factors. Data validation and analysis are completed using the CanReg software, developed by the IARC (141).

CanReg is an open-source software designed for managing data in PBCRs. It facilitates the process of entering, storing, and analyzing cancer data. The tool has quality control features, including

consistency checks based on international standards, code validation, and duplicate detection. CanReg ensures the application of the standardized coding and data verification essential for conducting reliable comparative analyses across different registries. The software has a user-friendly interface and includes features such as multi-user access, customizable data entry forms, and the ability to manage and integrate data from various sources. It provides descriptive statistical tools for case counting and incidence calculations, supports detailed analyses of specific subgroups through data stratification, and generates exportable incidence tables. Additionally, CanReg supports the export of data for advanced analysis in external statistical software or Excel spreadsheets (142, 143).

CanReg is available in multiple languages and is freely accessible, making it a valuable tool for cancer data management and research. However, it is not ideal for researchers looking to perform complex statistical analyses, such as modeling, to explore trends in incidence or associations between variables.

The SCR's central office publishes annual reports on cancer incidence statistics. To ensure data accuracy and reliability, the SCR employs quality control procedures, including data verification and consolidation, and case linkage (141). The registry is an IACR member, and its data from 2003 to 2012 are included in two volumes of Cancer Incidence in Five Continents (136).

The SCR is a valuable source for researchers to examine CRC incidence, identify which demographic groups are most affected, and observe temporal changes in rates. Such insights are essential for informing and guiding the country's CRC control and screening decisions. However, to provide a valid understanding of the CRC burden in Saudi Arabia and to enable accurate comparison with international rates, reliable and credible methods for calculating and reporting incidence should be employed.

1.13 Measuring CRC incidence rates and trends using cancer registry data

CRC is a global public health challenge, and understanding its epidemiology is crucial for developing effective cancer control policies and strategies. Incidence is a key epidemiological measure used to assess the populations' health status by quantifying the occurrence of new disease cases in a specific population over a defined period (144). Researchers have used various measures and methods to estimate CRC incidence rates and trends using PBCR data. One of the most basic measures for estimating incidence is the crude rate (CR), calculated by dividing the number of new cancer cases by the total person-years of observation. However, since age is a

significant factor in cancer incidence, the age-specific incidence rate (ASIR) accounts for age differences by calculating the number of new cases within specific age groups relative to the person-years of observation for that group. For comparisons across populations with different age structures, the age-standardized incidence rate (ASR) is often estimated, which adjusts ASIRs to the age structure of a standard population (145).

Comparing CRC incidence between studies and populations is valuable for examining long-term trends and the underlying environmental and lifestyle factors contributing to the disease. Comparisons of incidence are also essential for evaluating the effectiveness of prevention measures and their impact on CRC incidence and mortality. However, epidemiologic terminology has persistent ambiguity and inconsistencies across the literature (144). Fair comparisons between incidence findings are often compromised when using different definitions for the numerator, denominator, or the population at risk (144-146).

When defining the numerator, authors should clearly describe the disease of interest (e.g., anatomical site, codes) and the study population (147). Some researchers may exclude cases in individuals with hereditary factors, including family history or genetic syndromes. Authors are also expected to understand the distinction between primary cancers (new, first-time cancers) and secondary cancers (recurrence, extension, or metastasis) and ensure accurate reporting of the type included in the incidence calculation (146, 148). Variations in these definitions can lead to inconsistencies in estimated rates, especially in studies using the same data source. Such discrepancies can also distort the valid assessment of the cancer burden and hinder reliable comparisons across populations, thereby impacting public health decisions and practices.

In terms of CRC, the complexity of defining the disease stems from its occurrence across multiple anatomical sites, including the cecum, appendix, ascending colon, hepatic flexure, transverse colon, splenic flexure, descending colon, sigmoid colon, rectosigmoid segment, and rectum (149). When measuring CRC incidence, variations in the anatomical subsites included in the CRC definition can lead to discrepancies in generated rates, thus compromising reliable comparisons across studies. Additionally, colon tumors are frequently categorized into right/left or proximal/distal sections, and variations in the anatomical sites included under these categorizations can also impact fair comparisons of incidence rates. Therefore, it is crucial to determine whether there is a consensus within the research and scientific community regarding the definitions of CRC site categories and what is commonly reported in the literature. A clear

understanding of these definitions is essential to guide future CRC incidence analyses, ensuring they are more reliable and comparable.

In estimating the denominator for incidence rates, calculating person-years at risk is considered the correct method due to its accuracy in measuring the actual time each individual is at risk, but free from the disease. Defined as the sum of person-time contributed by each individual in the population, this method is particularly valued in longitudinal cohort studies where participants may join or exit the study at different times or when their risk status changes over time. It provides a valid measurement of risk exposure time, which is essential for accurately calculating incidence rates. However, applying this method may be challenging due to limitations in the available data, especially in sources like PBCRs. Thus, researchers usually use mid-year population estimates to approximate person-time at risk, an alternative method that is recommended by the IARC (145). To ensure an accurate interpretation of rates, authors should explain the used population estimates and how they were derived (144). Furthermore, for calculating an overall average incidence measure across multiple years, the IARC recommends summing mid-year population estimates (sourced from census data) for each year included in the study. When this method is not feasible, a less precise but acceptable approach is to use the population size from a single point within the study period—preferably the midpoint—and multiply it by the years observed (145). Other methods for population estimates used as denominators have been reported in the literature (144, 146).

Spronk et al. noted that differences in how the numerator and denominator are estimated can affect the magnitude of the generated rates. For example, when comparing person-years at risk with the mid-year population as denominators, generated incidence rates differed by as much as 13.3%. The authors highlighted the importance of explicit documentation and reporting of the terminology and methods employed in incidence calculations to ensure transparency and comparability (144). The quality and transparency of reporting incidence methods in epidemiological studies remain unclear. Investigating this area is crucial for identifying variations and limitations in reporting practices, which could mislead interpretations of epidemiological data and thus impact the planning and implementation of effective public health strategies and interventions.

For examining CRC trends, the annual percentage change (APC) in incidence rate is commonly used. The APC quantifies the annual change in incidence rates by calculating the slope of a regression model fitted to log-transformed incidence rates (150). However, since trends do not

always follow a linear pattern, joinpoint regression (also known as segmented analysis) is often used to estimate the APC when the assumption of linearity is not valid across the entire study period. This method helps identify points in time where significant shifts in incidence rates occur (151). Identifying such points is critical for understanding the impact of health interventions, medical advancements, or changes in risk exposure. Epidemiologists have used joinpoint regression to examine CRC incidence trends across various factors, including age (152), sex (153), anatomical sites (154), tumour stages (155), and geographic regions (156). While some studies measure trends in ASR (12, 157), others have analyzed trends in CR (158) and ASIR (159, 160). Furthermore, other descriptive and modelling methods, such as visual summaries, age-period-cohort analysis (161), and Poisson regression (162), have been used to evaluate CRC incidence trends. Variations in calculating trends can impact the interpretation of cancer rates within a population, ultimately influencing the assessment of public health interventions, the identification of emerging trends, and the development of healthcare policies.

Despite these variations in measuring incidence trends, no previous study has reviewed and summarized the most commonly used statistical methods for estimating trends, the software and tools employed, or the reported parameters. Furthermore, an examination of the quality of reporting incidence trends methods in epidemiological studies is lacking. As previously highlighted, this knowledge is vital for informing researchers about commonly used incidence trends methods. It also supports the development of recommendations to enhance reporting practices, thereby enabling more accurate interpretations and comparisons of the disease burden.

1.14 CRC epidemiology in Saudi Arabia

Few epidemiological studies have examined CRC incidence trends in Saudi Arabia using SCR data. While most studies reported increased CRC incidence over time, they varied in the methods used to estimate the incidence and often lacked clear explanations of how incidence rates and trends were calculated. Some studies used basic descriptive approaches to examine changes in the frequency or proportion of CRC cases. For example, Chaudhri et al. (163) examined trends by calculating the annual proportion of CRC cases among all cancers diagnosed between 2001 and 2014, depicting these figures graphically. Similarly, Mosli et al. (164) presented CRC incidence trends between 2001 and 2006 by plotting yearly case counts. While such methods provide a useful initial overview of the data, they do not consider the population size in incidence calculation and, therefore, do not accurately reflect disease risk. Hence, relying solely on these measures may lead to misinterpretation of the actual burden of disease within the population.

Other studies analyzed trends by displaying yearly ASR or CR, often stratified by sex (165-168). Almatroudi (166) calculated the absolute difference in crude and age-standardized rates between 2006 and 2016 to examine CRC trends. He also reported trends in the CRC stage at diagnosis by graphically presenting the annual percentage distribution of stages. Regarding observing age-specific changes in incidence trends, Almatroudi (166) examined the overall ASIR during the study period. However, by not analyzing annual changes in incidence by age groups, the study may have missed important changes within specific age groups, potentially masking emerging patterns. Identifying such patterns is essential for informing screening guidelines, planning interventions, and directing future health resources. Similarly, Alsanea et al. (165) assessed the overall ASR during the study period, stratified by age group. However, their analysis did not explore annual age-specific changes, limiting insights into emerging trends by age. Additionally, the use of an external reference population for standardization, while useful for comparisons across populations, may mask actual local shifts in disease burden. Both authors did not fully explain their analytical approaches, especially concerning denominator size estimations.

While simple descriptive methods provide useful information, statistical modelling can further illustrate trends and identify patterns within the changing CRC burden. Few researchers have recently started using modelling techniques to examine CRC incidence trends using SCR data. In 2020, Alzalabani estimated the APC in CRC age-standardized rates between 1994 and 2015, reporting a positive trend for both sexes, albeit a higher average APC in males (4.9% vs. 3.7%) (169). However, this study focused on the population-attributable fractions of CRC cases influenced by modifiable risk factors, lacking a detailed analysis of trends by age group. Therefore, its findings are limited in terms of informing age-specific CRC screening policies and program planning.

Given the current global attention to the rising EO-CRC incidence rates, a few recent Saudi reports have examined CRC incidence trends by age. In 2021, Alyabsi et al.(170) used joinpoint regression analysis to examine the APC in CRC age-standardized rates from 2001 to 2016, using two distinct age groups—early-onset (<50) and late-onset (50+). Although the study reported shifts in APCs over different time segments for the early- and late-onset groups, it presented average APCs for predetermined periods when analyzing trends across narrower age groups between 20 and 75+ years. This analytical approach may overlook changes occurring within these age groups over shorter periods. Similarly, in 2023, Basudan et al. analyzed CRC incidence patterns in Saudi Arabia between 2001 and 2018, reporting only a single APC for age-standardized rates and rates across eight age groups between 40 and 75+. In this study, it was unclear whether the values represented

an average APC for the entire study period or why segmented time-period results were not reported (171). Presenting segmented APC findings is crucial, as it can identify shifts in incidence trends over shorter periods, thereby supporting the evaluation and development of public health interventions. Producing reliable, replicable, and comparable incidence trends is essential for accurately monitoring the disease burden. The Saudi literature on CRC incidence by age remains limited, highlighting an area for further exploration.

Cancer stage is a critical determinant of patient prognosis, as later stages negatively impact survival outcomes (3). In 2020, 28% of female and 24% of male CRC patients in Saudi Arabia presented with distant metastasis (21). To the best of the researcher's knowledge, no previous study has examined CRC incidence patterns by stage at diagnosis. Monitoring incidence trends by stage is essential for monitoring the disease burden and establishing baseline data to evaluate the national screening program's impact on increasing early CRC diagnosis.

Limited research in the Saudi literature has examined risk factors associated with CRC development or its prognosis, and existing findings are sometimes inconsistent. In 2008, a case-control study on 50 CRC patients found that high consumption of red/processed meats and high-fat dairy products may increase CRC risk, while high dietary fiber intake could have a protective effect (172). Conversely, Azzeh et al. found that consuming dairy products decreased CRC risk in 164 participants from the Mecca region (173). In another case-control study using the same sample by Azzeh et al. (173), factors such as low CRC awareness, unemployment, low family income, sedentary lifestyle, and diabetes were associated with increased CRC risk, while a low BMI slightly increased the risk (174). Alqahtani et al. also noted a higher CRC risk among those with lower BMI, attributing this observation to weight loss associated with advanced cancer stages at diagnosis (175). However, these studies were based on small, region-specific samples rather than national data, which limits the generalizability of their findings to the broader Saudi population. Given the limited Saudi evidence relating to factors associated with CRC development, Al-Zalabani examined the population-attributable fraction (PAF) of CRC cases linked to modifiable risk factors using relative risk data from international systematic reviews and meta-analyses. PAF estimates the proportion of CRC cases in a population that could be reduced in the absence of exposure to certain risk factors. The study found that overweight and obesity, physical inactivity, and smoking contributed to the rising CRC burden in the country (169). However, these results should be interpreted with caution, as the reliance on international data may not reflect actual exposures within the Saudi population. Hence, analyses based on large-scale national data are necessary to accurately estimate CRC risk factors among Saudis.

Regarding factors impacting CRC outcomes, Aldiab et al. noted that presenting with distant metastasis was linked to poor prognosis and survival in Saudi CRC patients (176). Population-based studies examining CRC survival rates by cancer stage are scarce in Saudi Arabia, mainly due to difficulties in accessing death records. Al-Ahwal et al. reported that the five-year overall survival rate for Saudi CRC patients from 1994 to 2004 was 44.6%. Survival rates varied by cancer stage, with the highest for localized cancers (63.3%), followed by regional (50.2%) and distant metastasis (14.7%) (177). Research on risk factors associated with late-stage presentation in Saudi CRC patients is limited. Identifying high-risk populations for advanced-stage CRC is essential for informing future research plans and developing targeted interventions, enhancing the effectiveness of the national screening program and cancer-control efforts in the country (178).

The Saudi healthcare system is undergoing transformative reforms, with various efforts being implemented to prevent chronic diseases and improve public health outcomes. Ensuring efficient resource allocation and the delivery of high-quality healthcare is also prioritized. Developing a comprehensive understanding of CRC incidence trends—particularly age and stage-specific trends— and identifying demographic and clinical factors associated with late-stage CRC are warranted. Additionally, with the relatively recent launch of the national screening program, it is imperative to explore the public's awareness of CRC and their acceptance and perceptions of CRC screening.

A detailed analysis of the CRC burden will enhance cancer control promotional efforts, inform public health policies, such as screening age recommendations, and support evaluations of the recently established national screening program and integrated care model.

1.15 Chapter summary

CRC is a global public health concern associated with substantial health, economic, social, and psychological burdens. Recent trends in CRC incidence among individuals aged 50 and older have been stabilizing or declining, mainly in high-income countries, due to the implementation of screening programs. However, several reports highlighted increased CRC incidence among patients <50, defined as EO-CRC. This observation has stimulated global research efforts examining disease patterns and etiology within this demographic. Global screening guidelines are mostly consistent, with some recommending the initiation of screening at age 45 instead of 50. Existing evidence supports the cost-effectiveness of screening and its impact in reducing CRC incidence and mortality. Hence, understanding factors influencing screening uptake is crucial for improving health promotion and prevention strategies.

Cancer registries are essential in cancer control and surveillance, providing data to estimate CRC incidence rates and trends. However, inconsistencies in calculating and reporting incidence can hinder accurate comparisons and interpretations of regional and global data, which are necessary to inform public health efforts. Knowledge of the most commonly used incidence measures and the quality of reporting methods is currently lacking. Such understanding is imperative for investigators undertaking epidemiological research, informing their methodological approaches, and improving their reporting practices.

In Saudi Arabia, the healthcare system is undergoing major reforms to enhance disease prevention and improve healthcare quality and access. The SCR provides a valuable resource for data, facilitating the monitoring and understanding of CRC trends and potentially informing screening decisions in Saudi Arabia. A national CRC screening program was recently established to curb the rising CRC burden. The program targets average-risk individuals aged 45 to 75.

Despite these national efforts, reports examining the evolution of CRC incidence patterns by age are limited. A substantial proportion of CRC cases are diagnosed at an advanced stage, yet incidence rates trends by disease stage and factors associated with a late-stage diagnosis remain unclear. Moreover, the public's awareness, perceptions, and attitudes toward CRC screening and the current national program are currently unknown. A comprehensive examination of incidence trends, high-risk groups for advanced CRC, and factors influencing screening uptake is essential for informing public health policies, enhancing promotion strategies, and evaluating current healthcare reform efforts.

1.16 Aims and objectives

In this thesis, I aim to strengthen the evidence for CRC screening policies and programs in Saudi Arabia by providing robust, reliable, and comparable data on the disease's burden. I will use data from the SCR to monitor disease trends and identify high-risk groups. I will also explore public perceptions of screening. The insights gained from this comprehensive analysis will inform and guide recommendations for enhancing CRC control and prevention strategies within the country.

To achieve these aims, four objectives have been set, which were to:

1. Systematically review population-based studies measuring CRC incidence rates and trends to summarize and examine variations in estimating and reporting incidence and evaluate the quality of reporting incidence methods.

2. Conduct a retrospective cohort analysis to examine CRC incidence rates and trends in Saudi Arabia, with a focus on age and stage-specific trends stratified by sex.
3. Undertake a retrospective analysis of Saudi CRC cases to identify clinical and demographic characteristics linked to late-stage diagnosis.
4. Utilize qualitative interviews to explore Saudi's knowledge of CRC, their perceptions of CRC screening, and the factors influencing their screening decisions.

1.17 Thesis design and overview

Public health prevention efforts require more than just an understanding of quantitative data, the "what"; they also need an in-depth exploration of the perceptions, attitudes, and behaviours, the "why", that contribute to the disease burden (179). In this thesis, I used an explanatory sequential mixed methods design to comprehensively understand CRC epidemiology in Saudi Arabia and the factors influencing screening uptake. This mixed-method approach begins with quantitative methods, followed by qualitative methods, aiming to provide a deeper understanding of the findings (180). In this design, data integration, where quantitative and qualitative data are synthesized, can occur at one or more points during the research process—from formulating research questions and designing studies to interpreting the overall findings (181,182). Data integration was implemented at three points in this thesis. Initially, at the study design phase, an explanatory sequential mixed methods design was adopted, developing quantitative and qualitative research questions based on a literature review that highlighted gaps in CRC epidemiology and public perceptions of the CRC early detection program in Saudi Arabia. The qualitative phase aimed to delve deeper into insights that contextualize the quantitative data. Furthermore, the findings from the first quantitative study informed the research question of the subsequent quantitative analysis.

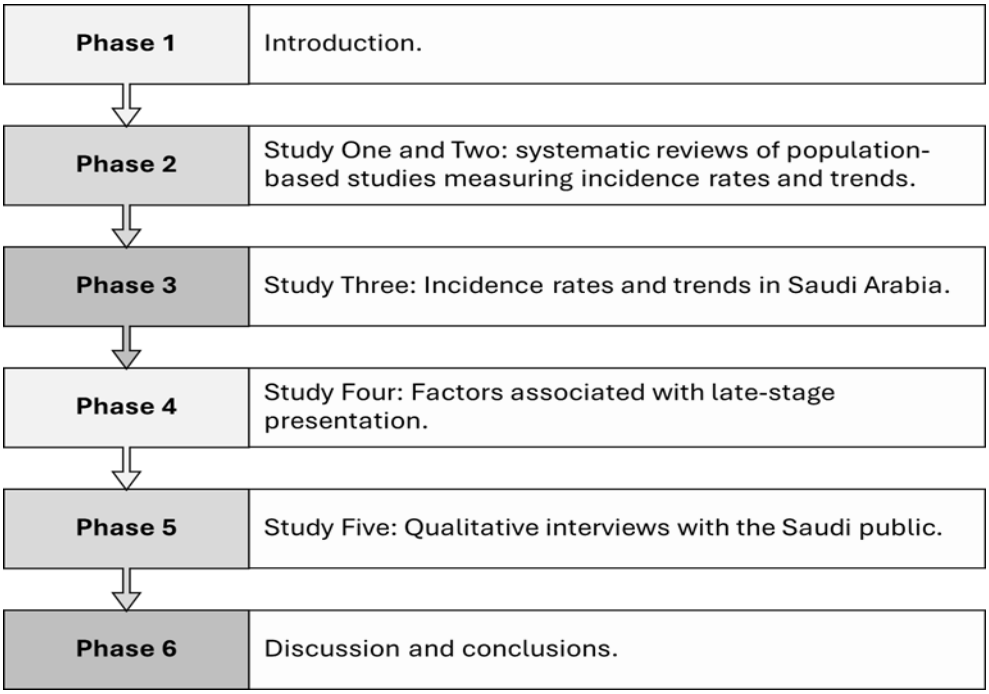
Further integration at the methodological level was achieved through two main connections: firstly, systematic reviews informed the methodologies and reporting practices in the quantitative studies; secondly, quantitative results guided the data collection methods, specifically sampling selection, for the qualitative analysis. The final integration occurred at the interpretative level within the discussion section of this thesis. Here, I presented the main results from both the quantitative and qualitative studies, followed by a comprehensive synthesis that highlighted combined conclusions and recommendations. Additionally, these results provided the basis for outlining implications for practice and future research directions. The following sections provide a more detailed description of the thesis phases and studies.

At the beginning of this thesis, I reviewed the literature to set the context for this thesis, describing the global burden of CRC, the role of screening in prevention and early detection, and the importance of cancer registries in monitoring CRC and guiding public health interventions. I highlighted the challenges in comparing CRC incidence due to variations in employed methodologies. Given the thesis's focus, I also described various aspects of CRC epidemiology in Saudi Arabia, including incidence rates, risk factors, and screening practices, and identified gaps that warrant further investigation.

Chapter Two describes a systematic review of population-based studies using cancer registries to examine CRC incidence rates. I summarized and described variations in commonly used incidence rate measures and evaluated the quality of reporting incidence estimation methods. In Chapter Three, I systematically reviewed population-based studies measuring incidence trends to summarize the commonly used incidence trend methods and assess the quality of their reporting. Findings from Chapters Two and Three provided overall guidance on the use of cancer registry data in understanding incidence rates and trends. They also informed methodological choices and reporting practices for the quantitative studies. Insights from the systematic reviews are valuable for improving the communication of incidence calculations and results, enabling accurate interpretations and comparisons of incidence across regional and global populations.

Chapter four presents a quantitative study to examine CRC incidence rates and trends in Saudi Arabia, focusing on evaluating trends by age, sex, and stage at diagnosis. Findings from this chapter informed the research question for the quantitative study presented in Chapter Five. This study aimed to identify clinical and demographic characteristics associated with late-stage presentation, thereby highlighting high-risk subgroups requiring further attention. The findings from Chapters Four and Five informed the sample selection for the qualitative study described in Chapter Six. In this study, I conducted interviews to explore Saudis' awareness and perceptions of CRC screening and identify factors influencing their screening behavior. Finally, Chapter Seven discusses the thesis results, implications, and conclusions. Figure 1.1 illustrates the phases of the thesis.

Figure 1. 1. Overview of thesis phases



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Chapter 2: A systematic review of methods to estimate colorectal cancer incidence using population-based cancer registries

Authors List: Norah Alsadhan[1,2], Alaa Almaiman[1], Mar Pujades-Rodriguez[2], Cathy Brennan[2], Farag Shuweihdi[2], Sultana A Alhurishi[1], Robert West[2]

Affiliation list:

1. Department of Community Health Sciences, College of Applied Medical Sciences, King Saud University, Riyadh, Kingdom of Saudi Arabia.
2. Leeds Institute of Health Sciences, School of Medicine, University of Leeds, Leeds, United Kingdom.

Study One	
Journal	BMC Medical Research Methodology.
Publication status	Published in May 2022.
Reference	Alsadhan N, Almaiman A, Pujades-Rodriguez M, Brennan C, Shuweihdi F, Alhurishi SA, West RM. A systematic review of methods to estimate colorectal cancer incidence using population-based cancer registries. BMC Med Res Methodoly. 2022;22(1):144.

Commentary

This chapter builds on the research context presented in Chapter One, highlighting the rising CRC burden and the importance of robust epidemiological evidence to guide cancer control plans. Chapter One indicated existing variability in how CRC incidence is calculated and reported, both globally and within the Saudi literature. This inconsistency is often related to variations in the operational definitions of the numerator, denominator, and population at risk—Key components of incidence calculation. Additionally, it highlighted the need for high-quality data and transparent reporting of incidence calculation methods to support accurate interpretation of data, meaningful comparisons of CRC burden across populations, and the development of effective cancer control strategies. However, the quality and transparency of reporting incidence methods in the epidemiological literature remain unclear, underscoring the need to examine and evaluate current practices.

One of the main objectives of this thesis is to examine CRC incidence rates and trends within the Saudi population. Thus, establishing a clear understanding of how to generate valid and comparable incidence estimates is essential. To support this aim, Chapter Two presents a systematic review of population-based studies using cancer registry data to measure incidence. The review assesses how CRC incidence rates are measured and reported. It also identifies common methodological and reporting limitations that require further attention to enhance the quality and comparability of future epidemiological research.

The inclusion and exclusion criteria presented in Table 2.1 in this chapter were selected to ensure the relevance of studies included and assessed in this review. Only population-based retrospective studies using cancer registry data to measure CRC incidence were included. These studies' focus aligns with the thesis's aim to examine and understand how incidence is measured and reported in population-level epidemiological research. Although limiting the review to English-language publications may introduce some bias, its impact on studies from Saudi Arabia and other Arab countries is likely minimal, as these are commonly published in English.

Excluded studies included those that examined the incidence of multiple cancer types, focused solely on benign tumors, or used external data sources for incidence estimates. Such studies often lack a specific focus on CRC or may not provide sufficient methodological information to assess the quality of incidence reporting based on the 11 predefined criteria used in this review. Case studies, clinical trials, and case-control studies were also excluded as they often lack the large-scale

population focus, and their main objective might not be to measure incidence, limiting the availability of relevant methodological details.

Similarly, commentaries, reviews, conference proceedings, abstracts, and posters were excluded due to the limited methodological information they usually present, hindering a meaningful evaluation of incidence estimation methods. Finally, as this review aimed to examine incidence reporting in general populations, studies restricted to selected patient groups were excluded.

2.1 Abstract

Background: Epidemiological studies of incidence play an essential role in quantifying disease burden, resource planning, and informing public health policies. A variety of measures for estimating cancer incidence have been used. Appropriate reporting of incidence calculations is essential to enable clear interpretation. This review uses colorectal cancer (CRC) as an exemplar to summarize and describe variation in commonly employed incidence measures and evaluate the quality of reporting incidence methods.

Methods: We searched four databases for CRC incidence studies published between January 2010 and May 2020. Two independent reviewers screened all titles and abstracts. Eligible studies were population-based cancer registry studies evaluating CRC incidence. We extracted data on study characteristics and author-defined criteria for assessing the quality of reporting incidence. We used descriptive statistics to summarize the information.

Results: This review retrieved 165 relevant articles. The age-standardized incidence rate (ASR) (80%) was the most commonly reported incidence measure, and the 2000 US standard population the most commonly used reference population (39%). Slightly more than half (54%) of the studies reported CRC incidence stratified by anatomical site. The quality of reporting incidence methods was suboptimal. Of all included studies: 45 (27%) failed to report the classification system used to define CRC; 63 (38%) did not report CRC codes; and only 20 (12%) documented excluding certain CRC cases from the numerator. Concerning the denominator estimation: 61% of studies failed to state the source of population data; 24 (15%) indicated census years; 10 (6%) reported the method used to estimate yearly population counts; and only 5 (3%) explicitly explained the population size estimation procedure to calculate the overall average incidence rate. Thirty-three (20%) studies reported the confidence interval for incidence, and only 7 (4%) documented methods for dealing with missing data.

Conclusion: This review identified variations in incidence calculation and inadequate reporting of methods. We outlined recommendations to optimize incidence estimation and reporting practices. There is a need to establish clear guidelines for incidence reporting to facilitate assessment of the validity and interpretation of reported incidence.

2.2 Introduction

Epidemiological studies of incidence play an essential role in quantifying disease burden, healthcare resource planning, and informing public health policies. Incidence is a crucial measure of epidemiology representing the number of new disease cases in a specific population divided by the population's size at risk during a particular period (1). A variety of measures for estimating cancer incidence in population-based studies have been reported in the literature. The magnitude and interpretation of incidence estimates depend on methodological choices such as the definition of numerator and denominator and the standard population used to calculate the age-standardized rate (ASR) (1-4).

Variations in incidence calculation influence comparisons of regional and global rates and trends and their interpretation. Thus, crucial requirements for generating comparable and reproducible incidence statistics include: i) a precise definition of the disease of interest with a specification of the classification used and coding, ideally validated within data source; ii) a clear description of the numerator data and the population at risk; and iii) an explicit explanation of the methods used to estimate denominator size (1, 5, 6). Additionally, quantifying and reporting uncertainty around health estimates in population-based studies is imperative to inform readers who draw conclusions from these estimates (7,8).

Population-based studies often utilize data from cancer registries to derive incidence statistics. The primary purpose of these registries is to provide a reliable source of information for assessing cancer risk. The International Agency for Research on Cancer (IARC) advises registries to continually evaluate data quality by several quantitative and qualitative methods (5, 9). Yet, the extent of detail provided by researchers about these quality indicators remains unclear, and results of evaluations are rarely publicly available.

Furthermore, cancer registries rely on trained registrars to abstract data from patients' medical records. Some abstracted data may be incomplete due to human error or poor quality documentation within the medical record, leading to inaccurate and missing values within cancer registries (10). Thus, quantification of missingness, explicit and detailed reporting of assumptions and handling of missing data help readers make informed interpretations of the findings.

There is a growing body of evidence to suggest that the level of reproducibility in scientific research is inadequate. Poor reporting of incidence methods might negatively affect research findings' credibility, comparability, and reproducibility (11). The Enhancing the Quality and

Transparency of Health Research (EQUATOR) network provides reporting guidelines for observational studies; yet none of the current guidelines adequately address the reporting of methods used in measuring incidence.

Because it was not practical to consider all cancers in this study, we chose colorectal cancer (CRC) as an exemplar. CRC is of particular interest due to its increasing global burden among women and men and to the role of screening in prevention and early detection. CRC is a type of cancer that starts in the rectum or colon. CRC can be categorized into three sub-types based on its anatomical site: proximal colon, distal colon, and rectum (12). According to the GLOBOCAN 2020 estimates of cancer incidence, CRC is the third most common cancer and the second leading cause of cancer-related deaths worldwide (13). The rate of CRC has been steadily increasing in some regions (14). Survival outcomes for CRC are closely related to the cancer stage at diagnosis (15), and thereby it is one of the few cancers where screening is considered a key preventive measure (16). A growing number of population-based studies globally have been closely monitoring CRC incidence. Yet, fair comparisons of CRC incidence estimates between different data sources or countries depend on the methods used, which must be explicitly reported.

This article aims to systematically review population-based studies using cancer registries to measure CRC incidence, summarize and describe variation in the commonly employed incidence measures, and evaluate the quality of reporting incidence methods. Our review was set up to answer the following questions: 1- What are the most reported incidence measures for estimating CRC incidence?; 2- What standard populations are commonly used to estimate the age-standardized rate in population-based studies?; 3- Are CRC incidence rates commonly stratified by anatomical site?; 4- What is the quality of reporting the methods used to estimate CRC incidence?

2.3 Methods

The reporting of this systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (17).

2.3.1 Study identification

We developed a search strategy in consultation with an information specialist. The search included keywords and a combination of subject headings incorporating “colorectal cancer,” “incidence,” “trends,” and “registry” (the complete search strategy is provided in Appendix A.1). We limited the search to articles written in English and to studies published from 1 January 2010 to 31 May 2020. Adding a time frame to the search strategy helped select the most up-to-date

studies. The electronic literature search included Embase, Medline, Web of Science, and the Cochrane Library. We also checked reference lists of identified articles for identification of additional potentially relevant articles missed.

2.3.2 Study selection

Studies were eligible for inclusion in this review based on the inclusion and exclusion criteria presented in Table 2.1.

Table 2. 1. Inclusion and exclusion criteria employed

Inclusion criteria	• Population-based retrospective studies using registry data to measure and report the incidence of colorectal cancer. • English language. • Full text published. • Published in a peer-reviewed journal.
Exclusion criteria	• Studies exclusively measuring the incidence of benign tumours. • Studies measuring incidence of multiple cancer types. • Studies reporting incidence measures from external resources. • Published commentaries. • Case studies, clinical trials, case-control studies, reviews. • Conference proceedings, abstracts, posters. • Studies conducted in selected population groups (i.e., incidence rates amongst patients with specific diseases).

2.3.3 Selection process

We imported all potential abstracts into the web app “Rayyan” (a screening software) (18), and two independent reviewers screened all titles and abstracts using the inclusion-exclusion criteria. Any disagreements between reviewers were resolved through discussion. If a consensus decision was not reached by screening the title and abstract, the reviewers examined the full text. We calculated the inter-reviewer agreement rate for title/abstract screening using Cohen’s κ statistic (results are presented in Appendix A.2). After the screening process, we further assessed articles

selected for full-text review. In cases where eligibility was unclear, we consulted a third reviewer for a final decision. Details of the selection process are displayed in Figure 2.1.

2.3.4 Data extraction and synthesis

We developed and piloted two standardized extraction forms. Form A was used to extract general details about the study, including author and publication year, country, cancer type, main study outcomes, observation period, measures of incidence rate, and the anatomical site used in incidence calculation. Form B was for extracting data necessary to assess the quality of reporting the methods used to calculate incidence. We defined a list of potential indicators to evaluate the reporting quality based on relevant literature on incidence calculation (1-3) and the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER) statement for reporting global health estimates (6). This criteria list included: the quality of cancer registry data, the definition of CRC, definition of the numerator, estimation of the denominator, the time interval over which incidence was calculated, presentation of incidence rates, standardization process of rates, age bands for measuring incidence, assessment of uncertainty, evaluation of missing data, and software information. A detailed description of each of these criteria is provided in Table 2.2. One reviewer extracted the data for all included studies, and a second reviewer cross-checked a random sample of 25% (n=41). Discrepancies were resolved by consensus agreement.

Table 2. 2. Criteria for assessing the quality of reporting incidence methods

Criterion	Description
Quality of cancer registry data	The extent to which each study reported details about the quality of the cancer registry data
Definition of colorectal cancer	Report the following: • The used classification system to define CRC. • CRC codes (including topography (anatomical site) and morphology (histology, behavior, and grade) codes). • Conversion of ICD codes, if needed. • Type of cancer (primary/secondary).
Definition of the numerator	Report any restrictions on included CRC cases
Definition of the denominator (population at risk)	Report the following: • The data source for the general population.

	• The used census years in estimating the at-risk population. • The methods used for obtaining postcensal and intercensal population estimates. • The estimation of annual mid-year population. • The calculation method for estimating average population size over several years of observation.
Age-standardized rates (ASRs)	Report the following: • The standardization method used to calculate age-standardized rates (ASRs). • The standard population used in the analysis and why this standard was chosen.
The time interval over which incidence is calculated	Report the time interval over which incidence is calculated (e.g., annual, overall average)
Presentation of incidence rates	Incidence rates are expressed with a time unit (whole years or person-time)
Age bands for measuring the incidence	Report the age bands used for measuring and documenting incidence
Assessment of uncertainty	Report the 95% confidence intervals for the Incidence rate
Assessment of missing data	Report missing data assessment and analysis
Software information	Report Software information in the manuscript

2.3.5 Quality assessment

We appraised the quality of all included studies using a prespecified checklist adapted for this review and based on the Joanna Briggs Institute Critical Appraisal tool for prevalence studies (19) and the Appraisal tool for Cross-Sectional Studies (AXIS) (20). Both of these tools were previously employed in a systematic review assessing CRC incidence rates (21). We chose relevant criteria from each tool to create a 10-item checklist for this study. Items were assigned a score of 1 if "demonstrated in the study" or 0 if "not demonstrated or unclear". We calculated and presented an overall quality score for each study. Quality appraisal checklist and results of quality assessment are presented in Appendices A.5 and A.6.

2.3.6 Data analysis

The characteristics of included studies, incidence methods, and the quality of reporting incidence were all described in tables. We used descriptive summary statistics to analyze the extracted data and reported the results as frequencies and percentages.

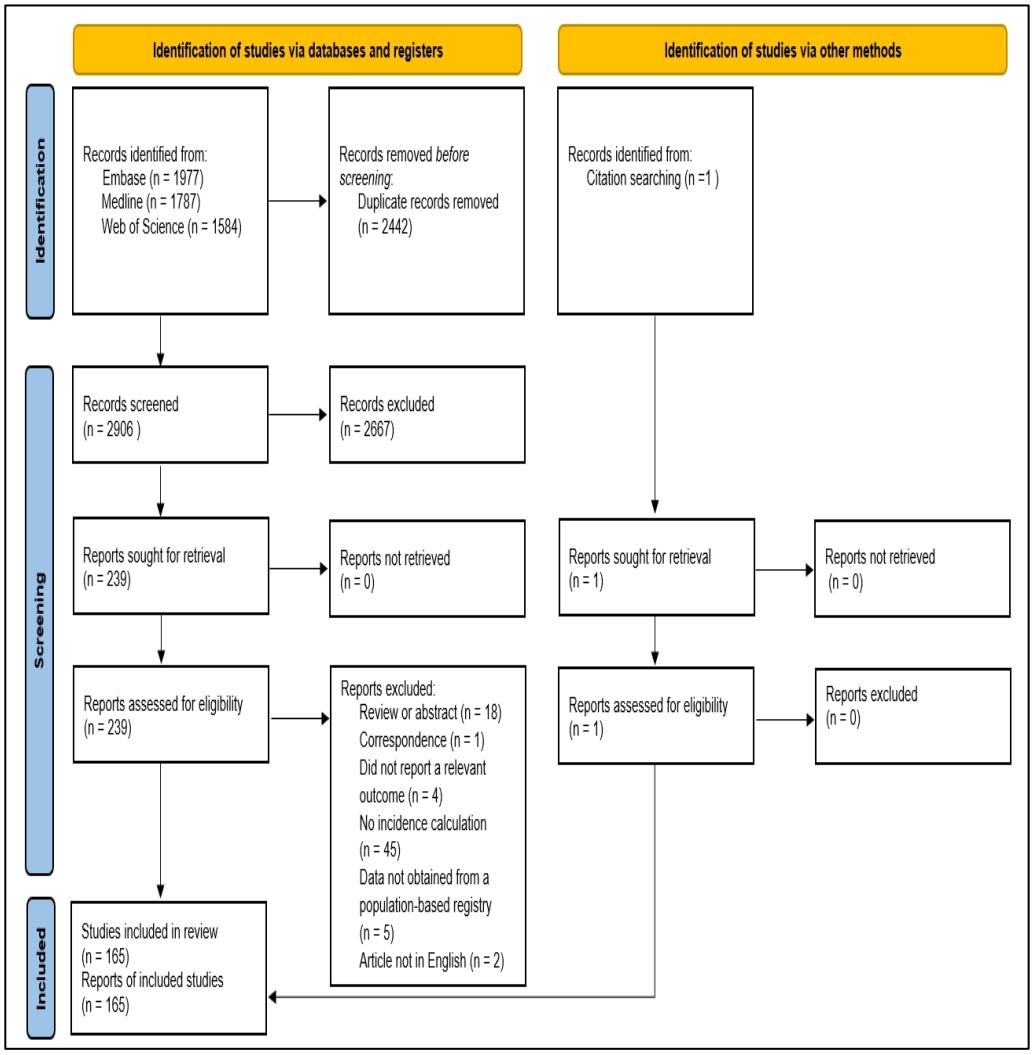
2.4 Results

The combined search initially yielded 5,348 papers, and after the deletion of duplicates, we identified and screened 2906 titles. The inter-reviewer agreement for the title/abstract screening had a Cohen's κ value of 94% (Appendix A.2). After applying the inclusion-exclusion criteria, 165 titles were deemed eligible for the systematic review. Details on excluded reports are depicted in the PRISMA flow diagram (Figure 2.1).

2.4.1 Characteristics of included studies

The eligible articles comprised studies from North America, including the United States of America (USA) (n=66, 40%) and Canada (n=5, 3%), Oceania (n=7, 4%), Europe (n=38, 23%), Asia (n=36, 22%), Africa (n=5, 3%), Central and South America (n=2, 1%), and six (4%) multi-country study. In addition to incidence, the two other study outcomes most commonly reported were mortality (n=41, 25%) and survival (n=36, 22%). Most studies evaluated the incidence of colorectal cancer (n=160, 97%), while the remaining evaluated the incidence of either rectal or colon cancer (n=5, 3%). All studies reported the observation period over which incidence was calculated. The periods covered ranged from a single year (n=5, 3%) to 55 years of observation, and 79% covered a study period of ten years or more. The characteristics and details of included studies (22-187) are provided in Appendices A.3, A.7, and A.8.

Figure 2. 1. PRISMA flowchart of the study selection process



2.4.2 Measures of incidence rate

The most commonly reported measure of incidence was the age-standardized incidence rate (ASR) (n=132, 80%), followed by the age-specific incidence rate (ASIR) (n=50, 30%), and the crude rate (CR) (n=31, 19%). Five studies reported the calculation of the ASIR but did not present the results of this analysis in the manuscript (22, 30, 34, 36, 62). The cumulative incidence rate and cumulative risk were reported in three and seven studies, respectively. Some studies also reported the truncated ASR (n=3, 2%), the delay-adjusted rate (n=4, 2%), and the risk-adjusted rate (n=1, 1%) (Table 2.3).

Eighteen studies (11%) reported the incidence rate with no further specification. Two of these studies described the incidence as mainly the frequency of new cases (77, 150), four obtained incidence rates via linear modelling (32, 41, 48, 159), and two defined incidence as the percentage

of CRC cases among different age groups (119, 120). Additional details are provided in Appendices A.3 and A.7.

Table 2. 3. Description of the types of measures used for reporting incidence

Incidence measure (as reported)[a]	**Definition** [1, 89, 132]	***N* (% out of 165)**
Age-standardized incidence rate (ASR)	A weighted average of the age-specific incidence rate (weights are from a standard population)	132 (80.0)
Age-specific incidence rate (ASIR)	The number of new cases in a specific age group divided by the corresponding person-years of observation in that particular age group, multiplied by a constant	50 (30.3)
Crude incidence rate (CR)	The number of new cancer cases divided by the total number of person-years of observation, multiplied by a constant	31 (18.8)
Cumulative incidence rate	The total age-specific incidence rate for each year during a specific age span (commonly expressed as a percentage)	3 (1.8)
Cumulative risk	The probability of developing cancer within a specific age span (usually between 0–74), in the absence of competing causes of death (calculated by a formula using the cumulative rate)	7 (4.2)
Truncated ASR	The ASR calculation is restricted to a specific age range (usually 35-64)	3 (1.8)
Delay-adjusted rate	The incidence rate is corrected for the lag in case capture, which affects recent data years	4 (2.4)
Risk-adjusted rate	The numerator in the rate calculation is adjusted for secondary cancers of the same site, and the denominator is adjusted for prevalent cases	1 (0.6)

Incidence rate: • **Derived from modelling** • **Reported as the frequency of new cases** • **Reported as the percentage of CRC cases among various groups**	The number of new disease cases in a specific population divided by the population's size at risk during a particular period	18 (10.9) 4 2 2

[a] Some studies reported more than one incident measure.

2.4.3 The standard population for calculating the age-standardized rate

The 2000 US standard population was the most commonly reported reference population (n=52, 39%), mainly by studies from the USA. The World standard population developed by the World Health Organization (WHO) was the second most reported reference population (n=27, 20%), followed by the European population (n=23, 17%), and the Segi standard population (n=16, 12%)- an older version of the World standard population. Appendix A.4 provides further details on the reported standard populations used in calculating the ASR.

Of the 127 studies that reported a standard population for ASR estimation, 64 (50%) reported a local reference, 71 (56%) employed an external standard, and four (3%) used both a local and an external standard population (65, 82, 143, 181).

All studies that aimed to conduct international comparisons of ASRs used an external reference population (n=13); three however compared their ASRs with studies that used a different standard population for measuring ASR (44, 97, 175). Among studies that used standardized rates to assess local incidence rates (n=114), 62 (54%) employed a local reference, while 52 (46%) used an external standard population.

2.4.4 Stratification of incidence rate by anatomical site

This review noted that 54% of the 160 identified studies that reported CRC incidence stratified rates by anatomical site. There were variations in terms of the anatomical sites chosen. Of the 86 studies that reported incidence stratified by anatomical location, 77 (90%) stratified rates according to the site (colon/rectum), 33 (38%) by colon site (proximal/distal), and 11 (13%) by the categorization of CRC into “right-sided” or “left-sided” tumour. Seven studies (8%) reported the incidence rate for multiple anatomical sites within the colon, and only four (5%) reported the anus incidence. Details on the anatomical sites used for CRC incidence stratification are provided in Appendices A.3 and A.7.

2.4.5 The quality of reporting incidence

Table 2.2 describes the 11 criteria employed to assess quality of incidence reporting. Detailed results for all indicators are provided in Appendices A.3 and A.8.

2.4.5.1 The quality of cancer registry data

Eight studies (5%) reported indicators of data validity, such as the proportion of morphologically verified cases (MV%), percentage of death certificate only cases (DCO%), and mortality to incidence ratio (M/I). Of these studies, five reported estimates for at least one of these indicators (62, 82, 109, 148, 181), and three reported estimates based on external references (139, 173, 184).

Ten studies (6%) cited a reference for previously conducted research as evidence of cancer registry data quality (8 referenced studies or reports including validation or completeness assessments; 2 referenced similar epidemiological studies conducted in the same data source). Six studies (4%) reported that data quality was checked by a cancer registration program such as CanReg4 and CANREGT, but none of these studies provided further details on their inspection results. Singh et al. (154) indicated complete case ascertainment of cancer data used to estimate incidence, but without referencing a specific study. Nine studies (6%) indicated that registration quality was being audited by a certification body. Seven reports (4%) stated that the cancer registry was meeting or utilizing standards for data quality set by national or international agencies. None of these studies provided details on specific quality indicators.

2.4.5.2 The definition of colorectal cancer

There were variations in how studies defined CRC. Only 31 studies (19%) reported whether primary or secondary cancers were considered in the incidence calculation. Forty-five articles (27%) failed to report the classification system used to determine CRC, and 63 (38%) did not provide information about the CRC codes considered. Some studies (n=32, 19%) failed to report both the classification system and CRC codes. In terms of CRC coding, six studies reported only morphological codes, 11 topography and morphology codes, and 85 only topography codes. Furthermore, only 28 articles (17%) explicitly stated whether malignant or in situ cancers were included in the incidence analysis.

Among the studies reporting the classification system used (n=120, 73%), the third revision of the International Classification of Disease for Oncology (ICD-O) was the most commonly reported (n= 63, 53%) to define CRC, followed by the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD) (n=40, 33%).

Of the 40 studies using the ICD-10 classification system, thirteen (33%) included data from years that preceded its development in 1992. Most of these 13 studies (n=12) failed to document whether they used a different classification system for earlier years or if they mapped codes. Only Wu et al. (174) reported converting earlier ICD codes into those used in the 10th revision. Similarly, of the 63 articles that used the ICD-O-3rd edition, 23 (37%) included data from years that preceded the development of the 3rd or even the 2nd edition of ICD-O with no information provided about conversion of earlier codes.

2.4.5.3 Definition of the numerator

Concerning the reporting of the numerator data, only 20 studies (12%) explicitly explained excluding certain CRC cases from the numerator. The exclusion of non-microscopically confirmed cases (25, 35, 50, 64, 68, 108, 110, 166), and in-situ cancers (54, 65, 68, 110, 145) were the most reported. Details on other restrictions for included CRC cases are provided in Appendix A.3.

2.4.5.4 Definition of the denominator

Concerning reporting of denominator size estimation, over half of the studies failed to state the source of population data used to analyze incidence (n=100, 61%). Only one study explained the calculation used to estimate the annual mid-year population (174). Twenty-four (15%) of the 165 identified studies indicated the census years employed to derive population counts. Ten studies

(6%) reported the method used to estimate yearly population counts (i.e., interpolation or extrapolation).

Only five studies (3%) explicitly explained the population size estimation procedure in calculating the overall average incidence rate (for a given study period). Of these, one study calculated actual person-time at risk by creating closed cohorts of the population on various census nights and following them over time (126). Three estimated the average population size by multiplying the population count in a particular census year by the number of years included in the study (54, 156, 157). Sammour et al. (118) estimated the denominator size by averaging population counts of two censuses conducted at the beginning and near the end of the study period.

2.4.5.5 Estimation of the age-standardized rate

Of the studies that calculated the ASR (n=132, 80%), 36 (27%) described the method used for standardization (direct or indirect), with the direct method being the only one reported. Five studies did not report the standard population used to derive ASR.

Of the 127 studies that reported the reference population used for standardization, only five (4%) justified their chosen standard population. Four studies explained that choosing an external (international) reference population will enable future comparisons of incidence rates with other published studies (25, 45, 49, 177). Jayarajah et al. (83) reported using the WHO World standard population due to its similarity to the age structure of Asian populations.

2.4.5.6 Time interval and presentation of the incidence

Concerning the time interval over which incidence was calculated, over half the studies (n=103, 62%) did not explicitly report whether they calculated a single year or an overall average rate. Assessing how incidence rates were expressed among all included studies, we noted that most articles (n=119, 72%) expressed rates without a time unit (i.e., whole years or person-time).

2.4.5.7 Age bands for measuring the incidence

Among the 165 identified studies, the majority (n=131, 79%) reported the age bands used to calculate incidence. The age bands used for calculating incidence ranged from one (n=12) to 33 (n=1). Detailed information on all reported age bands is provided in Appendix A.3.

2.4.5.8 Assessment of uncertainty and evaluation of missing data

Concerning uncertainty analysis, only 20% (n=33) reported the confidence interval (CI) associated with the incidence estimate. In examining the reporting of missing data (MD), seven studies (4%) reported details on how MD were handled in the analysis but failed to report assumptions on the reasons for the MD. Of these studies, five reported excluding incident cases with specific MD (53, 92, 99, 111, 114), another study estimated MD by multiple imputation (96), and Zorzi et al. (184) estimated missing variables via join point regression. Missing data in these studies included demographics (such as age, sex, race, country of residence), anatomic subsites, disease stage, and the number of incident cases for some of the years evaluated. One author assumed MD was missed at random, with no justification for this assumption or treatment method reported (115). Rejali et al. (151) vaguely indicated that incidence rates were corrected for the missing age-related data. Only two studies reported the exact amount of MD (96, 151).

2.4.5.9 Software information

More than half of the studies (n= 110, 67%) reported the software used for incidence rate analysis. The most common was The Surveillance Epidemiology and End Results (SEER) statistical software (36%) (188), mainly by studies from the USA. Other reported software included SAS (17%) (189), STATA (16%) (190), and SPSS (16%) (191) (Appendix A.3).

2.5 Discussion

To our knowledge, this is the first study to examine variations in the methods employed in calculating CRC incidence rates and the quality of reporting these methods. The 165 articles retrieved provided valuable findings and insights that will aid future investigators in making informed decisions about which methods and reporting practices will enhance the quality and comparability of their research.

2.5.1 Measures of incidence rate

Incidence is an essential measure in epidemiology that examines the burden of a disease in a population and highlights variations among different population subgroups. Therefore, incidence measures are imperative for underscoring health care needs and developing policies and interventions accordingly. This review noted that the age-standardized rate (ASR) was the most commonly reported measure of incidence. Only one-third of the studies examined the age-specific incidence rate (ASIR).

ASR is an artificial rate that facilitates comparative analysis as it controls for differences in the population age structure. Relying only on ASRs to describe incidence might conceal valuable information. Thus, the ASIR should always be the starting point when researchers want to derive an accurate measurement of cancer risk in a population (2, 192). Because ASIRs do not always have a consistent pattern over time, researchers should evaluate patterns of age-specific rates before applying standardization. This analysis would help determine how rates change over time in certain age groups and highlight any irregular patterns requiring further investigation. Furthermore, when possible, researchers should also assess potential effects of birth cohorts (exposures/experiences that vary from one generation to the next) and period (external factors that affect all age groups similarly at a specific calendar time) on age-specific trends (193). Thus, after initially calculating and graphically presenting the ASIR for different periods or cohorts, regression analysis could be employed to disentangle the effects of age, cohort, and period. This type of analysis however can only be performed when appropriate data is available for long time periods.

In addition to the ASIR, the cumulative rate, usually expressed as a percentage, can be calculated to understand the lifetime risk of developing cancer. This measure reflects the probability of developing cancer over a specified age range, usually from birth to 74 years. It is calculated by summing the ASIR for all age groups and multiplying the total by the width of the age group. The cumulative rate is considered a simplified form of direct age-standardization as it assumes equal population sizes across age groups, eliminating the need for an external, arbitrary standard population. Therefore, it may more accurately reflect the actual disease burden within a population. Furthermore, it offers an estimate of cumulative risk, defined as the lifetime probability of developing cancer in the absence of competing causes of death (1). Cumulative rates and risks are valuable estimates for understanding and communicating the overall cancer burden and guiding public health planning.

In calculating the ASR, only 12 studies, in addition to studies from the USA, employed a local reference, and no study used an internal standard population (the average age distribution of all groups studied). The selection of a standard population is somewhat arbitrary and depends on the study's goals (194). When the aim is to assess temporal patterns of incidence in a specific population, it is vital to carefully choose a standard that better reflects the study population's age distribution. On the other hand, when the goal is to compare rates between different populations, an international standard might better serve this purpose (192). This review noted that most studies failed to justify the selected standard population used to assess CRC incidence. External

standards were the most commonly reported, even when a study's goal was not to compare rates internationally.

The selected standard population can influence the interpretation of incidence. Thus, studies with no international focus but an intention to assess temporal trends could use an internal standard population or employ the base-year population at the start of the study period as the standard (192). Conversely, if a study aims to compare incidence rates between different countries, conventional external standard populations, such as the WHO World standard (194) and the European standard (195), could be used. To facilitate international comparisons, the WHO emphasized implementing the new revised World standard population, proposed in 2001, reflecting the average age structure of all populations (194). Using the most updated and appropriate standard population is essential for a more accurate and updated representation of rates. This review noted that 16 studies employed an older version of the World standard- proposed by Segi in 1960- although the new WHO standard was a better fit given the observation study period. Likewise, the European standard (presented in 1976) was employed in six studies where a newer version was available.

Among studies from the USA, a common practice was to standardize rates using the 2000 US standard population. Although this usage is understandably justified, international comparisons with USA rates would be compromised. Meaningful comparisons between populations are only possible when the same reference population is employed. Therefore, investigators could report different ASRs computed by distinct standard populations (an external and the study's local population) for comprehensive incidence analysis.

In cancer epidemiology, providing incidence estimates according to cancer subsite may highlight critical differences in disease risk. This review noted a lack of consensus concerning the categorization of anatomical subsite for measuring CRC incidence. While almost half of the studies reported only an overall incidence measure for CRC, the other half provided rates according to different categorizations of anatomical sites (e.g., colon/rectal, proximal/distal colon, and right/left colon). Furthermore, descriptions of these anatomical categories varied across studies. Ideally, there should be a consensus among the scientific community on which CRC subsites to consider and on the anatomical categories. Using a standard definition will guide future researchers in reporting comparable incidence rates.

Additionally, when the main study aim is to quantify CRC burden, reporting overall CRC incidence in addition to site-specific rates would facilitate comparison with other studies and evaluation of

time trends. Yet, due to data limitations, it might not be feasible for some researchers to include specific subsites in the analysis or to measure site-specific rates. Clarifying these limitations would help the reader better understand the chosen analytical approach.

2.5.2 The quality of reporting incidence

This review uncovered several limitations in the quality of reporting incidence methods. There was a substantial deficit in reporting registry-data quality control procedures and findings. Population-based cancer registries (PBCR) play a unique role in monitoring and evaluating cancer control efforts. In measuring incidence, PBCR captures all cancer cases in a specified geographical area (numerator) and retrieves population statistics (denominator) from census data. To provide reliable information on cancer burden, it is of utmost importance to ensure that the data are valid and of good quality.

In 1994, The IARC published a report describing standards and methodologies for evaluating data quality in cancer registries (196). In 2009, two articles updated and summarised these methods in terms of four primary standard indicators: comparability, timeliness, completeness, and validity (5, 9). Comparability relates to the extent to which used classification systems and coding practices, and definitions of incidence align with international standards. Timeliness measures how promptly reliable cancer data are collected and reported. Completeness refers to the extent to which all cancer cases within a population are identified and recorded in the registry. Validity refers to the accuracy of case identification and coding. This review noted that no study reported details about timeliness issues although many publications didn't cover recent years in their observation, which may be related to data collection and reporting delays in the registry.

Despite WHO advocacy for strengthening cancer registries, according to the last volume of Cancer Incidence in Five Continents (197), only 65 of 194 WHO Member States provided high-quality cancer incidence data. The proportion of high-quality cancer registries included in the report was 100% in Oceania, 97% in North America, 88% in Europe, 69%, 53%, and 23% in Central and South America, Asia, and Africa, respectively. Additionally, there were considerable discrepancies in total population coverage between continents. Transparent reporting and presentation of quality indicator measures and any registry limitations are essential for accurate interpretation of cancer incidence.

This review noted insufficient reporting of CRC definitions in terms of classification system, codes, and cancer type (primary or secondary tumours). More authors relied solely on topography codes and ignored the importance of reporting the morphology of CRC cases included.

There were also discrepancies across studies concerning the anatomical sites included in CRC incidence calculation; thus, it is essential to comprehensively describe the codes used to define CRC. We also noted limitations in reporting codes conversion between different classification versions. The SEER program and the IARC provide tools to facilitate ICD code mapping between different versions (198, 199). Authors should clearly document any code conversion implemented. Concerning cancer type, the IARC has set international rules for defining cancer cases as primary or secondary (200). Cancer registries should use these rules to describe cancer or explicitly acknowledge situations where obtaining this information is not feasible.

Furthermore, this review revealed limitations in reporting the numerator and denominator data used for incidence calculation (e.g., excluding certain CRC cases from the numerator). Being explicit about such information is valuable for interpreting and comparing rates. However, it is important to note that cancer registries differ in the type of data collected. For example, some registries collect data regarding hereditary syndromes or risk factors for CRC, while others do not. Limitations in terms of data availability should be acknowledged.

More than half of the studies included in this review presented an overall average incidence measure although only five articles described the calculation of the total population estimate (over several years of observation). Furthermore, there was an evident lack in reporting the source of population data, how yearly mid-year population statistics were estimated, and the census years used for obtaining population statistics. In analyzing incidence rates, describing the estimation of the denominator is usually overlooked, especially when calculating the ASR. Although the standardization process controls for the effect of population age structure, some might understand this process as eliminating the impact of population structure on incidence rates (2). Population size estimations used as denominators have their limitations that authors should explicitly recognize. Explaining how these estimates were derived is essential for understanding cancer risk and ensuring that readers have sufficient details to reproduce the findings.

The results of this review also highlighted other deficiencies in reporting incidence rates, such as the indication of the time interval over which incidence is calculated, the expression of rates, and the reporting of uncertainty estimates. In terms of quantifying and reporting uncertainty around incidence estimates, we noted that only 33 studies reported CI. Population-based studies tend to

underestimate the importance of reporting CIs for estimates drawn from population-level data (201). For some researchers, the observed rates represent accurate measurements for the population rather than estimates, and thus, accounting for random error might not be needed. However, Redelings et al. (201) argue that as rates and trends tend to fluctuate randomly over time, due to a myriad of factors, reporting the CI is imperative for assessing the reliability of these estimates and will consequently aid the formation of public health interventions and policies (201).

This review also highlighted inadequate reporting of MD analysis, including assumptions on the reasons for the missingness and their justification, the amount of MD, and the methods used to handle them in the analysis. Reporting guidelines for observational studies emphasized the need for a complete and transparent reporting of missing data and its analysis (6, 202). Thus, researchers should explicitly acknowledge and document all details pertaining to MD analysis.

2.5.3 Strengths and limitations

To our knowledge, this study is the first to comprehensively review the methods employed to estimate incidence rate and the degree of quality and transparency in their reporting. The identified studies were conducted in different populations and settings. We used multiple indicators for quality assessment, based on relevant literature on incidence calculation and guidelines for reporting methods, which enriches the evidence provided in this review. Although detailed reporting of methods might sometimes be limited by journal policies (i.e., word count restrictions), information could be made available as supplemental or web-based data.

This review is limited to studies assessing incidence in CRC using registry data. Despite this, our results inform about the most commonly used measures of estimating disease incidence and provide general considerations for improving the quality of reporting for other cancer types or diseases.

Another limitation was limiting the search to articles published within the past decade to limit the scope of the review. Given that there have been no substantial changes to the measures used for estimating incidence rates, we believe that the time-frame restriction did not affect the findings. Although we searched multiple databases and included studies from different countries, we included only English articles in this review. Thus, we might have missed relevant papers in other languages.

2.5.4 Future research

This review highlighted variations in reporting standards despite continuous efforts by scientific organizations, such as the EQUATOR Network, to provide guidance to help achieve an acceptable standardized level of reporting.

The GATHER statement promotes good quality reporting of global health estimates by providing a list of items that should be described when reporting health estimates (6). Our review emphasized reporting some of the GATHER items relating to the study's methodology, including data source, the uncertainty of estimates, handling missing data, and software package. This study, however, recommends other areas for consideration when reporting incidence measures. Future research on disease incidence should comprehensively describe their methodology based on these recommendations. We hope this study will be the starting point toward developing a specific guideline for reporting disease incidence in large-population studies.

2.5.5 Conclusion

This review summarized the most commonly reported incidence measures and examined variations in estimating CRC incidence over the past decade. We also highlighted many deficiencies in incidence reporting and provided recommendations for future studies on how to optimize their communication of the methods used for estimating incidence. Ideally, reporting should provide sufficient detail on the methodology to enable replicating the analysis. Better reporting will facilitate interpreting and comparing results with other studies and help identify and address limitations of the analysis.

Declarations

Ethics approval and consent to participate: Not applicable

Consent for publication: Not applicable

Competing interests: The authors declare that they have no competing interests. MPR is currently employed by UCB Biopharma.

Funding: This study is part of Norah Alsadhan's PhD study, funded by King Saud University, Riyadh, Kingdom of Saudi Arabia.

Acknowledgments: The authors wish to acknowledge Natalie King (Information Specialist, University of Leeds) for her help with the development of the search strategy for this systematic review.

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Chapter 3: Statistical methods for measuring trends in colorectal cancer incidence in registries: A systematic review

Authors List: Norah Alsadhan[1,2], Alaa Almaiman[1], Mar Pujades-Rodriguez[2], Cathy Brennan[2], Farag Shuweihdi[2], Sultana A Alhurishi[1], Robert West[2]

Affiliation list:

1. Department of Community Health Sciences, College of Applied Medical Sciences, King Saud University, Riyadh, Kingdom of Saudi Arabia.
2. Leeds Institute of Health Sciences, School of Medicine, University of Leeds, Leeds, United Kingdom.

Study Two	
Journal	Frontiers in Oncology.
Publication status	Published in November 2022.
Reference	Alsadhan N, Almaiman A, Pujades-Rodriguez M, Brennan C, Shuweihdi F, Alhurishi SA, West RM. Statistical methods for measuring trends in colorectal cancer incidence in registries: A systematic review. Frontiers in Oncology. 2022;12:1049486.

Commentary

This chapter was informed by insights from Chapter One, highlighting variations in statistical methods used to assess incidence trends, including joinpoint regression, age–period–cohort analysis, and Poisson regression. These methods differ in their underlying assumptions and analytical focus. Given the thesis's aim to examine CRC trends within the Saudi population and generate reliable, comparable estimates, it is imperative to develop a deeper understanding of how CRC incidence trends are measured and reported in the literature. This involves identifying commonly reported parameters, statistical methods and tools used, and evaluating the reporting of model validity assessment. The review presented in this chapter offers valuable insights for researchers conducting epidemiological studies and highlights areas where the reporting of trend analyses can be improved. Such insights are also necessary for enhancing the transparency and comparability of CRC incidence trend research across the literature.

3.1 Abstract

Background: Monitoring cancer trends in a population is essential for tracking the disease's burden, allocating resources, and informing public health policies. This review describes variations in commonly employed methods to estimate colorectal cancer (CRC) incidence trends.

Methods: We performed a systematic literature search in four databases to identify population-based studies reporting CRC incidence trends, published between January 2010 and May 2020. We extracted and described data on methods to estimate trends and assess model validity, and the software used.

Results: This review included 145 articles based on studies conducted in five continents. The majority (93%) presented visual summaries of trends combined with absolute, relative, or annual change estimates. Fourteen (10%) articles exclusively calculated the relative change in incidence over a given time interval, presented as the percentage of change in rates. Joinpoint regression analysis was the most commonly used method for assessing incidence trends (n= 65, 45%), providing estimates of the annual percentage change (APC) in rates. Nineteen (13%) studies performed Poisson regression and 18 (12%) linear regression analysis. Age-period-cohort modelling- a type of generalized linear models- was conducted in 18 (12%) studies. Thirty-nine (37%) of the studies modelling incidence trends (n=104, 72%) indicated the method used to evaluate model fitness. The joinpoint program (52%) was the statistical software most commonly used.

Conclusion: This review identified variation in the calculation of CRC incidence trends and inadequate reporting of model fit statistics. Our findings highlight the need for increasing clarity and transparency in reporting methods to facilitate interpretation, reproduction, and comparison with findings from previous studies.

3.2 Introduction

Quantifying and monitoring cancer incidence in a population are essential for tracking the disease burden and resource planning. Observing changes in cancer rates over time can enhance our understanding of its historical evolution, the potential social and environmental risk factors leading to cancer, and the impact of implementing interventions and policies. To produce reliable findings on population-level incidence trends, investigators usually rely on population-based cancer registries for providing valid cancer data.

Recent years have witnessed an extensive focus on studying the epidemiology of colorectal cancer (CRC). CRC is a major global health problem, and its incidence rate has increased over the past decades. According to the GLOBOCAN 2020 estimates of cancer incidence, CRC is the third most common cancer and the second leading cause of cancer-related deaths worldwide (1). In CRC, survival outcomes are associated with the clinical stage at diagnosis (2); thus, it is one of the few cancers where screening is considered a critical preventive measure (3). Many population-based reports and epidemiological studies have investigated trends in CRC incidence over time and what societal, environmental, or political changes have been related to these transitions in incidence. Time trend analysis of CRC by age group has also been critical in developing and evaluating secondary prevention efforts such as screening programs (4, 5).

Different methods have been utilized to assess CRC incidence trends. Visual summaries in the form of graphs and descriptive tables are widely used, most often complementing the use of advanced statistical methods. A well-known, established approach for quantifying trends is the estimated annual percentage change (APC), representing the yearly average change in incidence rate. The APC is usually estimated by computing the regression model's slope fitted to the log-transformed incidence rates (6). Different statistical models have been used to estimate the APC, such as linear, Poisson, and joinpoint regression. Some modelling strategies account for age, calendar period, and birth cohort effects on incidence trend estimates (7). The derived inferences from these modelling techniques are imperative for directing resource allocation and public health policies. Yet, the integrity of these inferences largely depends on the modelling procedure's validity. Thus, previous methodological studies have underscored the importance of assessing model validity, including evaluating candidate models, selecting the final model, and assessing model assumptions or performance (8, 9).

When choosing the statistical software to conduct the trend analysis, it is essential to note that different software uses different methods and permits different outputs to be reported. Also, not

all software requires the same technical skills; some need coding experience, while others are considered user-friendly in terms of learning the tool and implementing the analysis. Therefore, researchers should be aware of the most commonly used tools to assess trends and what output is usually reported.

To our knowledge, no previous study has examined and summarized the methods used to assess incidence trends in the literature and the extent of reporting model validity assessment. This review was set up to answer the following questions: 1-What are the various statistical methods reported in the literature for assessing CRC incidence trends, and what type of parameters are reported? 2- What model validity measures are reported in studies using statistical modelling? 3- What software is employed to conduct the analysis?

The current study was conducted in parallel with a comprehensive review describing incidence rate measures and evaluating the quality of reporting incidence methods (10).

3.3 Methods

The reporting of this systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (11).

3.3.1 Study identification

In May 2020, we searched Embase, Medline, Web of Science, and the Cochrane Library for studies reporting temporal trends in CRC incidence, published since 2010. In consultation with an information specialist, we developed a search strategy that included keywords and a combination of subject headings, including “colorectal cancer,” “incidence,” “trends,” and “registry” (the complete search strategy is provided in Appendix B.1) We also checked the reference lists of identified studies to detect potentially missed articles.

3.3.2 Study selection

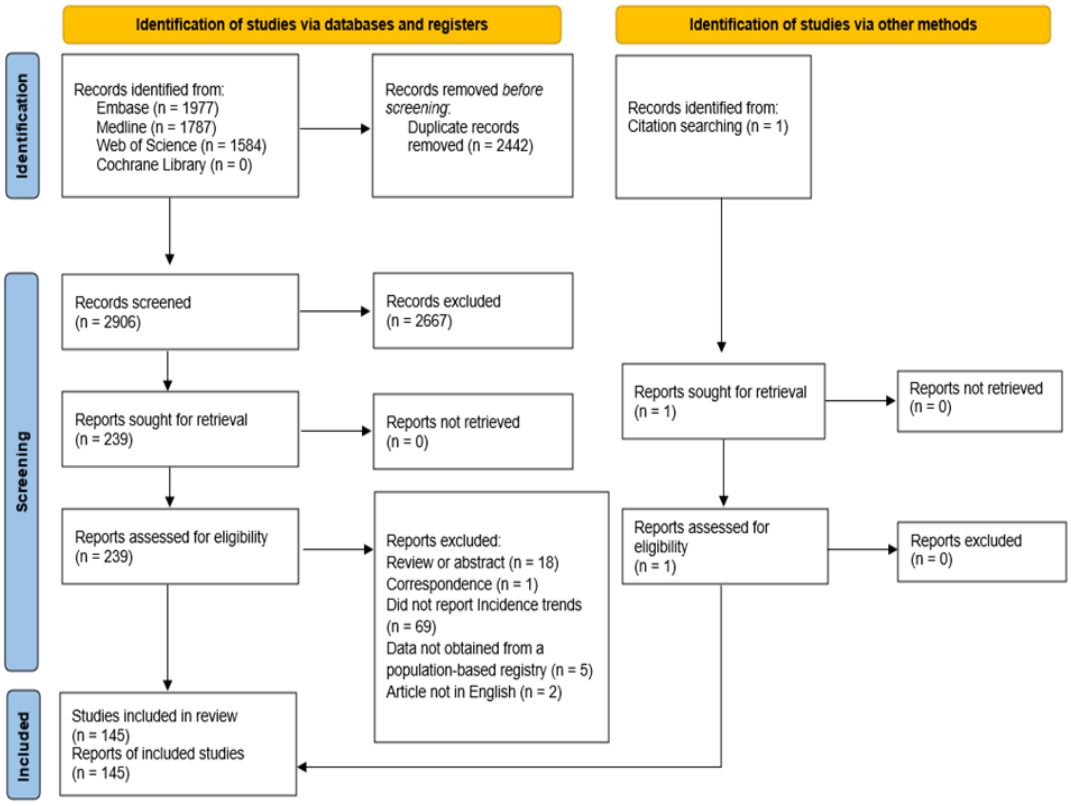
We included studies that fulfilled all of the following criteria: 1) population-based retrospective studies using registry data to measure and report the incidence trends of colorectal cancer, 2) written in English, and 3) a full text is published. We excluded studies conducted in selected population groups (i.e., CRC incidence trends amongst patients with specific diseases), measured the incidence of multiple cancer types, or only reported trend estimates calculated in previous research. Furthermore, studies published as commentaries, case studies, clinical trials, case-

control studies, reviews, conference proceedings, abstracts, or posters were excluded from this review.

3.3.3 Selection process

Figure 3.1 summarizes the selection process. After importing all potential abstracts into the screening web app “Rayyan” (12), two independent reviewers screened all titles and abstracts against the inclusion-exclusion criteria to exclude clearly irrelevant articles. Reviewers resolved disagreements through discussion, and in cases where a consensus decision was not reached by screening the title and abstract, the reviewers examined the full text. We used Cohen’s k statistic to calculate the inter-reviewer agreement rate for title/ abstract screening. After the screening process, we further assessed all articles selected for full-text review. If no consensus was reached, we consulted a third reviewer.

Figure 3. 1. PRISMA flowchart of the study selection process



3.3.4 Data extraction and synthesis

One reviewer independently extracted the data using a standardized form pilot-tested in ten studies. The form included details on the author and publication year, country, main study outcomes, observation period, methods for calculating incidence trends, model fit statistics (if applicable), and the software used. To ensure the robustness of the extraction process, a second reviewer cross-checked a random sample of 25% (n=36). Discrepancies were resolved by consensus agreement.

3.3.5 Quality assessment

We assessed the quality of all included studies using a prespecified checklist adapted for this review and based on the Joanna Briggs Institute Critical Appraisal tool for prevalence studies (13) and the Appraisal tool for Cross-Sectional Studies (14). We chose relevant criteria from each tool to create a 10-item checklist for this study (Appendix B.2). Items were assigned a score of 1 if "demonstrated in the study" or 0 if "not demonstrated or unclear". We calculated and presented an overall score for each study, with higher scores indicating studies of higher quality. This overall quality score should be interpreted cautiously, as each quality indicator's scores are often subjectively justified (15).

3.3.6 Data analysis

The general characteristics of included studies and the methods utilized to assess incidence trends were described using descriptive statistics, reported as frequencies and percentages.

3.3.6.1 Methods used to measure incidence trends

Based on the findings of this review, we classified the reported methods into explanatory and modelling methods (see Figure 3.2).

Explanatory methods

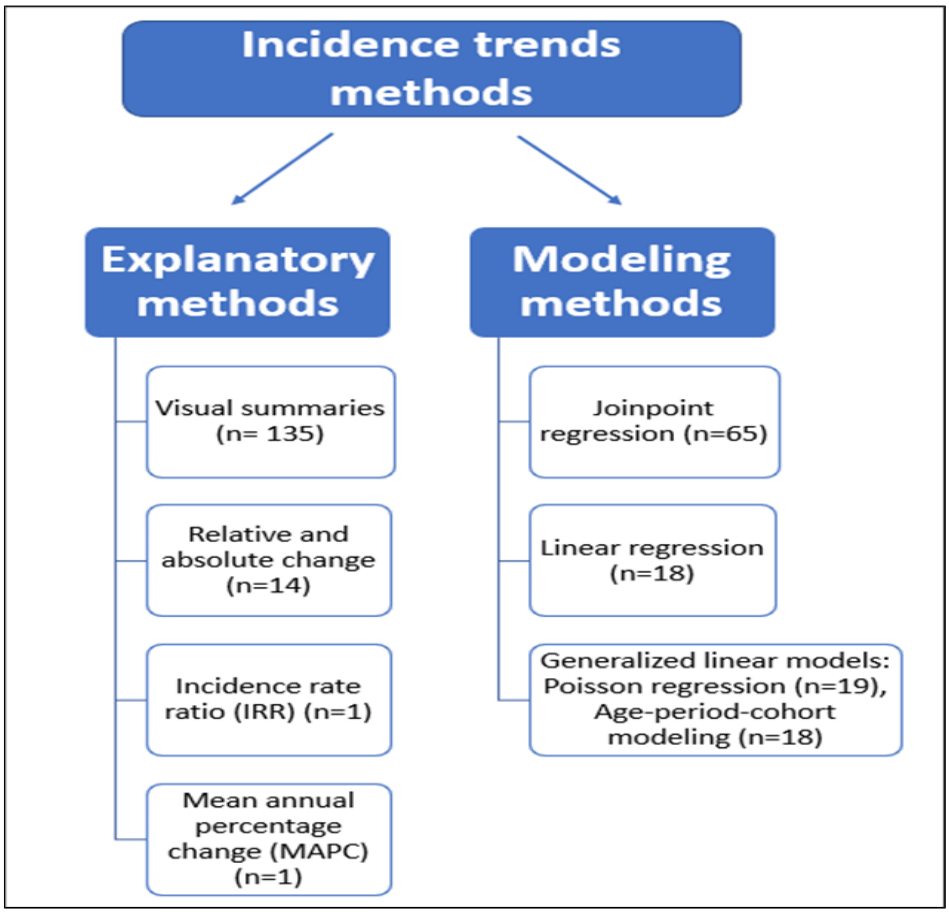
Our definition of explanatory methods included visual summaries (graphical and tabular presentation of trends) and simple arithmetic calculations employed to estimate incidence trends.

Modelling methods

The reviewed modelling methods used regression analysis to fit a relationship between a dependent variable (incidence rate) and an independent variable (time). This review's most

commonly reported statistical modelling methods were subdivided into the following groups: joinpoint regression, linear regression, and generalized linear models such as Poisson regression and age-period-cohort models. The choice of the modelling method will depend on the researcher's aim. When the interest is only to examine the annual percentage change in rates, linear or Poisson regression would be an appropriate option. However, joinpoint regression would be a suitable choice when the research aims to identify points in time where rates change in direction (join points) and magnitude. Thus, joinpoint analysis is especially useful when evaluating trends over a long time period when diagnostic techniques have changed, or relevant prevention or screening interventions have been implemented. Additionally, studies focusing on disentangling the simultaneous and independent effect of age (biological processes of aging), birth cohorts (exposures/experiences that vary from one generation to the next), and period (external factors that affect all age groups similarly at a specific calendar time) on cancer incidence should use age-period cohort modelling methods. Appendix B.3 provides a summarized description of each of the aforementioned statistical techniques.

Figure 3. 2. Classification of incidence trends methods



3.4 Results

The combined search initially yielded 5,348 articles, and after removing duplicates, we identified and screened 2,906 titles. Of these, 2,667 studies were excluded at the title/abstract level, and another 94 were excluded after full-text assessment. The remaining 145 articles were included in the review. The inter-reviewer agreement for the title/abstract screening had a Cohen's k value of 94% (Appendix B.4). The PRISMA flow diagram (Figure 3.1) shows details of excluded reports.

3.4.1 Characteristics of included studies

The eligible articles comprised studies from North America, including the United States of America (n=58, 40%) and Canada (n=3, 2%), Europe (n=34, 23%), Asia (n=33, 23%), Oceania (n=6, 4%), Africa (n=3, 2%), and eight (6%) multi-country study. In addition to incidence, the two other study outcomes most commonly reported were mortality (n=35, 24%) and survival (n=30, 21%). Overall, 21 (14%) studies covered a study period of fewer than ten years, and the remaining covered ten years or more of observation. The characteristics and details of the studies (16–160) are provided in Appendices B.5 and B.6. Detailed quality score information for all included studies is presented in Appendix B.7.

3.4.2 Summaries of incidence trends methods

3.4.2.1 Explanatory methods

The majority of included studies (93%) presented trends using visual summaries combined with other statistical methods. Yet, 23 (16%) studies analyzed trends through only graphical and tabular presentations of incidence rates. Garcia et al. (82) and Murphy et al. (128) reported the absolute change in incidence, representing the arithmetic difference between any two rates at different time points. Fourteen articles assessed trends by calculating the relative change in incidence over a given time interval, presented as the percentage of change in rates. None of these studies reported confidence interval estimates, and only two indicated the significance of trends (75, 140). Cheng et al. (39) and Garcia et al. (82) provided details on the calculation employed for deriving the relative change; the following formula was reported:

$$Relative\ change = \frac{Final\ rate - Initial\ rate\ (absolute\ change)}{Initial\ rate} \times 100$$

In one study, Nooyi et al. (87) measured trends by calculating the mean annual percentage change using the formulae:

$$\text{Mean annual percentage change} = \left[\frac{Final\ rate - Initial\ rate}{(Initial\ rate \times number\ of\ years\ between\ Final\ and\ initial\ rate)}\right] \times 100$$

Furthermore, Fedewa et al. (85) used incidence rate ratios to illustrate changing patterns in incidence by comparing more recent years versus earlier ones.

3.4.2.2 Statistical modelling methods

Joinpoint regression

Joinpoint regression analysis (n= 65, 45%) was the most commonly used method for assessing incidence trends by fitting a series of joined straight lines to estimate annual percentage change (APC) in incidence rates. More than half (n= 37, 57%) of the studies using this method calculated and reported only the APC. Of these, 15 (40%) reported one APC for the entire observation period, whereas 22 (59 %) reported several APCs for different time segments during the study period. Eleven (17%) studies only reported the calculation of the average annual percentage change (AAPC), and 16 (25%) studies reported both the APC and AAPC. Only four studies explicitly stated the difference in calculation between the APC and AAPC. Further details on the estimated trend parameters and the number of joinpoints in the regression model are provided in Appendix B.8. The joinpoint trend analysis software developed by the National Cancer Institute (NCI) (161) was the only tool reported for this type of regression modelling. Examining the reporting of parameter setting in the joinpoint software revealed an overall inadequacy, with the model selection method being the most reported information (52%). Details on parameter setting reporting for the joinpoint program are provided in Appendices B.6 and B.8.

Linear Regression Modelling

Of all included studies, 18 (12%) used linear regression analysis to estimate linear trends. The majority of them (89%) reported the percentage of change in rates. Chittleborough et al. (41) reported trends as the difference per decade, and Baniasadi et al. (26) reported only the model formulae with no estimates for trends. Only nine studies indicated the method used to fit the linear regression model. The least-squares estimation method was the only reported one, and eight studies further indicated that the weighted-least squares technique was employed. None of these studies justified chosen model estimation procedure. Five studies performed a log

transformation of the linear model (23, 25, 59, 105, 111). Different software was used for linear regression analysis, with SPSS (162) being the most commonly used (n=4, 22%).

Generalized Linear Models

Overall, 19 (13%) employed a Poisson regression model to quantify changes in incidence rates. Sixteen of these studies reported measures such as the incidence rate ratio or percentage of change to illustrate incidence trends. Abdifard et al. (17) and Abdifard et al. (16) indicated incidence trends by merely presenting the slope of the regression line. In one study, Dehghani et al. (46) explained only the significance of the incidence trend with no reporting of any other parameter indicating the pattern of rates over time. Five studies reported the use of Poisson regression to conduct age-period-cohort analysis. Only two studies (28, 63) reported consideration for dispersion, and only one (63) indicated the use of negative binomial distribution to correct overdispersion. The most commonly reported software for conducting Poisson regression was Stata (163) (n=6, 31%), followed by SAS (164) (n=5, 26%).

Age-period-cohort modelling- another type of generalized linear models - was employed to measure incidence trends in 18 (12%) studies. The model's parameters used to estimate trends varied across these studies. The period/cohort rate ratio (ratio of rates in a specific period/cohort relative to reference period/cohort) was the most reported measure presented in 14 studies. Although reference values are usually arbitrarily chosen, nine studies in this review used the middle calendar period and birth cohort as reference categories. Chambers et al. (34) and Wessler et al. (149) took the earliest periods and cohorts as the reference, while Siegel et al. (114) chose the cohort with the lowest incidence rates. Estimations for the Local drift (age-specific net annual percentage change) and Net drift (age-adjusted annual percentage change) were indicated in seven and six studies, respectively. Appendix B.6 provides details of all reported parameters. The most common software for this type of modelling was the publicly available age-period-cohort analysis web tool (n=8, 44%), developed by the NCI (165).

Other Methods

Models that were reported only once in the reviewed literature included: time-series analysis (144), interrupted time-series analysis (83), bayesian analysis of spatio-temporal conditional autoregressive models (142), and the LOESS method (66). Six studies reported the APC without explaining the used model to derive this estimate (31, 35, 39, 121, 145, 159).

3.4.3 Association Between Number of Years Covered and The Statistical Method Chosen

We further examined the studies to identify if the number of years studied had influenced the statistical method chosen (i.e., studies covering fewer years tend to use specific methods). We found no evidence to support any connection.

3.4.4 Model Validity Measures

Thirty-nine (37%) of the studies modelling incidence trends (n=104, 72%) explicitly indicated the method used to evaluate model fitness. Of all studies that utilized joinpoint regression analysis, 34 reported the method employed to select the final model. The permutation test (166), the only technique used, was either explicitly indicated in the text or cited in the reference list. Of these 34 studies, only five clearly reported the number of joinpoints in the best-fitting model.

Additionally, six studies (21, 34, 40, 62, 114, 149) indicated other approaches to assess model fitness. Of these, one study (21) failed to report the assessment's result, while the remaining indicated a good model fit. Detailed information on the employed model fit statistics is provided in Appendix B.6.

3.4.5 Software

Most studies (n=111, 77%) reported the software used for incidence trend analysis. The most common (52%) was the joinpoint program (161). Other reported software included SPSS (13%) (162), STATA (12%) (163), and SAS (11%) (164) (see Appendix B.6).

3.5 Discussion

To our knowledge, this is the first study to examine variations in the methods employed in calculating incidence trends of CRC. The 145 articles retrieved provided valuable information on the most commonly reported methods and parameters for measuring trends.

3.5.1 Methods used to measure incidence trends

3.5.1.1 Explanatory methods

Some studies in this review relied solely on explanatory methods to investigate trends. The exclusive use of visual summaries (graphical and tabular presentation of incidence) may lead to an erroneous and subjective interpretation of findings. We also noted that many studies that used

only visual summaries covered an observation period of ten years or more. Yet, it was unclear why other methods were not used in conjunction with visual summaries.

Fourteen studies in this review reported trends as the relative change or percentage of change (PC) in rates between different periods. A positive PC corresponds to an increase in incidence rates, while a negative PC corresponds to a decreasing trend. Relative changes in incidence can be misleading because an absolute small difference can result in a significant percentage change. Therefore, it is important to provide readers with estimates of absolute and relative differences with confidence intervals to interpret incidence trends accurately.

3.5.1.2 Statistical modelling methods

This review identified different statistical modelling techniques for characterizing CRC incidence trends. The most commonly reported method was the joinpoint regression analysis using the NCI's joinpoint program (161). Several APCs for varying periods could be generated depending on the number of joinpoints included in the model and the final selected model. Reporting the APC for each joinpoint segment provides a detailed description of how disease risk changes over time. Yet, to facilitate comparisons of incidence trends for various groups, it is essential to develop a summary measure of incidence trends that accounts for varying trends over sub-time intervals. Hence, in 2009, Clegg et al. (167) proposed the average annual percentage change (AAPC) as a summary measure of trends, computed as a weighted average of the slope coefficients of the joinpoint regression line, with weights corresponding to the length of each subinterval. The APC and AAPC have different interpretations, and thus, it is emphasized that both should be reported, if possible, to provide a comprehensive analysis of trends. The calculation of the AAPC has been incorporated into the joinpoint trend analysis Software (161).

In this review, 15 studies reported only one APC over the entire study period. These studies did not clarify why only a single APC was estimated, whether segmented analysis was not possible — due to the number of data points included—or has yielded insignificant findings, or if this measure reflects the AAPC. Eleven articles reported the AAPC without indicating if the final selected model provided APCs for different time segments, which would have provided an enhanced description of trends. Most studies failed to explain the interpretation of the AAPC, what it represents, and the calculation differences between the APC and AAPC. Providing the reader with a clear description of these parameters and their meaning is vital for understanding trends, reproducing findings, and making potential comparisons in future studies. Furthermore, this review highlighted inadequate reporting on the parameters set in the joinpoint program. Such details are essential

for replicating the analysis or justifying when the researcher's findings differ from previously published trends estimates using the same data source.

Poisson regression was the second most reported method in this review. Our results indicated underreporting of the verification of model assumptions concerning dispersion. Authors should inform readers if any model assumptions did not hold and how it was handled in the analysis.

When exploring cancer burden, disentangling the effects of age, cohort, and period is vital for a comprehensive analysis and understanding of incidence trends. Age–period–cohort analysis is particularly important for understanding generational trends in CRC incidence. It helps identify birth cohort effects, which reflect changes in early-life exposures, such as those during childhood, adolescence, and young adulthood, that influence cancer risk across different life stages. These insights are also crucial for guiding targeted prevention strategies (168). However, due to issues related to data availability and concerns about the statistical interpretability of age, period, and cohort analysis, researchers' uptake and interest in this type of assessment were limited. To facilitate the conduction of this analysis, Rosenberg et al. (165) developed a freely available and easy-to-use web tool that provides researchers with a panel of estimable functions for age-period-cohort analysis. This tool was the most used in this review. Furthermore, we noted that nine studies used age-period-cohort modelling and joinpoint regression to analyze their data. This analysis approach of combining methods is imperative for strengthening the analysis, revealing emerging cancer trends, and enhancing our understanding of cancer etiology and natural history.

Among all studies that assessed and reported CRC incidence trends via statistical modelling, less than half reported model fit statistics in this review. Most of them focused on documenting the method used without further explanation of the model fit analysis. Examining model fitness is one aspect of assessing the statistical model's validity; it is defined as "a measure of the discrepancy between the observed empirical distribution of the observations in the data set and the 'best-fitting' probability distribution computed from the estimated probability model" (8). Model fit statistics might include graphical assessment such as residual plots or quantitative evaluation such as log-likelihood tests and goodness-of-fit measures (8, 9). Despite the used methods, authors should provide details on model fit statistics in the manuscript or as supplemental or web-based data. Ensuring transparency by providing sufficient information on the modelling building procedure will support an accurate interpretation of the research findings and facilitate future analysis replication.

To our knowledge, this study is the first to review the methods employed to estimate incidence trends across different populations and settings. In cancer studies, the quality and reliability of the cancer registry data are essential for evaluating cancer trends. It was not within the scope of the current review to examine data quality reporting; yet, in a previous publication, we assessed reporting quality in CRC incidence studies and noted a substantial deficit in reporting registry-data quality control procedures and findings (10).

This review was limited to studies assessing the incidence of CRC using registry data. Thus, we might have missed other trend analysis methods used to analyze different data sources and diseases in the last decade. Despite this, our results inform well about a variety of commonly used incidence trends methods and thus support future researchers in choosing potential methods and parameters that will enhance the comparability of their research. Although we searched multiple databases and included studies from different countries, we included only English articles in this review. Thus, we might have missed relevant papers in other languages.

3.5.2 Conclusion

This review described the most commonly reported methods for measuring CRC incidence trends over the past decade. Visual summaries are always a good starting point for observing trends, preferably followed by modelling. Joinpoint regression was the most reported method, identifying points in time where incidence rates change. We also noted an increased uptake of age-period-cohort modelling to disentangle the effect of age, period, and birth cohort on incidence trends. Our findings highlighted the need for increased clarity and transparency in reporting incidence trends methods to facilitate interpretation and comparison of results with previous studies and help identify and address limitations of the analysis.

Declarations

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Funding: This study is part of Norah Alsadhan's PhD study, funded by King Saud University, Riyadh, Kingdom of Saudi Arabia.

Acknowledgments: The authors wish to acknowledge Natalie King (Information Specialist, University of Leeds) for her help with the development of the search strategy for this systematic review.

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Chapter 4: Temporal trends in age and stage-specific incidence of colorectal cancer in Saudi Arabia: a registry-based cohort study between 1997 and 2017

Authors List: Norah Alsadhan[1], Mar Pujades-Rodriguez[1], Sultana A Alhurishi[2], Farag Shuweihdi[3], Cathy Brennan[4], Robert M West[1]

Affiliation list:

1. Leeds Institute of Health Sciences, School of Medicine, University of Leeds, Leeds, United Kingdom
2. Department of Community Health Sciences, College of Applied Medical Sciences, King Saud University, Riyadh, Kingdom of Saudi Arabia
3. Dental Translational & Clinical Research Unit, School of Dentistry, University of Leeds, Leeds, United Kingdom
4. Psychological & Social Medicine, School of Medicine, University of Leeds, Leeds, United Kingdom

Study Three	
Journal	Cancer Epidemiology.
Publication status	Published in November 2024.
Reference	Alsadhan N, Pujades-Rodriguez M, Alhurishi SA, Shuweihdi F, Brennan C, West RM. Temporal trends in age and stage-specific incidence of colorectal cancer in Saudi Arabia: A registry-based cohort study between 1997 and 2017. Cancer Epidemiology. 2024;93:102699.

Commentary

Insights from Chapters Two and Three informed the methodological choices for the quantitative analyses presented in Chapter Four. Chapter Two emphasized the importance of using multiple incidence measures to provide a comprehensive assessment of CRC trends. While the age-standardized incidence rate (ASR) allows for comparisons across populations by adjusting for differences in age structure, relying solely on this measure may mask important variations in incidence within a population. Therefore, for a thorough evaluation of CRC incidence among the Saudi population, both the ASR and age-specific incidence rates (ASIR) were calculated in this chapter.

As guided by Chapter Two, I applied the most recent WHO world standard population in estimating the ASR to generate internationally comparable figures. Additionally, I provided detailed reporting of incidence methods to enhance the reliability, comparability, and reproducibility of the findings. These included clear definitions and descriptions of CRC, the numerator and denominator data, population estimates calculations for the denominator, time intervals for incidence calculation, uncertainty estimates (confidence intervals or p-values), and missing data analysis. Rates were expressed with a time-unit (person-years), and information on the analytical software used was also reported. Chapter Two underscored the importance of reporting data quality control procedures and findings to enhance the interpretation of cancer burden estimates. In line with this recommendation, I first reported the quality control measures indicated by the Saudi Cancer Registry in their published reports. I also calculated and reported two quality indicators to assess data validity: the proportion of morphologically verified cases and the percentage of cases identified through death certificates only.

Chapter Three guided the selection of statistical methods for trend analysis. The review indicated that joinpoint regression was the most used technique for estimating incidence trends and that the annual percentage change (APC) was the most reported parameter. In addition to its widespread adoption in the literature, I selected joinpoint regression for its ability to identify significant changes in the direction and magnitude of incidence over time. Unlike linear and Poisson regression models, which usually assume a constant rate of change, joinpoint regression can detect multiple segments with varying APC estimates across the study period. Such shifting points may reflect changes in risk exposure, screening practices, or health behaviors. To conduct the joinpoint regression analysis, I used the NCI's joinpoint regression program—the only software identified in the review for this purpose. It is freely available, methodologically robust, and user-

friendly. The software computes APC and average annual percentage change (AAPC) estimates. The AAPC is a summary measure that represents a weighted average of the APCs across the entire study period, facilitating the interpretation and comparison of the overall trend. As recommended in Chapter Three, I provided clear documentation of the calculation and interpretation of APC and AAPC values. I also described the software's parameter settings to support the reliability and reproducibility of the findings.

With regard to model fit and validity, the joinpoint regression program employs permutation tests to determine the optimal number and location of joinpoints. This process begins with a model assuming zero joinpoints and tests whether additional joinpoints significantly improve model fit. The software also provides statistical significance testing and 95% confidence intervals for both APC and AAPC estimates, supporting the validity of the reported trends.

Finally, limitations in the available data hindered certain aspects of the trend analyses presented in this chapter. The absence of regional population data impeded the assessment of geographic disparities in CRC incidence. Examining regional variations in incidence by disease stage could have provided valuable insights into potential differences in healthcare access or diagnostic pathways—areas that may require further investigation and targeted interventions. Additionally, the lack of incidence data following the introduction of the national CRC screening program precluded evaluating its long-term impact on CRC burden.

4.1 Abstract

Background: In Saudi Arabia, colorectal cancer (CRC) is the most common cancer in men and the third in women, posing a significant health burden. A comprehensive report of CRC incidence rates and trends in Saudi Arabia is lacking. This study aims to examine trends in CRC incidence among the Saudi population.

Methods: We used data from the Saudi Cancer Registry to examine CRC age-specific incidence rates (ASIR) and age-standardized incidence rates (ASR) between 1997 and 2017. Joinpoint regression analysis was used to determine the magnitude and direction of observed trends stratified by age, sex, and CRC stage at diagnosis. Trends were measured using the annual percentage change (APC) and the average annual percentage change (AAPC) in CRC incidence rates.

Results: In total, 19,463 new CRC cases were identified during the study period. Since 1997, ASR for CRC has steadily increased in men and women overall, irrespective of disease stages. The ASIR increased across all age groups and was more pronounced in older patients. Women aged 40-49 had a higher increase in incidence than men (AAPC= 5.3% vs.4.7%). Males aged 70-79 had an AAPC of 10.2%, twice that of females (AAPC= 4.9%). A consistent rise in ASIR was observed across all CRC stages and age groups in males and females. In recent years, males under 50 had a higher APC for distant CRC than females, while females aged 50-74 experienced a steeper increase in distant CRC than males.

Conclusion: We report a marked increase in the incidence of CRC over time in Saudi Arabia, affecting men and women across all age groups and disease stages at diagnosis. Our findings underscore the need to identify underlying risk factors and to develop and implement effective prevention policies and strategies, including screening programs to facilitate early detection and treatment.

4.2 Introduction

Colorectal cancer (CRC) is a major global health problem. With about 1.9 million cases and 0.94 million deaths worldwide in 2020, CRC ranks as the third most diagnosed and the second most deadly cancer (1). Despite advances in understanding and treating CRC, global projections suggest that there will be a 63% increase by 2040 (2), posing a substantial financial and public health burden (3). Ecological studies have found that countries with the highest Human Development Index (HDI), a composite measure of a country's overall achievements in social and economic growth (1), had about four times the incidence rate of low HDI countries (3). The CRC rates in high-income countries like North America and Australia have stabilized or declined, especially among the over-50 population. This trend has been explained by increased screening utilization and lifestyle modifications over recent decades (4-7). Yet, CRC rates are rising in low-income countries, possibly resulting from globalization and adoption of Western lifestyles, characterized by poor dietary choices, insufficient physical activity, and smoking, along with limited prevention efforts and participation in CRC screening (8).

In Saudi Arabia, CRC is the most common cancer in men and the third in women. In 2017, there were 1,719 cases diagnosed, accounting for 12.4% of all diagnosed cancers compared to 10.0% globally (1, 9). Age-standardized rates (ASR) per 100,000 were 12.5 for men and 10.9 for women (9). Evaluations of CRC incidence trends using the Saudi population-based cancer registry data are scarce (10-12), yet several reports have noted a rise in incidence over the past two decades (10-15).

Globally, there's a growing concern about the rising incidence of early-onset colorectal cancer (EO-CRC), defined as cases diagnosed before age 50 (16). EO-CRC presents a substantial health burden in young adults due to its aggressive nature (17). Its etiology remains unclear (18). A recent meta-analysis including 40 studies in five continents, 26 from North America, reported a pooled overall annual percentage change (APC) of 1.33% in EO-CRC. No studies from Saudi Arabia were included in the review (19). While EO-CRC trends in Saudi Arabia are not yet fully understood, some reports noted a rising incidence among young adults (11, 20). Emerging evidence highlights the advantages of beginning screening for CRC between the ages of 45 and 49, to reduce mortality (21). In response, the latest recommendations from the American Cancer Society (22) and the US Preventive Service Task Force have lowered the recommended age for screening from 50 to 45 (23). Similarly, recent CRC screening guidelines and programs in Saudi Arabia have adopted this

cutoff age (24, 25). Yet, further research is needed to confirm these screening age recommendations (24). A detailed evaluation of CRC incidence by age in Saudi Arabia is a first step.

The prognosis of CRC largely depends on the stage at diagnosis, with advanced stages leading to poorer outcomes (26, 27). As CRC usually develops over at least a decade (28, 29), early detection through screening is crucial for improving survival and reducing healthcare costs (30). In 2017, metastatic tumors constituted 27% of CRC cases in Saudi Arabia, partially reflecting the absence of a national screening program before 2017 (31). A temporal analysis of incidence by diagnosis stage will allow establishing benchmark values to assess the national screening program's impact on early diagnosis.

The Saudi literature lacks a detailed analysis of age and stage-specific CRC incidence rates. Hence, our study aims to examine temporal trends in CRC incidence among Saudis by age, sex, and stage.

4.3 Materials and methods

4.3.1 Study design and population

This is a population-based cohort study of Saudi individuals diagnosed with malignant CRC from 1997 to 2017 and registered in the Saudi Cancer Registry (SCR). Primary CRC cases were identified using the 2nd and 3rd editions of the International Classification of Diseases for Oncology (ICD-O). CRC codes C18.0- C18.9, C19.9, and C20.9 were included. A detailed description of anatomical sites is provided in Appendix C.1. No morphology codes were excluded. CRC stage at diagnosis was recorded according to the Surveillance, Epidemiology, and End Results (SEER) Summary Stage System, which categorizes stage into localized (confined to the organ of origin), regional (spread to nearby lymph nodes or tissues), or distant (metastasized to distant parts of the body) (32).

4.3.2 Data source

The SCR collects nationwide cancer data from governmental and private health institutions, coordinated by its main office in Riyadh and five regional offices to ensure kingdom-wide coverage. The registry team undertakes quality control procedures such as data verification, case linkage, and comprehensive data collection and is a member of the International Association of Cancer Registries (IACR). Collected cancer data includes demographic information (age, sex, marital status, region) and tumor details (date of the diagnosis, primary site, morphology, grade, stage, and basis of diagnosis). The registry does not collect data on hereditary disorders or CRC risk factors. Patient data are anonymized.

The General Authority of Statistics (GASTAT) provided mid-year population estimates by sex for 17 age groups (5-year intervals) for all years, excluding 1997, 1998, 2001, 2002, and 2003. Population data for missing years were extrapolated (see Appendix C.2). This study was reported according to the STROBE guidelines for epidemiological studies (33).

4.3.3 Statistical analysis

We used summary statistics to describe the frequency and percentage of the demographic and clinical characteristics of Saudi CRC patients. We examined patient distribution of cancer stage at diagnosis by sex and calendar period (1997–2001, 2002–2006, 2007–2011, and 2012–2017). All descriptive analyses were performed using R software *(R 4.3.2*) (34).

We estimated annual incidence rates per 100,000 person-years, including all reported new CRC cases. For a comprehensive analysis, we computed both the age-specific incidence rate (ASIR) and the age-standardized incidence rate (ASR) (35). We calculated the annual ASIR for six age groups (<40, 40-49, 50-59, 60-69, 70-79, and 80+), stratified by sex. To allow smoothing anomalies in trend analysis and comparability with existing literature (36-38), we calculated annual ASIR by stage and sex amongst three age groups (<50, 50-74, 75+). This was performed by dividing the number of new cases (Ri) by the corresponding population (Ni) and multiplying by a standard constant (39).

$$ASIR = \frac{Ri}{Ni} \times 100\,000$$

We calculated age-standardized incidence rate (ASR) to minimize the effect of variations in age distribution on incidence rates over time. We used the direct standardization method and the new 2000 WHO world standard population as a reference (40). The International Agency for Research on Cancer (IARC) recommends using this reference population to facilitate international comparisons of incidence trends. We estimated ASRs by weighting the ASIRs to the age structure of the standard population, calculated as follows:

$$ASR = \frac{\sum_{i=1} ai \times wi}{\sum_{i=1} wi} \times 100\,000$$

Where (i) represents each age group, (ai) is the age-specific incidence rate, and (wi) is the standard population in each age group (39). To calculate sex-specific ASRs, we used sex-specific population estimates from the GASTAT and standardized the rates to the total (male and female) WHO standard population. To compute the average ASR throughout the study period, we used as denominator the sum of the mid-point population estimates for each study year (39).

We used joint linear trends through the joinpoint regression program, developed by the National Cancer Institute (NCI) (41), to quantify the magnitude and direction of temporal changes in ASR and ASIR by sex and stage (42). Further details on the joinpoint regression parameters and software settings are provided in Appendix C.2. We calculated incidence rates and trends by disease stage amongst patients with complete stage data (90.1% of cases). We also excluded 11 cases with missing age from the incidence analysis. Characteristics of patients with and without missing stage are presented in Appendix C.3.

4.4 Results

For the period 1997 to 2017, a total of 19,463 new CRC cases were recorded, with 97.7% morphologically verified and only 1.5% identified by death certificate. Annual CRC counts by sex, age, and stage are provided in Appendices C.4-C.7. We observed a gradual increase in registered CRC cases over time (Appendix C.8). Appendices C.1 and C.9 show the demographic and clinical characteristics of cases. There was a higher proportion of CRC in males (54.9%) compared to females (45.1%), with an overall median age at diagnosis of 58 years. Females were diagnosed earlier than males (57 vs. 60 years). About 28% of patients were diagnosed before age 50, with the highest proportion of cases (36%) within the 50-69 age group. Most patients were married (79.2%), primarily from the Riyadh (30.5%), Makkah (24.7%), and Eastern Regions (17.1%).

Colon cancer was diagnosed in 59.7% of cases, while rectal and rectosigmoid cancers were found in 25.1% and 15.1% of cases, respectively. Adenocarcinoma, not otherwise specified (NOS), was the most prevalent histological type (77.1%), followed by mucinous adenocarcinoma (9.2%), neoplasm, malignant (2.0%), and adenocarcinoma in tubulovillous adenoma (2.0%). Most tumors (76.6%) were moderately differentiated. In terms of CRC staging, about 43% of diagnoses were regional cancers, followed by distant (29.3%) and localized tumors (27.8%). There was a shift in the proportion of cancer stages between 1997-2001 and 2012-2017, with distant-stage tumors increasing and localized and regional tumors decreasing over time (Appendix C.10). A detailed description of patients' characteristics by sex is provided in Appendices C.1 and C.9.

4.4.1 Age-standardized incidence rates (ASR)

During the study period, the average ASR of CRC was 8.5 cases per 100,000 person-years, with males experiencing a higher average ASR (9.3) than females (7.6). Analysis of incidence by disease stage indicated a higher average ASR for regional CRC, with local and distant stages having similar ASRs, as detailed in Table 4.1.

Table 4. 1. Average age-standardized incidence rates per 100,000 person-years of colorectal cancer in Saudi Arabia (1997-2017) by sex and stage at diagnosis

Characteristic	Average age-standardized incidence rate (AASR)		
	Total (95%CI)	Male (95%CI)	Female (95%CI)
Anatomical site			
All colorectal*	8.5 (8.4-8.6)	9.3 (9.1-9.5)	7.6 (7.5-7.8)
Stage of CRC at diagnosis			
Localized	2.1 (2.0-2.2)	2.4 (2.3-2.5)	1.9 (1.8-2.0)
Regional	3.3 (3.2-3.3)	3.6 (3.5-3.7)	2.9 (2.8-3.0)
Distant metastasis	2.2 (2.2-2.3)	2.4 (2.3-2.5)	2.1 (2.0-2.2)

Note: CI: Confidence interval. * The number of patients with cancer located in the colon was 11629, in the rectum 4886, and rectosigmoid 2948.

There was an overall increase in CRC incidence from 4.0 in 1997 to 12.9 per 100,000 person-years in 2017 (Appendix C.11). Rates were similar in males and females until 2001, after which male rates exceeded those of females (Figure 4.1). We observed temporal increases in incidence rate for all CRC stages, with regional tumors sustaining higher estimates of annual rates. Males had higher ASRs across all stages throughout most years (Figure 4.2).

Figure 4. 1. Annual age-standardized incidence rates of CRC per 100,000 person-years in Saudi Arabia (1997-2017), by sex

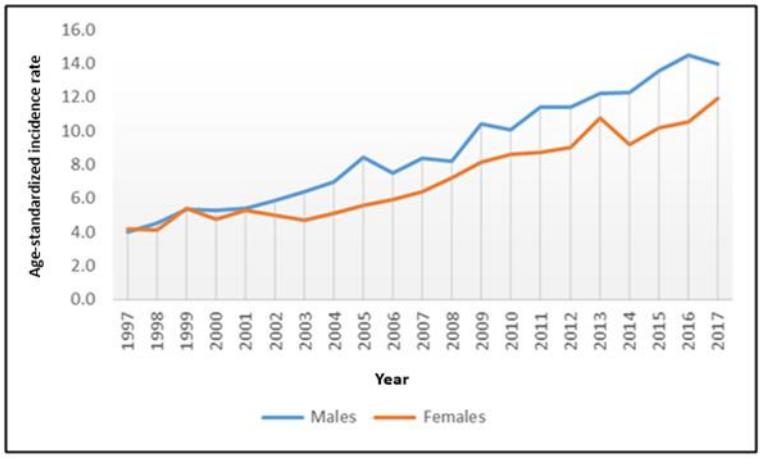
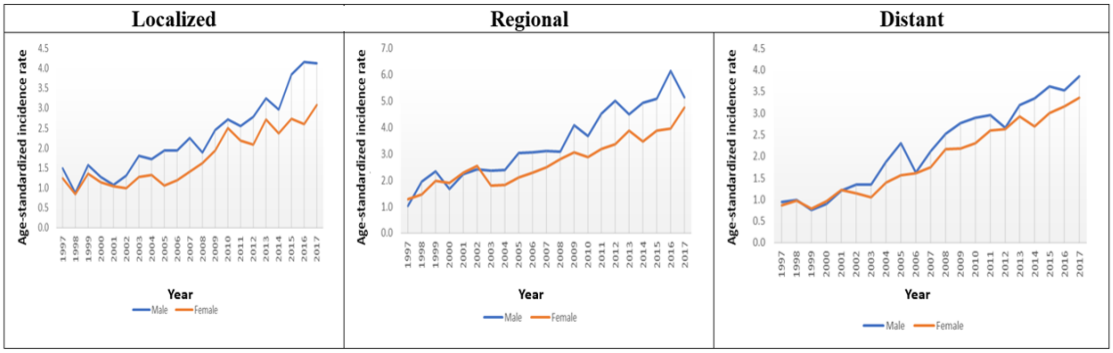


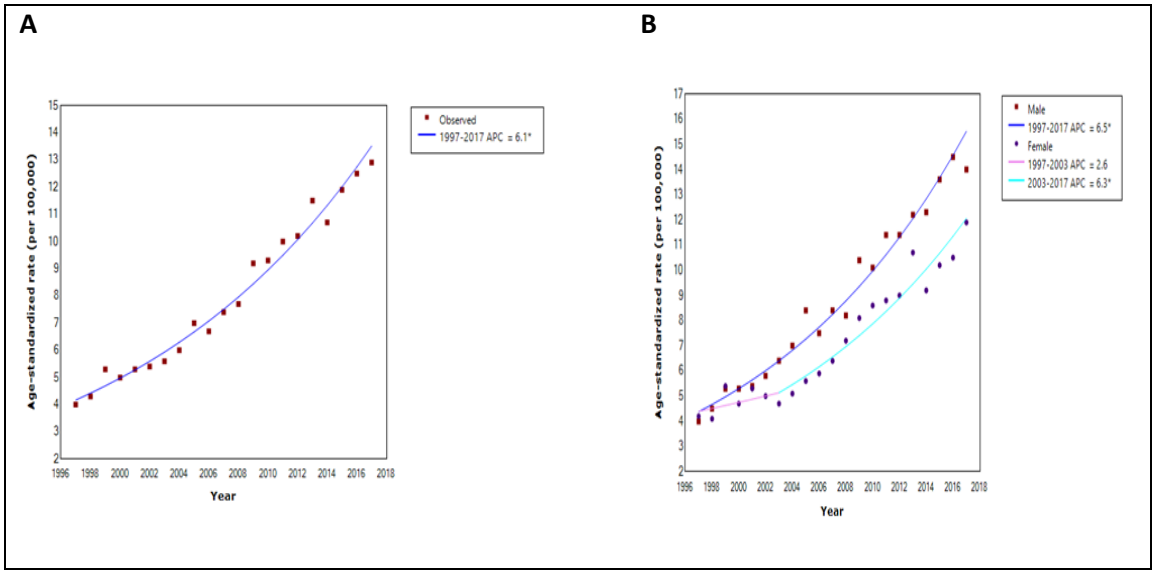
Figure 4. 2. Annual age-standardized incidence rates of CRC per 100,000 person-years in Saudi Arabia (1997-2017), by sex and stage



4.4.2 Age-standardized trends according to sex

Since 1997, the ASR of CRC steadily increased, with an APC of 6.1%. (95%CI=5.6-6.5). Males had higher AAPC than females (6.5% vs. 5.2%) (Table 4.2 and Figure 4.3).

Figure 4. 3. Trends in CRC age-standardized incidence rates for the overall population (A) and by sex (B), Saudi Arabia, 1997 to 2017



Note: Rates are per 100,000 person-years and are age-adjusted to the WHO world standard population. Plotted lines indicate the annual percentage change (APC). The scales of the y-axis of the figures are different to make trends more apparent. *Indicates APC is significantly different from zero at *P*<0.05. The use of different colors emphasizes the different changes in APC across calendar periods.

4.4.3 Age-standardized trends by CRC stage

Localized and regional CRCs had an annual ASR increase of 6.4%, while distant tumors had a steeper increase with an APC of 9.9% until 2009, decreasing to 4.9% through 2017 (Table 4.2 and Figure 4.4). The ASR for regional CRC in males increased more rapidly (APC= 7.1%; 95%CI= 5.8-8.3) than in females (APC= 5.5%; 95%CI= 4.5-6.4). Distant tumors ASRs in males rose sharply between

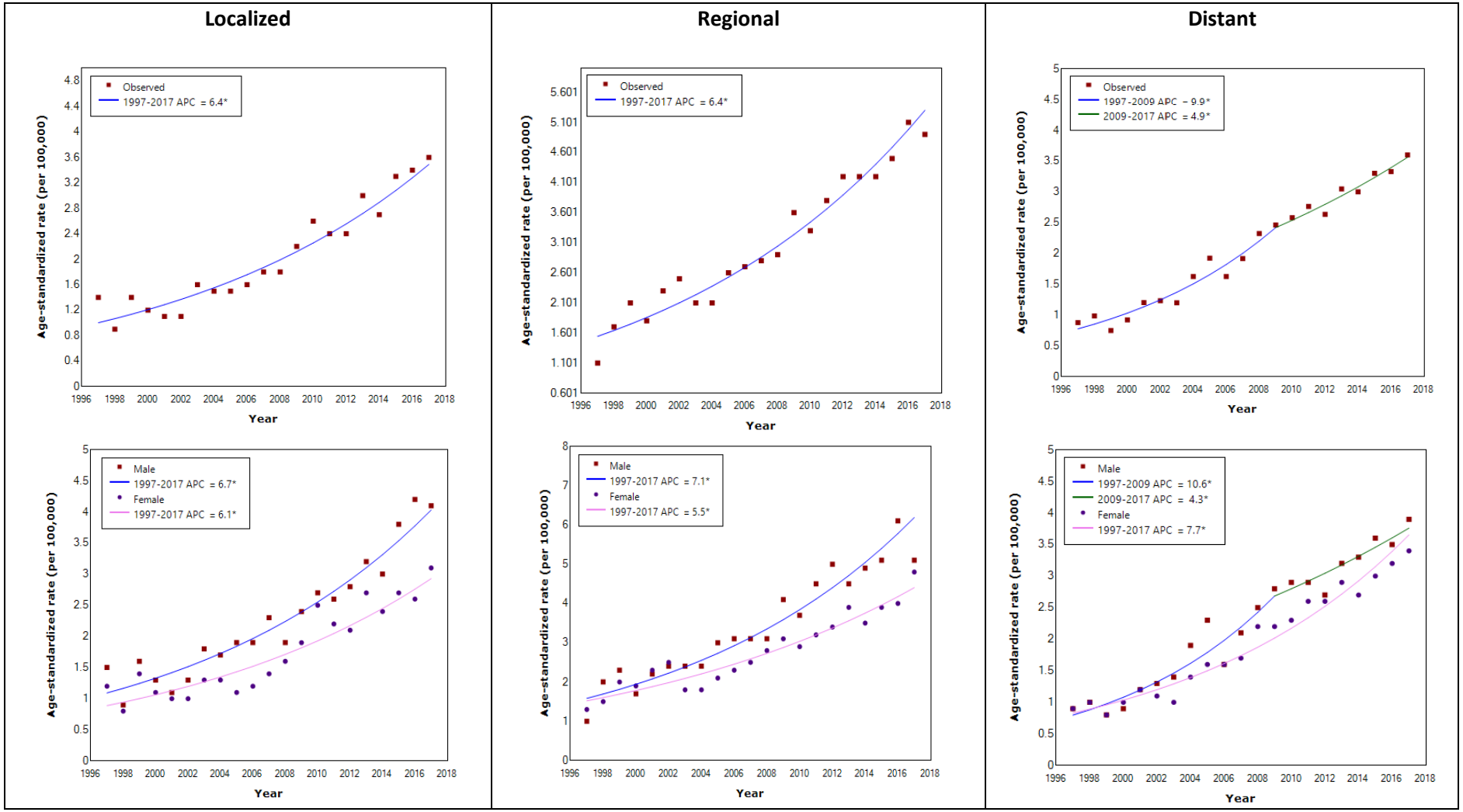
1997 and 2009 by 10.6 %, then dropped to 4.3% per annum until 2017. Conversely, females had a consistent increase in distant CRC rates (APC= 7.7%; 95% CI= 6.9-8.6) throughout the study period.

Table 4. 2. Annual percentage change (APC) of age-standardized colorectal cancer incidence rates by sex and stage in Saudi Arabia, 1997-2017

Characteristic		Trend 1		Trend 2		AAPC (95%CI)
		Years	APC (95%CI)	Years	APC (95%CI)	1997-2017
Sex	All (19,463)	1997-2017	6.1* (5.6, 6.5)	-	-	6.1* (5.6, 6.5)
Stage	Localized	1997-2017	6.4* (5.4, 7.5)	-	-	6.4* (5.4, 7.5)
	Regional	1997-2017	6.4* (5.4, 7.3)	-	-	6.4* (5.4, 7.3)
	Distant	1997-2009	9.9* (7.9, 12.0)	2009-2017	4.9* (1.4, 8.6)	7.9* (6.2, 9.7)
Sex	Males (10,688)	1997-2017	6.5* (6.0, 7.0)	-	-	6.5* (6.0, 7.0)
Stage	Localized	1997-2017	6.7* (5.6, 7.9)	-	-	6.7* (5.6, 7.9)
	Regional	1997-2017	7.1* (5.8, 8.3)	-	-	7.1* (5.8, 8.3)
	Distant	1997-2009	10.6* (8.2, 13.2)	2009-2017	4.3* (0.0, 8.8)	8.1* (5.9, 10.2)
Sex	Females (8,775)	1997-2003	2.6 (-1.3, 6.7)	2003-2017	6.3* (5.1, 7.5)	5.2* (3.8, 6.5)
Stage	Localized	1997-2017	6.1* (4.8, 7.5)	-	-	6.1* (4.8, 7.5)
	Regional	1997-2017	5.5* (4.5, 6.4)	-	-	5.5* (4.5, 6.4)
	Distant	1997-2017	7.7* (6.9, 8.6)	-	-	7.7* (6.9, 8.6)

Note: APC: annual percentage change; AAPC: average annual percentage change; CI: confidence interval. *Indicates APC or AAPC are significantly different from zero at $P<0.05$. Rates are reported per 100,000 person-years. Trends 1 and 2 refer to distinct calendar periods with significantly different rates of change. Joinpoints were selected using permutation tests, and the AAPC was pre-specified for the entire period 1997–2017.

Figure 4. 4. Overall and sex-specific trends in CRC age-standardized incidence rates by stage, Saudi Arabia, 1997 to 2017



Note: Rates are reported per 100,000 person-years and are age-adjusted to the WHO world standard population. Plotted lines indicate the annual percentage change (APC). The different scales of the y-axis of the figures are used to make trends more apparent. * Indicates APC is significantly different from zero at $P<0.05$. The use of different colors emphasizes the different changes in APC across calendar periods.

4.4.4 Age-specific incidence trends by sex

Annual ASIRs of CRC for the total population and stratified by sex are provided in Appendix C.12. CRC incidence increased across all age groups (Table 4.3 and Figure 4.5), with the AAPC magnitude rising with age. Between 1997 and 2017, females in the 40-49 age group experienced a higher increase in CRC incidence, marked by an APC of 5.3% (95% CI=4.3-6.4) compared to males (APC= 4.7%, 95% CI=3.6-5.9). Sex differences were also observed in adults aged 50-59, where females had a higher average yearly rate increase (AAPC= 6.6%, 95%CI= 5.5-7.8) than males (AAPC= 5.1, 95%CI= 2.5-7.8). While 50-59 years old females had a constant 6.6% annual change in incidence throughout the study period, males had an APC of 8.6% (95%CI= 5.9-11.3) during the second linear trend (2004-2017), where incidence increased from 11.8 per 100.000 person-years in 2004 to 30.2 per 100.000 person-years in 2017. In people aged 70-79, males had a significant positive trend with an AAPC of 10.2% (95%CI= 8.2-12.3), doubling that for females (AAPC=4.9%, 95%CI=3.2-6.6).

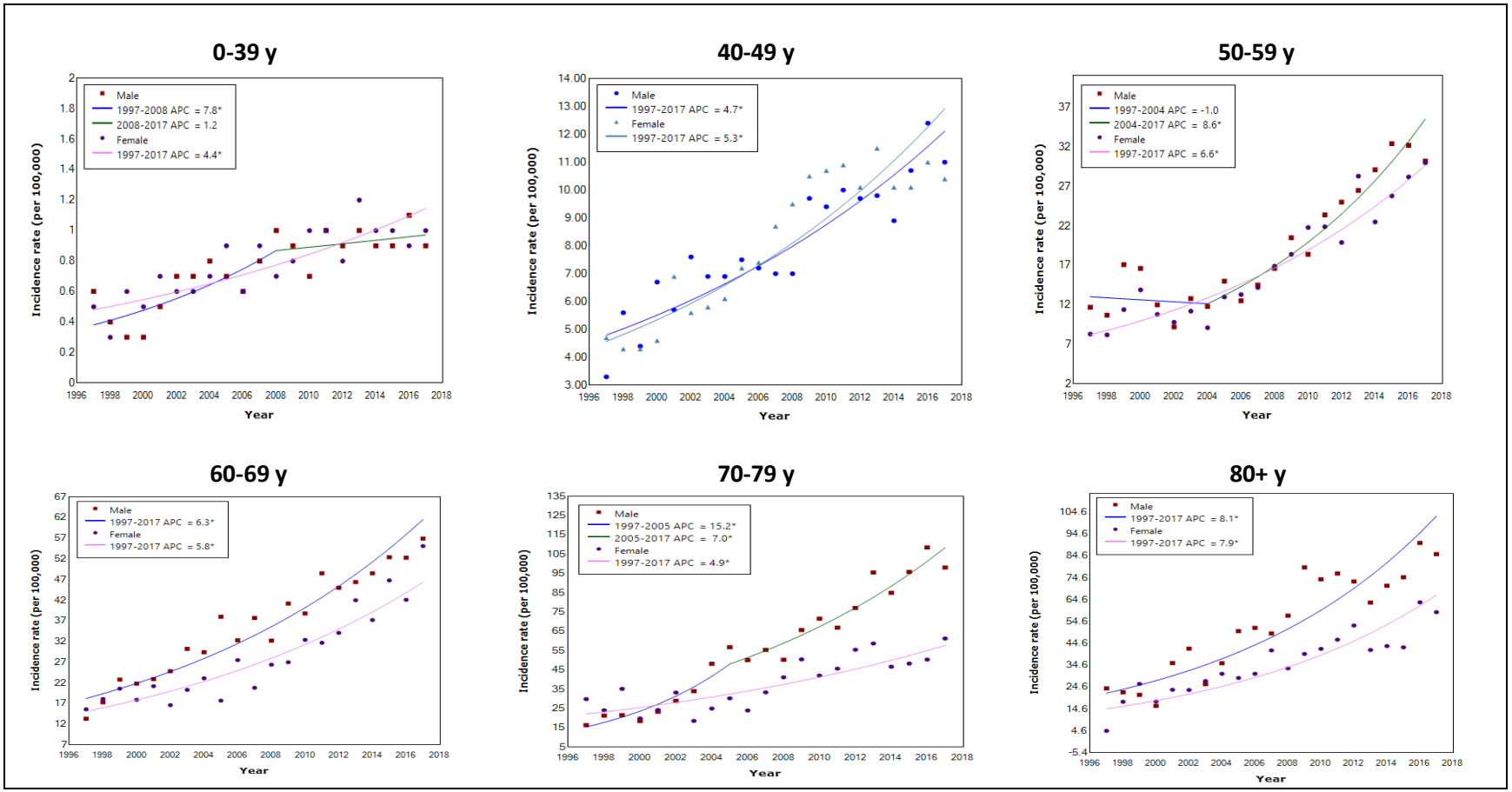
Table 4. 3. Annual percentage change (APC) of colorectal cancer incidence rates by age and sex in Saudi Arabia, 1997-2017

Sex	Trend 1		Trend 2		AAPC (1997-2017)
	Years	APC (95%CI)	Years	APC (95%CI)	AAPC (95%CI)
All					
0-39	1997-2017	4.4* (3.2, 5.5)	-	-	4.4* (3.2, 5.5)
40-49	1997-2010	6.5* (5.2, 7.8)	2010-2017	1.4 (-1.7, 4.6)	4.7* (3.4, 6.0)
50-59	1997-2004	1.1 (-4.1, 6.5)	2004-2017	8.4* (6.2, 10.6)	5.7* (3.6, 8.0)
60-69	1997-2017	6.0* (5.5, 6.6)	-	-	6.0* (5.5, 6.6)
70-79	1997-2017	7.7* (6.8, 8.7)	-	-	7.7* (6.8, 8.7)
80+	1997-2009	10.0* (7.4, 12.6)	2009-2017	2.9 (-1.5, 7.5)	7.1* (4.9, 9.3)
Male					
0-39	1997-2008	7.8* (2.9, 12.9)	2008-2017	1.2 (-4.9, 7.8)	4.8* (1.2, 8.6)
40-49	1997-2017	4.7* (3.6, 5.9)	-	-	4.7* (3.6, 5.9)
50-59	1997-2004	-1.0 (-7.1, 5.5)	2004-2017	8.6* (5.9, 11.3)	5.1* (2.5, 7.8)
60-69	1997-2017	6.3* (5.3, 7.2)	-	-	6.3* (5.3, 7.2)
70-79	1997-2005	15.2* (10.9, 19.7)	2005-2017	7.0* (4.8, 9.3)	10.2* (8.2, 12.3)
80+	1997-2017	8.1* (6.3, 9.9)	-	-	8.1* (6.3, 9.9)
Female			-	-	
0-39	1997-2017	4.4* (3.0, 5.9)	-	-	4.4* (3.0, 5.9)
40-49	1997-2010	5.3* (4.3, 6.4)	-	-	5.3* (4.3, 6.4)

50-59	1997-2017	6.6* (5.5, 7.8)	-	-	6.6* (5.5, 7.8)
60-69	1997-2017	5.8* (4.7, 6.8)	-	-	5.8* (4.7, 6.8)
70-79	1997-2017	4.9* (3.2, 6.6)	-	-	4.9* (3.2, 6.6)
80+	1997-2017	7.9* (5.3, 10.5)	-	-	7.9* (5.3, 10.5)

Note: APC: annual percentage change; AAPC: average annual percentage change; CI: confidence interval. *Indicates APC or AAPC are significantly different from zero at $P<0.05$. Rates are reported per 100,000 person-years. Trends 1 and 2 refer to distinct calendar periods with significantly different rates of change.

Figure 4. 5. Trends in CRC age-specific incidence rates by sex, Saudi Arabia, 1997 to 2017



Note: Rates are reported per 100,000 person-years. Plotted lines indicate the annual percentage change (APC). The different scales of the y-axis of the figures are used to make trends more apparent. * Indicates APC is significantly different from zero at $P<0.05$. The use of different colors emphasizes the different changes in APC across calendar periods.

4.4.5 Age-specific incidence trends by CRC stage and sex

Annual ASIR rates of localized, regional, and distant CRC for the total population and stratified by sex are provided in Appendices C.13-C.15. A consistent upward trend in CRC incidence was observed for males and females across all disease stages and age groups (Table 4.4 and Figure 4.6). Average yearly increases in incidence rates in the whole population were more pronounced in distant CRC across all age groups.

Localized CRC incidence trends were similar between males and females across all age groups, with APCs ranging between 6.0% and 6.5% for those under 75 and around 10.0% for those aged 75 and older. Males with regional CRC had a higher average annual increase in incidence than females across all age groups, particularly in those over 75 years (AAPC=9.4% vs. 6.9%). Males younger than 50 experienced a substantial annual increase in regional CRC of 15.8% (95% CI=7.6-24.6) from 1997 to 2003, which decreased to an APC of 3.2% (95% CI=1.1-5.3) until 2017. In contrast, regional CRC in females under 50 steadily increased during the study period, with an APC of 6.3% (95% CI=4.6-8.0).

Young females (<50) with distant CRC had a higher average annual percentage change in rates than males (AAPC=11.5% vs. 8.5%). Yet, the APC for distant CRC in young females was initially high at 24.1% (95% CI=13.7-35.4) until 2005, then dropped to 3.8% (95% CI=-1.0-8.8) through 2017. Conversely, young males (<50) maintained a constant APC of 8.5% (95% CI=6.3-10.7) over the entire period. Males older than 50 had higher AAPC in distant CRC than females. Yet, in more recent years, females aged 50-74 had a more rapid increase in distant CRC than males (9.3% vs. 3.8%).

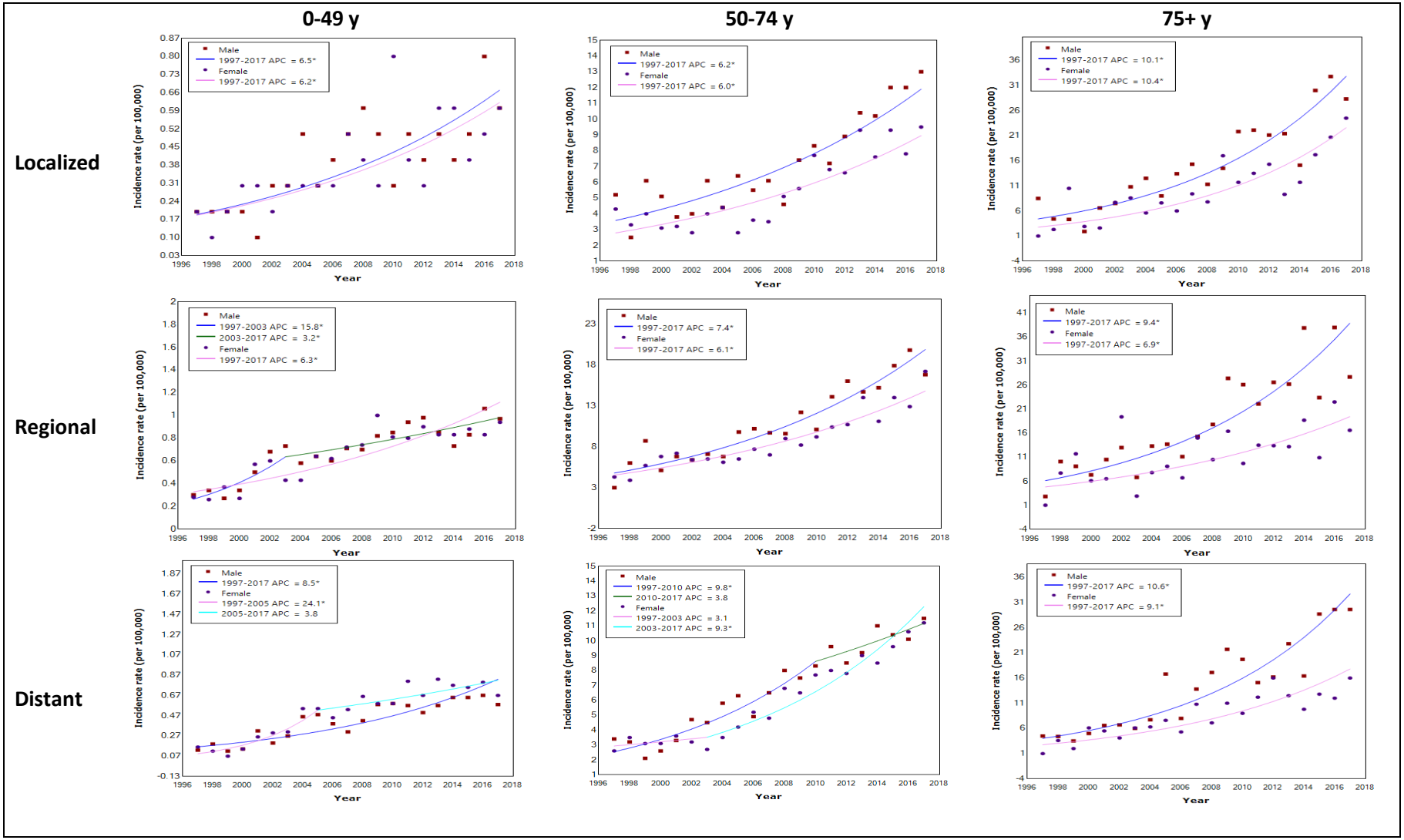
Table 4. 4. Annual percentage change (APC) of colorectal cancer incidence rates by sex, age, and stage, 1997-2017, Saudi Arabia

Stage	Trend 1		Trend 2		AAPC (95%CI)
	Years	APC (95%CI)	Years	APC (95%CI)	1997-2017
Localized					
All					
0-49	1997-2017	7.4* (5.5, 9.3)	-	-	7.4* (5.5, 9.3)
50-74	1997-2017	6.0* (4.6, 7.5)	-	-	6.0* (4.6, 7.5)
75+	1997-2017	9.4* (7.2, 11.6)	-	-	9.4* (7.2, 11.6)

Males					
0-49	1997-2017	6.5* (4.0, 9.1)	-	-	6.5* (4.0, 9.1)
50-74	1997-2017	6.2* (4.4, 8.0)	-	-	6.2* (4.4, 8.0)
75+	1997-2017	10.1* (7.4, 13.0)	-	-	10.1* (7.4, 13.0)
Females					
0-49	1997-2017	6.2* (3.8, 8.7)	-	-	6.2* (3.8, 8.7)
50-74	1997-2017	6.0* (4.2, 7.8)	-	-	6.0* (4.2, 7.8)
75+	1997-2017	10.4* (7.0, 13.9)	-	-	10.4* (7.0, 13.9)
Regional					
All					
0-49	1997-2003	14.3* (6.9, 22.1)	2003-2017	4.0* (2.1, 5.9)	6.9* (4.6, 9.3)
50-74	1997-2017	6.7* (5.8, 7.7)	-	-	6.7* (5.8, 7.7)
75+	1997-2017	8.0* (5.3, 10.9)	-	-	8.0* (5.3, 10.9)
Males					
0-49	1997-2003	15.8* (7.6, 24.6)	2003-2017	3.2* (1.1, 5.3)	6.8* (4.2, 9.4)
50-74	1997-2017	7.4* (5.9, 8.9)	-	-	7.4* (5.9, 8.9)
75+	1997-2017	9.4* (7.1, 11.8)	-	-	9.4* (7.1, 11.8)
Females					
0-49	1997-2017	6.3* (4.6, 8.0)	-	-	6.3* (4.6, 8.0)
50-74	1997-2017	6.1* (5.1, 7.1)	-	-	6.1* (5.1, 7.1)
75+	1997-2017	6.9* (2.9, 11.1)	-	-	6.9* (2.9, 11.1)
Distant					
All					
0-49	1997-2004	23.9* (11.8, 37.4)	2004-2017	4.4* (0.2, 8.7)	10.8* (6.4, 15.5)
50-74	1997-2017	7.9* (7.1, 8.8)	-	-	7.9* (7.1, 8.8)
75+	1997-2017	9.6* (8.0, 11.2)	-	-	9.6* (8.0, 11.2)
Males					
0-49	1997-2017	8.5* (6.3, 10.7)	-	-	8.5* (6.3, 10.7)
50-74	1997-2010	9.8* (6.9, 12.9)	2010-2017	3.8 (-3.2, 11.2)	7.7* (4.7, 10.7)
75+	1997-2017	10.6* (8.6, 12.6)	-	-	10.6* (8.6, 12.6)
Females					
0-49	1997-2005	24.1* (13.7, 35.4)	2005-2017	3.8 (-1.0, 8.8)	11.5* (6.9, 16.2)
50-74	1997-2003	3.1 (-2.2, 8.6)	2003-2017	9.3* (7.8, 10.9)	7.4* (5.6, 9.3)
75+	1997-2017	9.1* (6.6, 11.8)	-	-	9.1* (6.6, 11.8)

Note: APC: annual percentage change; AAPC: average annual percentage change; CI: confidence interval. *Indicates APC or AAPC are significantly different from zero at $P<0.05$. Rates are reported per 100,000 person-years. Trends 1 and 2 refer to distinct calendar periods with significantly different rates of change.

Figure 4. 6. Trends in CRC age-specific incidence rates by sex and stage at diagnosis, Saudi Arabia, 1997 to 2017



Note: Rates are reported per 100,000 person-years. Plotted lines indicate the annual percentage change (APC). The different scales of the y-axis of the figures are used to make trends more apparent. * Indicates APC is significantly different from zero at $P<0.05$. The use of different colors emphasizes the different changes in APC across calendar periods.

4.5 Discussion

This observational registry-based study examined the magnitude and direction of CRC incidence trends in the Saudi population by age, sex, and disease stage at diagnosis. Our detailed epidemiological analysis showed increased incidence of CRC in men and women across all ages and disease stages during the past two decades.

The median age at diagnosis for Saudi women (57 years) and men (60 years) was younger compared to figures documented in several Western nations, such as the US (66 years for both sexes) (43). This discrepancy may partially reflect the younger age distribution in Saudi Arabia (44). We found that CRC incidence rates, both annually and on average, were consistently higher in men than women, with the disparity becoming more pronounced after age 50. This pattern aligns with existing literature, suggesting a higher likelihood of developing CRC in men (45). In 2020, the global CRC incidence rate was 44% higher in men than women (3). The higher rates in men have been linked to the higher prevalence of visceral fat and increased alcohol consumption and smoking among men (46-48). Conversely, in women, endogenous estrogens and the use of oral contraceptives have been linked to a reduced CRC risk (49-51).

Despite sex-related disparities in incidence, we observed a consistent rise in all age-specific incidence rates across both sexes over time. This finding is consistent with reports from the Global Burden of Disease (GBD), which evaluated CRC rates from 1990 to 2019 across 204 countries. These reports described similar upward trends in CRC incidence, especially in regions such as East Asia, Latin America, and the Middle East (52). An increase in CRC rates among neighboring Gulf Cooperation Council (GCC) countries was also noted, with Saudi Arabia recording the highest incidence (53). The rise in trends has often been linked to socio-economic growth and a shift towards Westernized diets and lifestyles (52).

The GBD report also highlighted a 136.9% increase in EO-CRC incidents worldwide in 2019 compared to 30 years ago (54). EO-CRC has even increased in many high-income countries, where rates were stabilizing or decreasing among >50 adults (55). Saudi Arabia was identified in the 2019 GBD report as having the highest APC in EO-CRC rates among all included countries. Although our study highlighted a similar increasing trend in EO-CRC, incidence rates among individuals over 50 increased at an even steeper pace and more than the global APC of 0.6% indicated in the GBD study for 50-74 years adults (56). This continued rise in older Saudi adults may be partially attributed to the lack of a national CRC screening program (24), compounded by low public awareness (57, 58) and inadequate physician screening recommendations (59).

Approximately 60-65% of CRCs are categorized as sporadic, occurring in individuals without any known family history or genetic predispositions (51). The etiology of sporadic CRCs has been primarily linked to modifiable risk factors related to personal habits and lifestyle choices (3, 45, 60). Obesity has also been identified as a major risk factor contributing to the tumorigenesis of CRC (61). In recent decades, Saudi Arabia has undergone rapid and major economic and social advancements, leading to an obesogenic environment marked by poor dietary habits and sedentary lifestyles (62). The 2017 Global Burden of Disease Study highlighted an upward trend in high body-mass index levels from 1999 to 2017 among all age groups in Saudi Arabia (63). Despite the absence of cohort studies assessing risk factors for CRC development among Saudis, it is still plausible to believe that lifestyle factors have played a significant role in escalating the disease's burden over time. Al-Zalabani quantified the proportion of CRC cases associated with certain risk factors (the population-attributable fraction). Insufficient physical activity emerged as the leading risk factor, responsible for 16% of CRC cases, with obesity and smoking also identified as major lifestyle-related risk factors (10).

The increasing rates of EO-CRC within the Saudi population call for a more in-depth examination of the associated factors. Although family history, hereditary syndromes, and Inflammatory bowel disease are established risk factors for EO-CRC (64), most incidents are sporadic with unknown causes (65). The association between sex and EO-CRC remains elusive, with being male identified as a risk factor in certain studies (66, 67). Our study found a similar number of EO-CRC in men and women despite a slightly higher proportion in women. We noted, however, a higher APC of EO-CRC incidence in women compared to men during the second decade in our study period, an observation that warrants further investigation into the reasons behind this difference between sexes.

Our analysis of CRC incidence trends by disease stage revealed an overall increase across all stages and age groups. Yet, among young males (under 50), a more significant rise in the incidence of distant CRC was observed compared to localized and regional stages. This trend aligns with findings from the US and Canada, showing an upward trend in late-stage CRC among younger individuals (37, 38). US SEER data between 2000 and 2014 showed a decline in CRC incidence across all stages for individuals over 49, a trend largely attributed to effective CRC screening (36). Conversely, our study observed increased CRC incidence across all stages for individuals over 49. Additionally, among females aged 50-74, a sharper increase in distant CRC was noted compared to localized and regional CRCs and males of the same age with distant CRC. Given Saudi Arabia lacked a CRC screening program during our study period, an increase in incidence across all stages was

anticipated. Yet, our study's finding of a higher APC in advanced-stage CRC in more recent years among screening-age women compared to men warrants further exploration to understand the reasons behind this trend.

According to the 2022 Saudi Census, over half (54%) of the Saudi population are under 25, and 34% are between 25 and 49 (44). Considering the high prevalence of CRC-related lifestyle factors such as obesity and smoking in Saudi Arabia (68), along with the high proportion of the young, the burden of CRC is expected to rise. Moreover, global predictions in 2012 indicated that cancer incidence among older adults will double by 2035 across all regions, with CRC being a significant contributor. Specifically, 58% of all new CRC cases are expected to occur in individuals aged 65 and over (69). Our study highlighted a positive trend in CRC incidence among older Saudi adults, which, coupled with rising life expectancy (70), suggests a future surge in the economic, societal, and healthcare burdens due to CRC within this demographic. Although screening beyond age 75 is often not recommended (71), developing cancer control strategies for the elderly remains essential (72). Lifestyle interventions for the 45-64 age group are crucial for reducing future cancer burdens (73). Additionally, previous research indicated that physical activity and healthy dietary practices among older adults (>60) could effectively prevent CRC (74, 75).

To our knowledge, this study is the most comprehensive analysis of CRC trends in Saudi Arabia using the national, population-based registry. It is also the first to examine trends by CRC stage at diagnosis. Our findings underscore the critical importance of CRC screening as a strategic intervention to combat CRC increasing rates (76). We also support the current national screening program's guideline that recommends initiating screening at 45 (25). The data in this study revealed a rise in CRC incidence across all sexes, stages, and age groups. The positive incidence trend among individuals under 50 aligns with global patterns in EO-CRC, indicating an escalating risk before the traditional screening age of 50. Furthermore, the rising incidence of distant-stage CRC among younger individuals, emphasizes the need for earlier detection to improve patient outcomes. Finally, given the growing prevalence of CRC lifestyle-related risk factors across all ages within the Saudi population, starting screening at 45 is a sensible and strategic public health measure.

This study has several limitations. Using registry data inherently carries the risks of missing information, coding errors, and data collection and reporting inconsistencies, especially in the registry's earlier years. This might potentially result in masking of early-year changes in CRC trends. Furthermore, the trend analysis by CRC stage in patients over 80 should be interpreted cautiously

due to the lower percentage of stage data completeness (Appendix C.3) in this age group. We could not access regional population data, and thus, a thorough examination of geographic disparities in CRC incidence was not feasible. Such evaluation could have provided insights into geographic-specific needs for targeted health interventions. We also did not examine incidence rates by anatomical subsite or histology, which could have yielded valuable information for understanding CRC epidemiology and informing cancer control efforts. Finally, the absence of long-term data following the CRC screening program's introduction limited our ability to assess its impact on CRC incidence rates.

4.5.1 Conclusion

Between 1997 and 2017, the incidence of CRC in Saudi Arabia increased across all ages, sexes, and disease stages. Future research should assess changes in CRC rates following the launch of the screening program, study lifestyle-related risk factors, and identify those influencing incidence across various age groups. There is also a critical need to analyze factors related to the diagnosis of CRC at advanced stages. Such explorations are key to gaining valuable insights and developing more targeted and efficient screening and awareness strategies.

Declarations

Ethics approval: This study was approved by the Research Ethics Committee of the School of Medicine at the University of Leeds (MREC 19-069) and by the Ethics Committee of King Saud University (E-20-4644)

Funding: This study is part of Norah Alsadhan's PhD study, funded by King Saud University, Riyadh, Kingdom of Saudi Arabia.

Declaration of Competing Interest: The authors declare that they have no competing interests. MPR is currently employed by UCB Biopharma.

Acknowledgments: The authors wish to acknowledge the Saudi Health Council/ National Health Information Center for providing the Saudi Cancer registry data that formed the foundation of this study.

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Chapter 5: Demographic and Clinical Characteristics Associated with Advanced Stage Colorectal Cancer: a registry-based cohort study in Saudi Arabia

Authors List: Norah Alsadhan[1], Sultana A Alhurishi[2], Mar Pujades-Rodriguez[1], Farag Shuweihdi[3], Cathy Brennan[4], Robert M West[1].

Affiliation list:

1. Leeds Institute of Health Sciences, School of Medicine, University of Leeds, Leeds, United Kingdom
2. Department of Community Health Sciences, College of Applied Medical Sciences, King Saud University, Riyadh, Kingdom of Saudi Arabia
3. Dental Translational & Clinical Research Unit, School of Dentistry, University of Leeds, Leeds, United Kingdom
4. Psychological & Social Medicine, School of Medicine, University of Leeds, Leeds, United Kingdom

Study Four	
Journal	BMC Cancer.
Publication status	Published in April 2024.
Reference	Alsadhan N, Alhurishi SA, Pujades-Rodriguez M, Shuweihdi F, Brennan C, West RM. Demographic and clinical characteristics associated with advanced stage colorectal cancer: a registry-based cohort study in Saudi Arabia. BMC cancer. 2024;24(1):533.

Commentary

This chapter builds on insights from Chapter Four, revealing a steady increase in CRC incidence across all age groups, sexes, and disease stages between 1997 and 2017. Moreover, it was noted that distant-stage CRC rates increased more rapidly than those of localized or regional stages. Given the association between advanced-stage presentation and poor prognosis, identifying the factors contributing to late-stage diagnosis among Saudi CRC patients is vital. Such insights are essential for recognizing high-risk subpopulations, informing targeted health promotion efforts, and guiding future research priorities on examining the determinants of advanced disease. To address this gap, Study Four in this chapter examines the clinical and demographic characteristics linked to advanced-stage CRC at diagnosis.

Recommendations from Chapter Two regarding the importance of transparent incidence methods reporting informed the clear and explicit reporting of the CRC case definition used in Study Four in this chapter. Chapter Two insights also guided the documentation of data quality control procedures used by the Saudi Cancer Registry and the calculation of data validity indicators, including the proportion of morphologically verified cases and the percentage of cases identified through death certificates only. These reporting practices were crucial to enhancing the interpretability of the findings presented in this chapter.

In this Chapter, I adopted an exploratory rather than a causal inference analytical approach. The primary objective was to explore associations between clinical and demographic characteristics and the likelihood of being diagnosed with late-stage CRC. Initially, I intended to use ordinal logistic regression to model the relationship between the independent variables and the CRC stage, which is ordinal in nature, progressing from localized to regional and then to distant stage. However, upon implementation, the proportional odds assumption of ordinal logistic regression did not hold. As a result, I decided to proceed with multiple logistic regression and redefined CRC stage as a binary outcome variable. Distant-stage CRC was classified as late-stage disease, while localized and regional stages were grouped together as early-stage CRC. This categorization was informed by five-year survival data from the SEER program, which reports survival rates of approximately 91% and 72% for localized and regional cancers, respectively, compared to only 13% for distant-stage CRC. Due to this substantial disparity in prognosis, distant-stage CRC was deemed an appropriate definition of late-stage disease for the analysis in this study. Risk factors considered in the logistic regression analysis included age at diagnosis, sex, marital status, administrative region, time of diagnosis, and tumor site. These factors were selected not merely based on their availability within

the Saudi Cancer Registry, where additional variables were also accessible. They were chosen because their associations with and relevance to disease stage at diagnosis have been hypothesized and explored in Western literature, while information specific to the Saudi population remains limited.

To guide model development, I first used the likelihood ratio test to assess the overall significance of each covariate. All covariates were then included in the initial logistic regression model as main effects. The model was subsequently stratified by sex to explore potential sex differences in risk factors. Model fit for the initial logistic regression model was assessed using McFadden's R-squared, which yielded a value of 0.005, indicating limited explanatory power. Furthermore, it is important to note that an alternative modelling approach to the one presented in this chapter could have been employed. Instead of including all covariates simultaneously in the initial model, a more refined modelling strategy would involve selecting one exposure of interest at a time and identifying confounders that are specifically relevant to that association. Such an approach would offer a better understanding of the relationships under investigation.

Although I was initially interested in further stratifying the analysis by region, the small sample sizes in some regions limited the feasibility and statistical robustness of such an approach. To assess the contribution of regional variability to the likelihood of late-stage CRC diagnosis, a likelihood ratio test was conducted. The test revealed that including region as a random effect significantly improved model fit, highlighting the presence of regional differences in late-stage diagnosis risk. To explore regional differences in greater depth and enable more statistically robust subgroup analysis, decision tree analysis was used to aggregate regions into clusters with sufficient sample sizes. These regional clusters were then used to stratify the logistic regression analysis by region and sex, examining variations in risk factors across these subpopulations.

Although more advanced modeling approaches, such as multilevel models of region and time, could have been employed, the use of decision tree analysis was considered appropriate given the exploratory aims of this study. This method is flexible, data-driven, and easily interpretable. It also captures interactions between variables and highlights the strongest associations, thereby enabling the generation of new insights from the data. Furthermore, using multiple analytical approaches, such as logistic regression and decision tree analysis, enhanced the rigor of the investigation.

5.1 Abstract

Background: In Saudi Arabia, approximately one-third of colorectal cancer (CRC) patients are diagnosed at an advanced stage. Late diagnosis is often associated with a worse prognosis. Understanding the risk factors for late-stage presentation of CRC is crucial for developing targeted interventions enabling earlier detection and improved patient outcomes.

Methods: We conducted a retrospective cohort study on 17,541 CRC patients from the Saudi Cancer Registry (1997-2017). We defined distant CRCs as late-stage and localized and regional CRCs as early-stage. To assess risk factors for late-stage CRC, we first used multivariable logistic regression, then developed a decision tree to segment regions by late-stage CRC risk, and finally used stratified logistic regression models to examine geographical and sex variations in risk factors.

Results: Of all cases, 29% had a late-stage diagnosis, and 71% had early-stage CRC. Young (<50 years) and unmarried women had an increased risk of late-stage CRC, overall and in some regions. Regional risk variations by sex were observed. Sex-related differences in late-stage rectosigmoid cancer risk were observed in specific regions but not in the overall population. Patients diagnosed after 2001 had increased risks of late-stage presentation.

Conclusion: Our study identified risk factors for late-stage CRC that can guide targeted early detection efforts. Further research is warranted to fully understand these relationships and develop and evaluate effective prevention strategies.

5.2 Introduction

Colorectal cancer (CRC) is the third most common type of cancer and the second leading cause of cancer-related deaths worldwide, despite existing prevention strategies to lower its risk (1). According to the latest incidence report from the Saudi Cancer Registry (SCR), CRC is the most commonly diagnosed cancer in men and the third in women. In 2020, 1,729 cases were diagnosed, accounting for almost 12.3% of all newly diagnosed cancers, and around 26% of diagnosed patients had distant CRC (2).

The Surveillance, Epidemiology and End Results (SEER) Summary Stage System classifies cancer stage based on the tumor's potential impact on prognosis and survival, distinguishing between: i) localized cancer, which is contained to the site of origin, with no evidence of adjoining invasion or metastasis beyond the organ; ii) regional cancer, with involvement of local lymph nodes, tissues, or other organs; and iii) distant cancer, which has spread to parts of the body distant from the organ of origin (3). The prognosis of CRC largely depends on the stage at diagnosis (4). Five-year survival rates for patients with localized and regional cancers are approximately 91% and 72%, respectively, while the survival rate for patients with distant-stage CRC is 13% (5). Treatment costs are also considerably higher for distant CRC (6). Therefore, identifying and targeting preventive interventions to patients and populations most prone to present with distant CRC is essential for improving survival and reducing healthcare costs.

Previous studies, primarily conducted in Western countries, have reported risk factors associated with the late-stage diagnosis of CRC. These factors include age, sex, race/ethnicity, marital status, geographic regions, family history of CRC, and cancer site (7-13). However, results from published studies are inconsistent, highlighting the necessity for a deeper examination of these factors and their potential role in targeting CRC prevention strategies in different settings. Limited information is available in the Saudi context.

In 2016, Saudi Arabia initiated its 2030 vision, targeting strategic objectives across various sectors, including healthcare transformation under the Health Sector Transformation Program (14). This program seeks to restructure the health sector by improving service quality, access, and disease prevention. A colorectal cancer control initiative was developed under this program. As a result, the Ministry of Health introduced the first Saudi national CRC screening program targeting individuals aged 45 and above (15). It has been postulated that the effectiveness of such programs could be enhanced by identifying subpopulations at risk and subsequently adopting a strategic, targeted approach to screening and symptom-awareness campaigns (16). Adopting CRC screening

among the public is anticipated to improve early detection rates and facilitate timely interventions and treatment, potentially reducing the CRC burden for patients, their relatives, and the healthcare system. This study will advance the knowledge of CRC in Saudi Arabia by assessing risk factors for late-stage presentation. Regional, sex, and age dependent differentials in risk factors were also examined.

5.3 Methods

5.3.1 Study design and Data source

This is a retrospective cohort study using anonymized data from the SCR. Established in 1994, the registry collects cancer data nationwide from governmental and private health institutions. Data includes demographics (i.e., age, sex, marital status, and region) and tumor characterization (i.e., date of diagnosis, primary site, stage, and basis of diagnosis). The registry's main office undertakes quality control procedures, including data verification and case linkage (17). Cancer topography (primary site) and morphology (histology) from CRC neoplasms are coded using the second and third editions of the International Classification of Diseases for Oncology (ICD-O-2 for cancers diagnosed between 1994 and 2000 and ICD-O-3 after 2000). For CRC, coding is identical in both ICD-O versions (18).

5.3.2 Study population

The study used registry data from all Saudi patients diagnosed with malignant CRC between 1997 and 2017. Colon cancer was defined as a diagnosis with any of the following topography codes: cecum (C18.0), appendix (C18.1), ascending colon (C18.2), hepatic flexure of colon (C18.3), transverse colon (C18.4), splenic flexure of colon (C18.5), descending colon (C18.6), sigmoid colon (C18.7), overlapping lesion of colon (C18.8), and colon, not otherwise specified (NOS; C18.9). Cancer of the rectosigmoid junction and rectum, NOS were defined by codes C19.9 and C20.9, respectively.

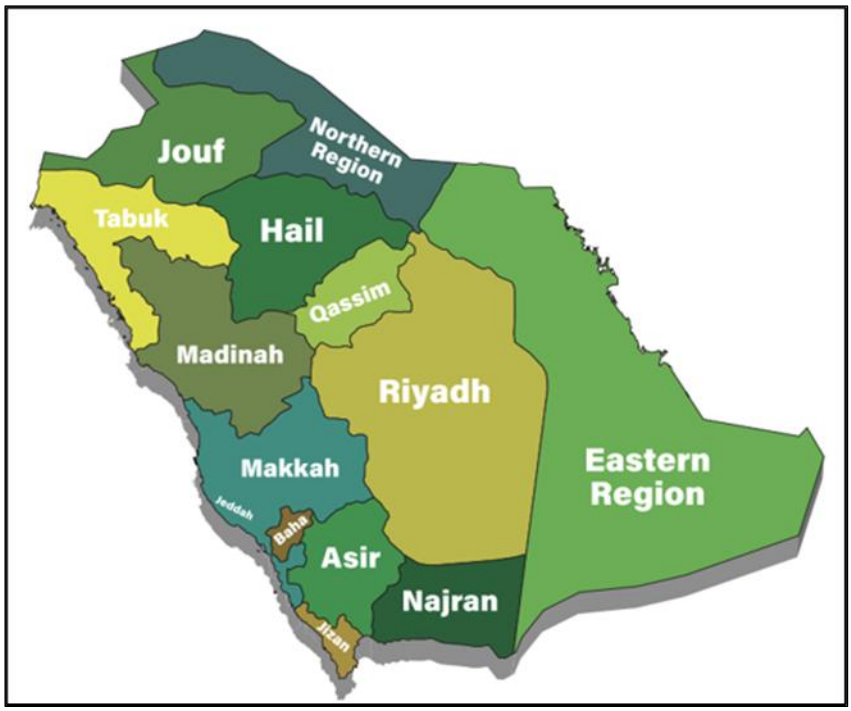
5.3.3 Study outcome

The study outcome was late-stage CRC diagnosis, which was defined as distant CRC. Localized and regional CRCs were categorized as early-stage CRC.

5.3.4 Covariates

Risk factors considered included age at diagnosis (<40, 40-49, 50-59, 60-69, 70-79, and 80+ years), sex, marital status (married and unmarried, which comprised single, divorced, and widowed individuals), region (each of the 13 administrative Saudi Arabian regions; Figure 5.1), diagnosis date (grouped into four 5-year intervals), and tumor site (colon, rectosigmoid, and rectal). The registry recorded age as a continuous variable, but we categorized it into six groups for this analysis to account for nonlinear effects.

Figure 5.1. Regions of Saudi Arabia (2)



5.3.5 Statistical analyses

We used summary statistics to describe the frequency and percentage of CRC patients according to disease stage at diagnosis. We then assessed the association between cancer stage at diagnosis and patients' demographic and clinical characteristics using multivariable logistic regression. The initial model included all study covariates. We chose the 50-59 age group as the reference category in our analysis, based on the epidemiological literature defining young-onset CRC as diagnoses before age 50 and our interest in assessing ratios for patients diagnosed at younger ages (19, 20).

In a second stage, we stratified the model by sex to examine potential sex differences in risk factors. The unequal sample sizes of the 13 regions posed a methodological challenge for

stratifying our logistic regression analyses by region. Thus, we used Fast and Frugal Trees (FFT)(21), a type of decision tree analysis, to identify regions that could be grouped according to their risk of developing late-stage CRC, allowing for more statistically robust analyses. Detailed explanation of the FFT method is provided in Appendix D.1. We finally assessed associations with late-stage diagnosis within each identified geographical group of similar CRC risk profile, stratified by sex, to quantify variation in risk factors.

We used multiple imputation by chain equations, generating ten datasets, to impute covariate data. There were 1,922 (9.9%) CRC patients with missing stage information. In primary analysis, we performed a complete stage-data analysis to prevent potential bias introduction associated with outcome imputation. To assess the robustness of the estimates, we also imputed missing stage data using multiple imputation with chained equations as a sensitivity analysis. Detailed explanation of the imputation method and the handling of missing covariate data in multivariable logistic regression and FFT analyses is provided in Appendix D.1.

All analyses were conducted in *R 4.3.2*, (22), including the "FFTrees" package for the decision tree classifier (21). P-values were two-sided. Results with P-values less than 0.05 were considered statistically significant. We used the likelihood ratio test to assess the overall significance of each risk factor considered.

5.4 Results

A total of 19,463 new cases of CRC were registered during the study period, and 17,541 of them had known CRC stage. Of cases with recorded CRC stage, 98.8% were morphologically verified (MV), and only 50 (0.3%) were identified through death certificate only (DCO). In contrast, among the 1,922 cases with unknown CRC stage, 83.6 % were MV, and 12.5% had been identified through DCO. There were 5,139 (29%) patients with late-stage presentation (Table 5.1). We observed consistent demographic characteristics across both early and late-stage CRC diagnoses. The overall mean age was 58 years. Most patients were males, married, lived in Riyadh, and had colon cancer.

Table 5.1. Distribution of patient characteristics at diagnosis by disease stage and associated adjusted odds ratios for late versus early-stage CRC presentation

Characteristics		Early-stage N (%)	Late-stage N (%)	OR (95%CI)
		12402 (70.7)	5139 (29.3)	
Age in yrs, mean (SD)		57.93 (14.8)	57.81 (14.9)	
Age group in yrs	0-39	1383 (11.2)	598 (11.6)	1.10 (0.99, 1.22)
	40-49	2103 (17.0)	936 (18.2)	1.13 (1.03, 1.23)
	50-59	3113 (25.1)	1222 (23.8)	1.00 *P*=0.01
	60-69	2941 (23.7)	1170 (22.8)	1.03 (0.93, 1.12)
	70-79	2013 (16.2)	859 (16.7)	1.11 (1.00, 1.21)
	80+	843 (6.8)	353 (6.9)	1.09 (0.95, 1.23)
Sex	Male	6930 (55.9)	2713 (52.8)	1.00 *P*<0.001
	Female	5472 (44.1)	2426 (47.2)	1.12 (1.06, 1.19)
Marital status	Married	10,020 (89.9)	4169 (88.0)	1.00 *P*<0.01
	Unmarried	1126 (10.1)	568 (12.0)	1.09 (0.98, 1.19)
Region	Riyadh	3787 (30.8)	1583 (31.1)	1.00 *P*<0.0001
	Eastern	2031 (16.5)	961 (18.9)	1.13 (1.03, 1.23)
	Makkah	3150 (25.6)	1200 (23.6)	0.91 (0.83, 1.00)
	Madina	705 (5.7)	235 (4.6)	0.81 (0.65, 0.96)
	Asir	911 (7.4)	346 (6.8)	0.91 (0.77, 1.05)
	Jazan	239 (1.9)	77 (1.5)	0.77 (0.51, 1.04)
	Najran	115 (0.9)	53 (1.0)	1.09 (0.76, 1.42)
	Hail	224 (1.8)	108 (2.1)	1.15 (0.91, 1.39)
	Qassim	564 (4.6)	250 (4.9)	1.06 (0.90, 1.22)
	Baha	198 (1.6)	57 (1.1)	0.68 (0.38, 0.98)
	Jouf	86 (0.7)	59 (1.2)	1.63 (1.30, 1.97)
	Northern	67 (0.5)	45 (0.9)	1.59 (1.21, 1.98)
	Tabuk	237 (1.9)	118 (2.3)	1.18 (0.95, 1.41)
Diagnosis date	1997-2001	1112 (9.0)	348 (6.8)	1.00 *P*<0.0001
	2002-2006	2054 (16.6)	823 (16.0)	1.28 (1.14, 1.43)
	2007-2011	3336 (26.9)	1492 (29.0)	1.43 (1.30, 1.57)
	2012-2017	5900 (47.6)	2476 (48.2)	1.34 (1.21, 1.47)

Anatomical site	Colon	7513 (60.6)	3027 (58.9)	1.00 *P*<0.01
	Rectosigmoid	1847 (14.9)	873 (17.0)	1.17 (1.08, 1.27)
	Rectal	3042 (24.5)	1239 (24.1)	1.01 (0.93, 1.09)

Note: CI: Confidence interval; N: Number; OR: odds ratios adjusted for all factors in the table using complete stage data and multiple imputation of covariates; SD: Standard deviation. The p-values are derived from the overall likelihood ratio tests for association. Number and percentage of missing values relative to the dataset with known cancer stage: Age at diagnosis (n=7, 0.04%); Marital status (n=1658, 9.5%); Geographical region (n=135, 0.8%). Percentages are presented by column to characterise patients' profiles for patients with late-stage and early-stage CRC.

5.4.1 Factors associated with late-stage CRC

Age and sex were associated with late-stage CRC, with slightly higher adjusted ORs observed for the 40-49 and 70-79 age groups (1.13, 95%CI=1.03-1.23; and 1.11, 95%CI=1.00-1.21, respectively, overall *P*=0.01) compared with the 50-59 group; and in women (1.12; 95%CI=1.06-1.19; overall *P*<0.001) compared to men (Table 5.1). Regional variations were also noted; with the highest estimates of late-stage diagnosis found in the Jouf, Northern, and Eastern regions (1.63; 95%CI=1.30-1.97; 1.59; 95%CI=1.21-1.98 and 1.13; 95%CI=1.03-1.23; respectively, overall *P*<0.0001) compared to Riyadh. Patients with rectosigmoid cancer had a higher risk of late-stage diagnosis (1.17; 95%CI=1.08-1.27) than those with colon cancer, as were patients diagnosed within calendar periods following 1997-2001. Results from the sensitivity analysis using imputed cancer stage data (Appendices D.2-D.4) were similar to the primary analysis findings.

We found an increased risk of late-stage CRC presentation in younger age (<50) and unmarried women and in men aged 80 years or more (Table 5.2). We also found regional sex-related disparities in late-stage disease risk. The highest estimates were found for Jouf in men and for the Northern area in women (2.08; 95%CI=1.63-2.52; and 2.14; 95%CI=1.60-2.68; respectively, overall *P* <0.0001) compared with Riyadh. Furthermore, in the Hail region, men had increased risk of late-stage presentation (1.43; 95%CI=1.11-1.74), while no evidence of increased risk was observed amongst women (0.88; 95%CI=0.51-1.24). Risk estimates for cancer location were similar irrespective of sex, and similar risk patterns were also found for calendar periods.

Table 5.2. Adjusted and unadjusted odds ratios for late versus early-stage CRC presentation, by sex

Characteristics	Males (N=9,643)		Females (N=7,898)	
	Adjusted OR (95%CI)	Unadjusted OR (95%CI)	Adjusted OR (95%CI)	Unadjusted OR (95%CI)
Age group in yrs				
0-39	0.95 (0.78, 1.12)	0.98 (0.83, 1.16)	1.26 (1.09, 1.42)	1.22 (1.04, 1.44)
40-49	1.04 (0.90, 1.19)	1.06 (0.92, 1.22)	1.22 (1.08, 1.37)	1.20 (1.04, 1.39)
50-59	1.00 *P*=0.01	1.00 *P*=0.01	1.00 *P*<0.01	1.00 *P*<0.01
60-69	0.95 (0.82, 1.08)	0.95 (0.84, 1.08)	1.10 (0.96, 1.24)	1.10 (0.96, 1.26)
70-79	1.11 (0.98, 1.25)	1.11 (0.97, 1.27)	1.06 (0.90, 1.22)	1.07 (0.91, 1.25)
80+	1.19 (1.00, 1.37)	1.18 (0.98, 1.41)	0.91 (0.68, 1.14)	0.93 (0.74, 1.16)
Marital status				
Married	1.00 *P*=0.32	1.00 *P*=0.32	1.00 *P*=0.01	1.00 *P*=0.01
Unmarried	1.14 (0.94, 1.35)	1.14 (0.95, 1.38)	1.23 (1.10, 1.37)	1.20 (1.05, 1.37)
Region				
Riyadh	1.00 *P*<0.0001	1.00 *P*<0.0001	1.00 *P*<0.0001	1.00 *P*<0.0001
Eastern	1.21 (1.08, 1.34)	1.21 (1.06, 1.38)	1.04 (0.90, 1.18)	1.06 (0.92, 1.22)
Makkah	0.97 (0.84, 1.09)	0.96 (0.85, 1.08)	0.86 (0.73, 0.99)	0.87 (0.76, 0.99)
Madina	0.88 (0.67, 1.10)	0.88 (0.71, 1.09)	0.71 (0.47, 0.96)	0.72 (0.56, 0.91)
Asir	0.88 (0.69, 1.07)	0.88 (0.72, 1.06)	0.95 (0.75, 1.15)	0.95 (0.78, 1.16)
Jazan	0.95 (0.60, 1.30)	0.93 (0.66, 1.32)	0.60 (0.20, 1.01)	0.62 (0.41, 0.92)
Najran	1.35 (0.89, 1.81)	1.35 (0.85, 2.12)	0.86 (0.37, 1.34)	0.88 (0.55, 1.43)
Hail	1.43 (1.11, 1.74)	1.42 (1.04, 1.95)	0.88 (0.51, 1.24)	0.90 (0.62, 1.29)
Qassim	1.18 (0.96, 1.40)	1.18 (0.94, 1.46)	0.93 (0.70, 1.17)	0.95 (0.75, 1.20)
Baha	0.78 (0.34, 1.22)	0.80 (0.52, 1.24)	0.60 (0.18, 1.02)	0.59 (0.39, 0.89)
Jouf	2.08 (1.63, 2.52)	2.03 (1.30, 3.15)	1.21 (0.68, 1.73)	1.26 (0.75, 2.13)
Northern	1.16 (0.58, 1.73)	1.12 (0.63, 2.00)	2.14 (1.60, 2.68)	2.22 (1.30, 3.79)
Tabuk	1.25 (0.95, 1.55)	1.27 (0.94, 1.71)	1.11 (0.76, 1.47)	1.13 (0.79, 1.60)
Diagnosis date				
1997-2001	1.00 *P*<0.01	1.00 *P*<0.01	1.00 *P*<0.001	1.00 *P*<0.001

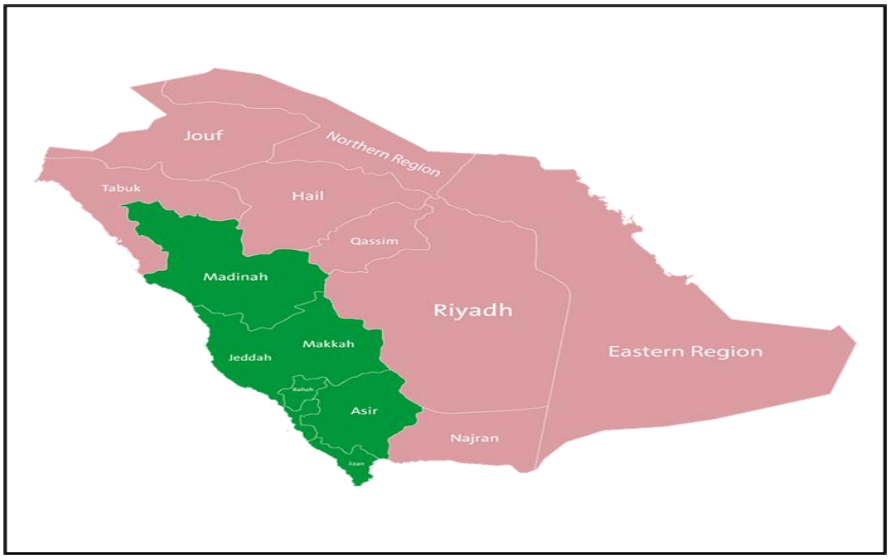
2002-2006	1.24 (1.04, 1.44)	1.24 (1.02, 1.51)	1.33 (1.12, 1.55)	1.33 (1.08, 1.65)
2007-2011	1.39 (1.20, 1.57)	1.39 (1.15, 1.67)	1.49 (1.29, 1.69)	1.48 (1.21, 1.80)
2012-2017	1.24 (1.06, 1.42)	1.25 (1.05, 1.49)	1.48 (1.29, 1.67)	1.46 (1.21, 1.76)
Anatomical site				
Colon	1.00 *P*=0.03	1.00 *P*=0.03	1.00 *P*=0.05	1.00 *P*=0.05
Rectosigmoid	1.18 (1.05, 1.30)	1.17 (1.04, 1.33)	1.18 (1.04, 1.31)	1.18 (1.03, 1.35)
Rectal	0.99 (0.88, 1.10)	0.99 (0.89, 1.10)	1.04 (0.92, 1.16)	1.05 (0.93, 1.18)

Note: CI: Confidence interval; N: Number; OR: Odds ratio. Adjusted ORs represent estimates adjusted for all factors in the table using complete stage data and multiple imputation of covariates. The p-values are derived from the overall likelihood ratio tests for association.

5.4.2 Regional disparities in factors associated with late CRC

Through FFT analysis (Appendices D.5 and D.6), we defined two geographical areas based on late presentation risk (Figure 5.2). Group A (high risk for late-stage CRC) included Riyadh, Eastern, Najran, Hail, Qassim, Jouf, Northern, and Tabuk regions; and Group B included Makkah, Madina, Asir, Jazan, and Baha.

Figure 5.2. Geographic distribution of late-stage CRC risk in Saudi Arabia, based on FFT analysis: high-risk regions (Group A) are colored in red, and low-risk regions (Group B) in green



In Group A, identified as high-risk, women under 50 and unmarried had an increased risk of late-stage CRC (Table 5.3). These differences were not found in Group B. Increased risk of late-stage rectosigmoid cancer was observed for women in Group A (1.34; 95%CI=1.16-1.51; overall *P*=<0.01) and for men in Group B (1.29; 95%CI=1.09-1.49; overall *P*=0.04). Compared to the 1997-2001

period, the risk of presenting with late-stage CRC in men and women was increased in subsequent periods across all regions. This increase was particularly pronounced for females in Region B.

Table 5.3. Adjusted odds ratios for late versus early-stage CRC presentation, by region and sex

Characteristics	Group (A) regions (N= 10,370)		Group (B) regions (N=7,171)	
	Males (N=5,658)	**Females** (N=4,712)	**Males** (N=3,985)	**Females** (N=3,186)
	OR (95%CI)	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**
Age group in yrs				
0-39	0.95 (0.73, 1.17)	1.34 (1.14, 1.55)	0.95 (0.67, 1.23)	1.12 (0.84, 1.39)
40-49	1.02 (0.83, 1.20)	1.32 (1.14, 1.50)	1.11 (0.88, 1.34)	1.05 (0.81, 1.29)
50-59	1.00 *P*=0.22	1.00 *P*<0.01	1.00 *P*=0.01	1.00 *P*=0.02
60-69	1.01 (0.84, 1.18)	1.09 (0.91, 1.27)	0.87 (0.66, 1.08)	1.10 (0.88, 1.33)
70-79	1.11 (0.93, 1.28)	1.11 (0.90, 1.33)	1.10 (0.88, 1.32)	0.94 (0.69, 1.20)
80+	1.13 (0.88, 1.37)	1.09 (0.80, 1.38)	1.23 (0.95, 1.52)	0.63 (0.26, 1.01)
Marital status				
Married	1.00 *P*=0.85	1.00 *P*=0.02	1.00 *P*=0.30	1.00 *P*=0.38
Unmarried	1.07 (0.82, 1.31)	1.25 (1.09, 1.42)	1.23 (0.97, 1.49)	1.19 (0.99, 1.40)
Diagnosis date				
1997-2001	1.00 *P*<0.0001	1.00 *P*=0.02	1.00 *P*=0.06	1.00 *P*<0.0001
2002-2006	1.16 (0.90, 1.42)	1.18 (0.91, 1.45)	1.40 (1.08, 1.71)	1.81 (1.44, 2.18)
2007-2011	1.56 (1.32, 1.80)	1.39 (1.14, 1.64)	1.20 (0.90, 1.50)	1.85 (1.50, 2.19)
2012-2017	1.34 (1.11, 1.57)	1.28 (1.05, 1.52)	1.13 (0.84, 1.42)	2.07 (1.73, 2.41)
Anatomical site				
Colon	1.00 *P*=0.47	1.00 *P*<0.01	1.00 *P*=0.04	1.00 *P*=0.92
Rectosigmoid	1.09 (0.93, 1.25)	1.34 (1.16, 1.51)	1.29 (1.09, 1.49)	0.98 (0.76, 1.20)
Rectal	0.99 (0.85, 1.12)	1.04 (0.89, 1.19)	0.98 (0.86, 1.15)	1.06 (0.86, 1.26)

Note: CI: Confidence interval; N: Number; OR: odds ratios adjusted for all factors in the table using complete stage data and multiple imputation of covariates. The p-values are derived from the overall likelihood ratio tests for association.

5.5 Discussion

The escalating incidence and mortality rates associated with CRC have rendered it a critical public health concern in Saudi Arabia (23, 24). Considering the essential role of the stage at diagnosis in CRC prognosis (25), it is vital to identify patients at increased risk for late-stage CRC to enhance early detection strategies. This study is the first in Saudi Arabia to explore factors associated with late-stage CRC presentation using a large national registry database.

In our study, 29.3% of patients were diagnosed with late-stage CRC, higher than the 23% reported by the US SEER program (26). While the US has benefitted from a long history of CRC screening leading to early detections (27), Saudi Arabia only recently initiated its screening program (15). Differences in referral pathways and diagnostic timelines (28), and societal and cultural factors, including low public awareness regarding CRC screening (29, 30), might also contribute to delays in diagnosis and reduced screening uptake in Saudi Arabia.

We report a higher risk of late-stage CRC in women than men. This is consistent with previous studies in Saudi Arabia and the US (31, 32) but contrasts with findings from other countries. A review of U.K. national data showed no differences in the proportion of men and women diagnosed at advanced CRC stages (33). Conversely, Nguyen et al.'s systematic review and meta-analysis, including seventeen studies conducted between 1993 and 2008 in North America, Europe, and Asia, reported a pooled estimate of 83% higher risk of advanced CRC diagnosis in men than in women (8). The discrepancy between men and women in CRC stage presentation could arise from differences in tumor locations: men often have distal colon cancer, which is easier to detect early, while women have tumors in the harder-to-detect proximal colon (34, 35). Our study, however, highlighted that men and women were more likely to present with distal disease at the rectosigmoid junction.

A possible explanation of the observed sex-related disparity in late-stage CRC risk could be differences in screening utilization and in psychosocial factors, such as perceived or real screening barriers. A systematic review of 134 international studies on CRC screening participation found women less likely to be screened (36), possibly due to receiving fewer physician referrals, viewing CRC as a 'male disease', and perceiving more barriers to screening uptake (36, 37). A recent Saudi study supported this, as women faced more screening barriers than men, including fear and embarrassment of the screening procedure (38). Additionally, the lower CRC incidence rates in Saudi women compared to men may also perpetuate the view of CRC as predominantly a male

disease (2, 23). This perception could thereby affect screening uptake and early diagnosis among Saudi women.

Another plausible explanation may be the existence of gender disparities in healthcare access and provision. Gender bias in clinical care, particularly in cardiovascular disease and chronic pain treatment, has been well documented (39-41). Prior research indicated that women, more often than men, are less likely to receive adequate pain management. Evidence suggests that women's complaints are often dismissed as emotional or of psychogenic origin, potentially leading to delayed diagnoses compared to men (39). Although this issue, to our knowledge, has not been explored within the context of colorectal cancer, its potential impact cannot be overlooked, and further research into this area is needed. Alcalde-Rubio's recent review underlines that health systems and providers continue to neglect gender disparities in healthcare and that developing gender-oriented intervention strategies and training of healthcare providers is essential to address and mitigate these biases effectively (42).

Our results revealed that young women are at an increased risk of late-stage CRC diagnosis, consistent with prior research linking CRC in people under the age of 50 to aggressive tumor characteristics (43-46). Yet, a direct link between young women and advanced CRC is not established. CRC in the young might involve diagnostic delays due to misattributing symptoms to benign conditions (47). We also hypothesize that factors like health-seeking behaviors, cultural perceptions, patient-practitioner communication, and CRC screening practices, which have also been emphasized in previous studies (31, 48), might affect late-stage diagnoses in young women, highlighting the need for more detailed research to explore these potential associations. While the current Saudi guidelines for initiating CRC screening at the age of 45 align with current recommendations in the US (49, 50), it's important to note that these guidelines were formulated based on limited Saudi data. Our findings emphasize the potential advantage of starting screenings at 45. Yet, they also underscore the need for further research into the increased risk among women under 45 years and potential consideration of gender-specific recommendations for the age of initiation of CRC screening to achieve earlier and more effective detection and treatment of CRC amongst women.

Unmarried women, but not men, had a higher risk of late-stage CRC. This finding is consistent with a recent systematic review of 18 studies, mainly from the US, indicating the positive effect of marriage on the likelihood of presenting with early-stage cancer (13). In their analysis of about 1,26M patients with major cancers, including CRC, Aizer et al. found that unmarried patients,

across all cancers, were more likely to be diagnosed with advanced stage cancer compared to those who were married (51). A previous study also highlighted that being unmarried is associated with delayed CRC diagnosis, resulting in more advanced stages at presentation (52). This observation may arise from a higher financial status, facilitating access to healthcare services (13, 53).

Additionally, married individuals often benefit from emotional and informational support from their spouses, promoting positive health-related behavior, including regular medical check-ups and greater use of screening services (51, 54, 55). Cross-sectional studies in Saudi Arabia have also reported higher knowledge of CRC and its screening among married individuals (56, 57). While CRC screening is freely available in Saudi Arabia, access alone does not ensure equitable utilization. Further research is needed to confirm and further explain observed disparities in cancer outcomes based on marital status. Exploring unique barriers and concerns in accessing healthcare for unmarried women is also essential for developing targeted awareness and social support interventions and training for healthcare providers to recognize and address any potential related biases in the diagnosis process.

Emerging evidence suggests that the anatomical location of CRC impacts the prognostic characteristics of the disease (58). Some studies noted differences in tumor biology, clinical presentation, and outcomes between proximal (right) and distal (left) CRC (12, 59, 60). These differences were usually attributed to the distinct embryologic origins, gross macroscopic pathology, and metastatic patterns of the right and left colon segments (12, 61, 62). In our study, rectosigmoid cancers in men and women were more likely to be diagnosed at a late stage compared to colon cancers. This aligns with findings from a recent registry-based study of 25,282 Australian CRC patients that showed an association between distal tumors and presentation at a distant CRC stage (46). Saudi Arabia lacked established guidelines for CRC screening modalities and frequency during our study period. However, the recently introduced Saudi national CRC screening program recommends the Fecal Immunochemical Test (FIT) for asymptomatic individuals at average risk and colonoscopy for those at higher risk (15). The FIT test has greater sensitivity in detecting left-sided colon lesions (63, 64). Therefore, given the increased risk of late-stage CRC associated with rectosigmoid cancers identified in our study, these findings reinforce the recommendation for using immunochemical testing methods for early detection.

Our findings showed an increased risk of late-stage CRC presentation in recent years, contrasting with findings from countries with well-established screening programs. For example, Vather et al.

suggested that Australia's enhanced CRC screening uptake could be linked to a recent decline in advanced CRC diagnoses (46). There were no national screening guidelines or awareness initiatives in Saudi Arabia during the study period; therefore, it is not possible to correlate screening implementation with CRC trends. Plausible explanations for our findings might be an increasing proportion of patients diagnosed before death (who might have been missed in earlier years) or advancements in the documentation and reporting of CRC stage over time. It is essential to analyze trends in late-stage diagnosis following the launch of the Saudi CRC screening program to ascertain its effectiveness and the impact of screening on disease presentation.

Previous studies in Saudi Arabia have primarily focused on the incidence of CRC, with findings indicating the highest disease rates in the Riyadh and Eastern regions, possibly due to the high population density in these areas (65). However, no previous studies have investigated the disparities in colorectal cancer outcomes and stages across different regions. The unconventional approach of utilizing FFT analysis for regional grouping was chosen to address the variability in regional sample sizes. Yet, decision trees are considered a powerful decision-making tool for identifying distinctive homogeneous subgroups to develop tailored interventions (66, 67). It also recognizes interactions between factors- a distinctive feature often overlooked in other methods to simplify analysis (68). In our FFT analysis, region was identified as the primary influencing factor on disease stage, while sex was recognized as the second most significant factor (Appendices D.5 and D.6). This highlights the critical need to account for geographical and sex-specific factors when examining CRC stage at presentation.

In Saudi Arabia, free oncology care is provided to all nationals through public cancer facilities concentrated mainly in Riyadh, Makkah, and the Eastern regions (69). Though we anticipated these centralized resources would result in earlier CRC stage presentations in these areas compared to other regions, our results showed otherwise. Patients in Makkah, Madina, Asir, Jazan, and Baha were at a lower risk of presenting with late-stage CRC, whereas those in Riyadh, Eastern, Najran, Hail, Qassim, Jouf, Northern, and Tabuk regions faced an increased risk of late-stage CRC. Because of the centralization of cancer facilities, there might be a travel barrier for patients referred from other areas for further diagnostic confirmation, potentially resulting in diagnostic delays. Alahmadi et al. emphasized this viewpoint by noting that the extended travel times to cancer facilities in Saudi Arabia's Northern and Southern regions might contribute to worse cancer outcomes (69). This hypothesis, however, contrasts with our findings, mainly as Jazan and Baha patients (categorized as Southern regions by Alahmadi et al.(69)) had a lower likelihood of a late-stage disease than Riyadh patients.

There are several challenges in explaining the regional differences in disease stage observed in our study. The Saudi national CRC screening initiative was established after 2017, and our data reflected the period from 1997 to 2017. CRC screening was opportunistic during this period, mainly based on healthcare providers' recommendations and referrals (70). A study conducted in 2014, including 130 family physicians in Riyadh, found that 56% did not recommend CRC screening despite a positive attitude (71). Given that this study was confined to Riyadh and lacked comparative data from other regions, it remains unclear whether this trend is specific to Riyadh and contributes to its increased rates of late-stage CRC or if it mirrors a more widespread pattern across the other regions. Additionally, several Saudi studies showed a general lack of awareness about CRC and its screening that was not confined to any particular region (30, 56, 72, 73).

There is limited Saudi evidence on screening rates and modalities by geographical area during the study period. The only Saudi national study that assessed CRC screening use across all 13 administrative regions surveyed 2,945 individuals over 60 years old from 2006 to 2007. This study found a low screening prevalence of 5.6% but did not provide region-specific data. Within this cohort, the fecal occult blood test was administered to 4.4% of subjects, while endoscopic procedures were performed in only 0.6% (74).

Behavioral risk factors like low physical activity and smoking, and obesity are known risk factors for CRC (75). Their association with a worse disease prognosis has been suggested (76, 77), as well as with CRC incidence in the Saudi population (78, 79). However, whether variations in the prevalence of these factors across regions could explain the observed discrepancies in late-stage CRC presentation cannot be established. The 2019 Saudi World Health Survey included 10,000 households across all 13 administrative regions and assessed behavioral risk indicators, healthcare system satisfaction, and chronic disease prevalence. While regional differences in behavioral risk factors and health indicators were reported, these did not correlate with our study findings on late-stage disease presentation. For example, while the Baha region showed a lower risk of late-stage CRC in our study, the survey indicated high smoking and obesity rates and poor dietary habits in that region (80).

Multiple factors might contribute to explaining the observed regional differences in CRC stage at diagnosis. One key factor is the disparity in quality, access, and utilization of primary healthcare services across regions, which is vital for early detection. A comprehensive review of studies assessing primary healthcare services in Saudi Arabia highlighted issues such as limited access and poor effectiveness in managing chronic diseases, patient-doctor interactions, and health

education. Communication barriers with non-Arabic speaking care professionals further increased these difficulties. Regional disparities were not reported in this study (81). In 2017, Alfaqeeh et al. examined primary healthcare access and utilization disparities between urban and rural areas in Riyadh province, revealing significant healthcare inequalities. Rural populations faced more barriers, including distance to health centers and limited availability of health promotion and prevention services (82). These disparities may partly account for our study's observed higher incidence of late-stage CRC in Riyadh.

Additionally, cultural factors such as stigma and health-seeking behaviors could vary regionally, impacting diagnosis stages (83-85). Issues related to inconsistencies in data collection and reporting methods across regions might also play a role. A more in-depth investigation into these aspects is needed to fully understand the causes of these regional variations and develop effective intervention strategies.

Our decision tree analysis also identified a higher risk of late-stage CRC among younger, unmarried women in specific regions. These findings underscore the need to understand unique regional factors, including health practices, barriers to healthcare access, and experiences related to oncology service referrals among this demographic. Such understanding is vital for developing targeted awareness initiatives and enhancing screening uptake in these areas. Similarly important is improving access to screening facilities through primary healthcare services and training primary care providers to effectively identify and refer at-risk individuals, thereby optimizing early detection strategies.

5.5.1 Limitations

While this study provides valuable insights into factors associated with CRC presentation, it is important to acknowledge certain study limitations. The SCR database lacks data on genetic syndromes, family history, lifestyle habits, and comorbidities, all essential factors in understanding CRC dynamics. Additionally, to help interpret the findings in our study, there is a lack of comprehensive Saudi data regarding screening rates, diagnostic delays, and health-seeking behaviors, both on a national scale and across different regions. Data collection on potential CRC risk factors at SCR registration could help better understand predictors of late-stage CRC at diagnosis and monitor changes over time.

The higher likelihood of late-stage presentation at the rectosigmoid junction reported in our study should be interpreted with caution, given that this site is the least common with a notably small

sample size, which may limit the generalizability of this finding. The concentration of specialized cancer care facilities in Riyadh, Eastern, and Makkah, possibly led to overrepresentation of cases in these regions, potentially influencing findings from the regional comparisons.

Finally, using registry data involves inherent limitations related to potential coding errors, missing information, or inconsistencies in data collection and reporting methods across regions, particularly in early periods. Excluding 1,922 CRC cases due to missing stage information from the primary analysis, particularly from 1997 to 2001 (Appendix D.7), could potentially lead to an underestimation of late-stage diagnoses during this early period. However, our sensitivity analysis showed consistent findings when missing stage data were imputed.

5.5.2 Conclusion

Our study identified risk factors for late-stage CRC that can guide targeted early detection efforts, particularly for younger women in specific regions. A deeper exploration of attitudes and barriers to CRC screening, especially among women, is crucial to enhancing screening uptake and awareness in this high-risk group. As the risk of late-stage CRC presentation has increased in recent years, future research should evaluate the effectiveness of the CRC screening program and its impact on disease stage at diagnosis.

Declarations

Ethics approval and consent to participate: This study was approved by the Research Ethics Committee of the School of Medicine at the University of Leeds (MREC 19-069) and by the Ethics Committee of King Saud University (E-20-4644) and was performed in accordance with the Declaration of Helsinki. The Research Ethics Review Committees of the University of Leeds and King Saud University waived the need for informed consent due to the retrospective and anonymous study design.

Consent for publication: Not applicable.

Competing interests: The authors declare that they have no competing interests. MPR is currently employed by UCB Biopharma.

Funding: This study is part of Norah Alsadhan's PhD study, funded by King Saud University, Riyadh, Kingdom of Saudi Arabia.

Acknowledgments: The authors wish to acknowledge the Saudi Health Council/ National Health Information Center for providing the Saudi Cancer registry data that formed the foundation of this study.

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Chapter 6: Factors influencing colorectal cancer screening decisions among Saudi women: A qualitative study

Authors List: Norah Alsadhan[1], Cathy Brennan[2], Sultana A Alhurishi[3], Farag Shuweihdi[4], Robert M West[1]

Affiliation list:

1. Leeds Institute of Health Sciences, School of Medicine, University of Leeds, Leeds, United Kingdom
2. Psychological & Social Medicine, School of Medicine, University of Leeds, Leeds, United Kingdom
3. Department of Community Health Sciences, College of Applied Medical Sciences, King Saud University, Riyadh, Kingdom of Saudi Arabia
4. Dental Translational & Clinical Research Unit, School of Dentistry, University of Leeds, Leeds, United Kingdom

Study Five	
Journal	PLOS One.
Publication status	Published in April 2025.
Reference	Alsadhan N, Brennan C, Alhurishi SA, Shuweihdi F, West RM. Factors influencing colorectal cancer screening decisions among Saudi women: A qualitative study. PLoS One. 2025;20(4):e0321086.

Commentary

The findings from the quantitative studies in this thesis informed the research focus and participant selection for the qualitative study presented in Chapter Six. Study Three revealed that CRC incidence rates were rising across all sexes, age groups, and disease stages. Yet, increases in distant-stage CRC were often steeper than those observed for localized or regional stages. In particular, women aged 50–74 experienced a faster increase in distant-stage CRC incidence compared to their male counterparts. Study Four showed that approximately one-third of CRC cases were diagnosed at an advanced stage, with younger females at increased risk of presenting with late-stage disease. These earlier findings identified women as a subpopulation warranting further investigation to better understand the factors underlying these observations. This recognition prompted the focus on exploring women's perspectives and attitudes towards CRC screening, addressed in Chapter Six.

6.1 Abstract

Background: Colorectal cancer (CRC) is a major global health challenge and one of the most prevalent cancers in Saudi Arabia. Studies show that young Saudi women are often diagnosed with CRC at more advanced stages, leading to poorer prognoses. Despite the recent launch of the first Saudi national CRC screening program, public awareness and acceptance of CRC screening (CRCS) remain limited.

Methods: We conducted semi-structured interviews with 17 women aged 40 or older to explore their awareness, views, and attitudes toward CRC and CRCS. Data were analyzed using reflexive thematic analysis, and the Social-Ecological Model was applied to guide the structuring and organization of the developed themes.

Results: We identified a multifaceted interplay of knowledge, beliefs, and social-cultural factors influencing CRCS decisions among Saudi women. Although there was a general awareness of CRC, understanding of risk factors, signs, and symptoms was limited. Many participants adopted a reactive approach to screening, prompted by symptom manifestation or family history, rather than preventive health measures. Concerns such as fear of a cancer diagnosis and discomfort with the stool sample collection process hindered screening participation. Social support from family and community, and physician recommendations were crucial in encouraging screening uptake. Logistic and digital literacy challenges in accessing health services were noted for older adults. Participants stressed the need for increased CRC awareness, equitable access to screening services, and reminders to improve CRCS participation.

Conclusion: Factors influencing CRCS uptake among Saudi women are complex and multifaceted. Comprehensive and tailored health promotion interventions that meet community needs are essential. Further research is needed to develop and evaluate the effectiveness of these interventions in increasing screening uptake.

6.2 Introduction

Colorectal cancer (CRC) is a major global health challenge and one of the leading causes of cancer-related deaths worldwide (1). In high-income countries, CRC rates among individuals over 50 years have stabilized, mainly due to effective screening programs (2, 3). However, there is a concerning rise in EO-CRC, affecting individuals <50 years (4). In 2020, CRC was the most commonly diagnosed cancer among males and the third among females in Saudi Arabia, with 1,729 new cases representing 12.3% of all new cancer diagnoses (5). Over the past three decades, the incidence of CRC in Saudi Arabia has steadily increased across all age groups (6, 7). According to the 2019 Global Burden of Disease (GBD) report, Saudi Arabia recorded the highest annual percentage change in EO-CRC incidence rates among all included countries (8). EO-CRC tends to be more aggressive, thus presenting a considerable health burden for young adults (9).

The prognosis of CRC varies according to the disease stage at diagnosis (10). Early diagnosis of CRC leads to better treatment outcomes, enhanced survivorship, reduced healthcare costs, and improved patient quality of life (11, 12). In 2020, approximately one-third of Saudi CRC cases were diagnosed late with distant metastasis (5). Sex disparities in the CRC stage at diagnosis have been reported in the Saudi literature. A 2015 cohort study of 1016 Saudi CRC patients found that women were 20% more likely than men to present with a metastatic tumor (13). A recent retrospective cohort study of 17,541 CRC patients from the Saudi Cancer Registry indicated that young (< 50 years) women had an increased risk of late-stage CRC (14). Additionally, Zacharakis et al. noted a female predominance in EO-CRC among participants aged 45-50 in the Al-Kharj pilot screening program conducted from 2017 to 2022 (15). These findings underscore the need for further research to elucidate the underlying causes contributing to late-stage diagnoses in females. Additionally, tailored interventions to enhance early detection rates among this population are warranted.

CRC screening (CRCS) has been shown to decrease the incidence and mortality rates associated with CRC in the general population (16). In line with the Saudi 2030 vision, the Ministry of Health (MOH) launched the first Saudi national CRC screening program in 2017. Based on the individual's risk, this program provides screening services such as fecal occult blood tests and colonoscopies. The program operates across the kingdom's 13 administrative regions through participating primary healthcare centers (17). Average-risk individuals- those who are asymptomatic and aged between 45 and 75- are advised to undergo annual Fecal Immunochemical Test (FIT) screening. Participants are instructed to collect a stool sample using a provided container and return it to the

healthcare center for analysis. If the FIT results are positive, a follow-up diagnostic colonoscopy is recommended.

The MOH's screening program is currently the only initiative targeting the general Saudi public. To our knowledge, there is limited data on public awareness, participation, and attitudes towards this program. Additionally, publicly available reports on program metrics such as attendance rates, adherence, and patient outcomes are lacking.

A recent report on the Al-Kharj pilot CRC screening program, conducted exclusively in the Al-Kharj city, showed a high participation rate of 73% over five years. Data on participation rate by sex are not available (15). In 2023, Almadi and Basu identified various operational challenges in CRCS implementation in Saudi Arabia that warrant attention. They highlighted the need to address issues such as workforce shortages, limited coordination between healthcare facilities, the absence of a quality assurance system to monitor the program, and inefficiencies in system design that negatively impact the patient's journey (18). Additionally, a recent review of CRCS challenges in Saudi Arabia indicated two major concerns relating to low physician recommendation rates and limited participation among females (19).

Knowledge and perceptions about cancer and screening practices can influence the decision to participate in CRCS (20, 21). Although several studies have examined the knowledge and acceptance of CRC among the Saudi population, findings consistently show low CRC awareness and screening uptake (22, 23). A nationwide survey in 2019 revealed that males were more likely to accept CRCS than females (24). However, an in-depth exploration of Saudi women's views on CRCS is lacking. The existing literature on CRCS awareness in Saudi Arabia predominantly comprises survey-based studies. These studies, while informative, do not explore the deeper perceptions and attitudes that influence CRCS uptake. Thus, qualitative research is needed to capture the complexities of personal and cultural beliefs that structured surveys might not fully address (25).

We aim to explore Saudi women's awareness of CRC and their perceptions and attitudes toward CRCS. These insights are crucial for enhancing national screening efforts, tailoring public health promotion strategies, and improving CRC outcomes among women in Saudi Arabia.

6.3 Methods

6.3.1 Design

We conducted semi-structured one-to-one interviews with participating women. The Consolidated Criteria for Reporting Qualitative Studies (COREQ) guided the conduct of the study and the reporting of findings (26). This study was approved by the Research Ethics Committee of the School of Medicine at the University of Leeds (MREC 22-101) and by the Ethics Committee of King Saud University (KSU-HE-23-680).

6.3.2 Study participants

We recruited female employees aged 40 or older from King Saud University, Saudi Arabia. To capture diverse perspectives and experiences, we used purposive sampling to recruit individuals with varying ages and educational backgrounds. To further enhance diversity, snowball sampling was used, where initial participants were encouraged to refer individuals of different ages and education levels. Women who were currently under investigation or diagnosed with any cancer were excluded. The recruitment process, coordinated by (NA), began with a study advertisement emailed to all potential participants. Interested participants were notified via follow-up emails that the invitation process might be delayed to prioritize diversity and that not all who expressed interest would be selected. Interviews were scheduled at the convenience of the participants.

Based on the objectives of this study, we initially aimed to recruit a minimum of 10 participants, focusing on a diverse sample of age and educational levels. The decision regarding sample size was not driven by the traditional concept of data saturation; instead, it was based on pragmatic considerations such as time constraints and the principle of information power (27). This principle underscores the importance of iterative evaluation during data collection, ensuring that the depth and quality of data obtained from interviews were sufficient to address the research questions meaningfully (28). Given our use of reflexive thematic analysis in this study, these considerations proved more appropriate for guiding our approach to sampling (27).

6.3.3 Data collection

(NA) and (CB) developed a semi-structured interview guide (Appendix E.1) after a thorough review of the literature (29-32). The guide included open-ended questions that explored women's health-seeking behavior, awareness of CRC and CRCS, and perceptions about the benefits,

barriers, and facilitators of CRCS. The guide was piloted with two women and amended according to their feedback.

Participants received an information sheet and completed a written consent form before the interview. They all chose to be interviewed via Microsoft Teams with the video feature turned off. The interviews were conducted from October 17, 2023 to November 26, 2023 by (NA), a researcher with training and expertise in qualitative research methods. Participants were asked about their general knowledge of CRC and CRCS at the beginning of the interview. The CRC national Screening Program was then explained using infographics published by the MOH (17). Participants then shared their perceptions of the benefits, barriers, and facilitators influencing their decision to undergo screening. All interviews were conducted in Arabic, audio-recorded, and transcribed verbatim. Once transcription was completed and verified, all audio recordings were deleted. To ensure confidentiality, all transcripts were anonymized and pseudonymized, with participants identified solely by assigned numbers and initials. Any identifiable information, such as names of individuals or institutions, was also pseudonymized. Transcripts were labeled using each participant's assigned pseudonym initials and the interview date. All research data, including transcripts, audio recordings, and consent forms, were securely stored in a password-protected folder on the lead researcher's university-provided OneDrive account, with access restricted to the research team.

6.3.4 Data analysis

Our analysis was conducted in two stages. First, we used Reflexive Thematic Analysis (RTA), a theoretically flexible method for analyzing qualitative data to explore participants' experiences and perceptions. Braun and Clarke (33) outlined six main phases for RTA: familiarization with the data, generation of initial codes, searching for themes, reviewing themes, defining and naming themes, and producing the final report. A core principle of RTA is its acknowledgment of the researcher's subjectivity and assumptions as valuable resources for generating knowledge. Unlike other thematic analysis approaches, RTA discourages using structured codebooks or reliability measures. Instead, it adopts an iterative and interpretative reflexive approach to analysis, where coding evolves organically through the researcher's active engagement with the data (34).

In the first stage, the lead author (NA) became familiar with the data by repeatedly listening to the audio files and reading the interview transcripts. Following familiarization, NA began coding all transcripts using MAXQDA software (Version 24) (35). An inductive approach to coding was adopted, allowing the development of codes and themes directly from data without the

constraints of predefined or existing theoretical frameworks (34). Both semantic coding, which focuses on the explicit meaning of data in relation to the research questions, and latent coding, which identifies underlying assumptions and implicit meanings, were employed (34).

To enhance the depth and richness of the analysis, another author (SA) contributed to the coding process by double-coding a sample of transcripts. This collaboration aimed to discuss and refine initial thoughts about the data, not to ensure accuracy or reliability, as such practices are not aligned with RTA principles (36). Coding was iterative, with regular team meetings (NA, SA, and CB) to review, refine, and collate codes. Codes with similar meanings were grouped together to develop initial themes, which were iteratively reviewed and refined by the research team. NA and SA iteratively reviewed the transcripts to ensure that the thematic structure accurately represented coherent patterns of meanings within the data. All authors jointly reviewed and discussed the findings and agreed on the final themes reported in the study.

Upon reviewing these themes in the second stage, we determined that the Social Ecological Model (SEM) provided a useful framework to further structure our analysis (37). According to the SEM, health decisions like participating in CRCS are influenced not only by personal factors but also by various determinants at multiple levels—individual, interpersonal, organizational, community, and policy (38). We aligned our identified themes with these SEM levels to refine our interpretation of the findings. This alignment is crucial for developing targeted interventions that address multiple factors, potentially increasing CRCS uptake among women. The lead author (NA) mapped these themes to the SEM levels, which all authors reviewed. The quotes presented in the findings were translated from Arabic to English by (NA) and verified by (SA).

6.4 Results

6.4.1 Participant characteristics

We interviewed 17 women to explore their views on CRC screening (Table 6.1). The participants represented diverse age groups and educational backgrounds. While none of the women reported having a personal history of cancer, eleven (65%) disclosed a family history of the disease, with four mentioning a history of CRC in their families. Interview duration ranged from 16 to 42 minutes. Findings were organized into ten themes mapped onto the five levels of the SEM: individual, interpersonal, organizational, community, and policy (Table 6.2 and Figure 6.1).

Table 6.1. Participant's characteristics

Charachteristic	Number of participants
Age	
40-49	9
50-59	5
>59	3
Educational level	
University degree	15
High school	2
Family history of cancer	
Yes	11
No	6
Family history of CRC	
Yes	4
No	13

Note: CRC: colorectal cancer.

Figure 6.1. A Social Ecological Model illustrating levels of influence and factors affecting CRCS decisions.

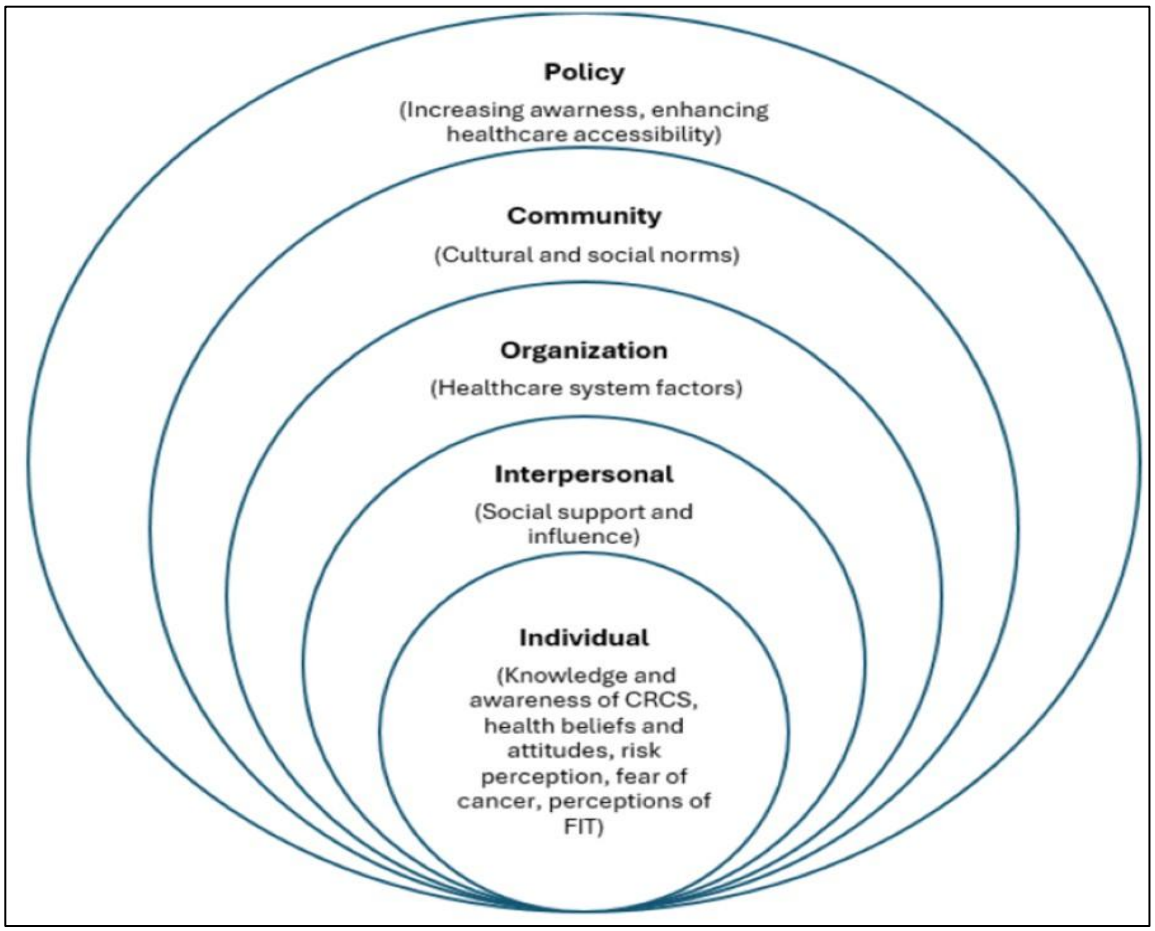

Table 6.2. Factors influencing CRC screening uptake among Saudi women

1. Individual-level factors	2. Interpersonal-level factors	3. Organizational-level factors	4. Community-Level Factors	5. Policy-Level Factors
1.1 Knowledge and awareness of CRCS*: • Awareness gaps • Misunderstandings • Influence of personal/family experience 1.2. Health beliefs and attitudes*: • Importance of early detection • Priority of health • Self-efficacy 1.3. Risk perception*: • Symptom-driven testing • Misconceptions • Influence of family history 1.4. Fear of cancer* (fear as a barrier/motivator) 1.5. Perceptions of FIT*: • Aversion to sample collection (embarrassment, disgust) • Test administration • Accuracy concerns • Acceptance • Physical discomfort	2.1. Social support and influence*: • Influence of family and friends on motivation/ decision • The dual impact of family influence	3.1. Healthcare system factors*: • Influence of physicians • Holistic and proactive healthcare approach • Satisfaction with the primary healthcare services • Logistical and practical challenges to seeking care • Sterilization and hygiene concerns • Special consideration for older adults	4.1. Cultural and social norms*: • Cultural attitudes towards screening • Word-of-mouth influence • Role of social influencers and community leaders in promoting health • Religious beliefs	5.1. Increasing awareness*: • Comparison with other successful health promotion campaigns • Health education topics • Use of multiple media channels • Use of official information channels • Effective and tailored education • Influence of storytelling 5.2. Enhancing healthcare accessibility*: • Uniform availability of screening • Access in remote and rural areas • Automated reminders and government platforms

Note: CRC: colorectal cancer; CRCS: colorectal cancer screening; FIT: fecal immunochemical test. *Indicates key themes within each SEM level, with bullet points summarizing the main findings under each theme.

6.4.2 Factors influencing CRCS decisions

6.4.2.1 Individual level factors

Knowledge and awareness of CRCS

When asked about preventive health practices, most women expressed general awareness of cancer screening. However, they were unfamiliar with the screening tests for CRC or the targeted age group. Many women noted that despite their general awareness of CRC, they were uncertain about its risk factors, signs, and symptoms. Some women attributed their knowledge deficit to the perceived low prevalence of CRC in the Saudi community.

> *"We hear about it, but I don't know exactly what symptoms or pains the patient might feel. I hear a lot about it, but I don't know what specific tests are involved."* P12

> *"We lack awareness about these issues because, fortunately, they are not prevalent in our community."* P10

Several participants seemed confused by medical terminology and concepts, such as the meaning of "family history," and demonstrated a lack of understanding regarding basic human anatomy.

> *"We hear about colon disorders and irritable bowel syndrome, but colon cancer doesn't come to mind. I mean colon cancer, I don't know, it doesn't come to mind because they always say the colon isn't an organ, so it's surprising when they mention colon cancer."* P12

Personal and community experiences seemed to influence an individual's understanding of CRC. For example, women who had undergone CRCS, had a family history of CRC, or knew others in the community affected by the disease seemed to have a better understanding and provided details about treatment. However, some still reported a lack of knowledge.

> *"Honestly, I don't know much about it, but because we [the family] had a case of death from it, I have heard about it. However, I have no idea about its symptoms or anything like that."* P10

Health beliefs and attitudes

Most participants recognized the importance of early CRC detection for cancer prevention, better treatment outcomes, and higher survival rates. Women also underscored the psychological benefits of screening, emphasizing the mental relief it provides.

> *"Certainly, if the doctor tells me to get tested, God willing, I will do it. First and foremost, it's to reassure myself about my health and to understand my medical condition. Secondly, it helps me feel mentally at ease. Getting the tests done means that if anything is detected early, I expect the treatment will be easier and better than if it were discovered in later stages."* P12

Several women highlighted the connection between personal health and family well-being. They discussed the necessity of prioritizing health due to familial responsibilities and expressed concern about the emotional and psychological impact their potential illness could have on their loved ones.

> *"You are helping yourself and those around you from potentially losing you. They might not experience physical pain like you, but they will endure psychological pain and the fear of loss."* P14

Despite recognizing the benefits of health screenings, several participants expressed that balancing these practices with other life demands can be challenging. This reflects how health is often prioritized and valued relative to other responsibilities. However, one woman with high self-efficacy expressed strong determination and a proactive approach to overcome these barriers.

> *"People are preoccupied with their families, homes, and daily lives, so they don't remember."* P5

> *"I'll do anything to find the right time to do the test. What occupies me the most is my job and work hours, but I'll do anything to make the time to go and do it."* P13

Risk perception

Participants reacted differently to information about the CRC screening program. While some showed interest in participation, many demonstrated a conditional approach to preventive health care, often weighing the perceived necessity of screenings against their current health status. This ambivalence reflects a broader reactive trend, where the absence of immediate symptoms diminishes the perceived urgency for regular checkups and tests.

> *"Sometimes I think I want to go and get checkups and tests done, but other times I think, as long as I'm thankfully healthy and well, there's no need."* P12

> *"If I were sick and feeling bad, I'd do everything necessary, but as a preventive measure, I'm not sure."* P17.

Misconceptions about the risk of CRC also influenced decisions to undergo screening. Several participants believed CRC was uncommon in their community or predominantly affected men. These perceptions foster a false sense of security and diminish the perceived need for proactive health measures.

> "*This is quite common among men, actually. I know of two men who have died from this issue. Thankfully, there haven't been any cases among the women.*" P10

Family history seemed to impact participants' perceptions of personal risk and their motivation to engage in screening. Women with a family history of CRC or other cancers perceived an increased risk of CRC and recognized the importance of preventive actions. Conversely, participants without a CRC family history felt less urgency about screening; however, some acknowledged that if a hereditary risk were present, they would be more encouraged to undergo screening.

> *"In our family, colon cancer is present among the men, so as a preventive measure, I wanted to check myself. I didn't have any symptoms or anything; I just wanted to be proactive."* P2

> *"The first thing that encourages me to get checked is having a CRC family history, which means there's a hereditary factor. This means I could potentially be affected, especially if it's among first-degree relatives."* P4

Fear of cancer

Fear of cancer seemed to influence the decision-making process regarding CRC screening, affecting individuals regardless of their family history of cancer. Yet, fear appeared to operate differently across individuals, affecting their screening behaviors in diverse ways. For some, fear acts as a barrier; the dread of uncovering an illness can provoke anxiety, leading to avoidance behaviors aimed at escaping potential bad news. Conversely, others view fear as a motivator, compelling them to engage in proactive health behaviors. A woman with a family history of breast cancer normalized the fear associated with screening and viewed it as an impetus for action.

> *"Everyone is naturally afraid of disease, but I acknowledge my fear of disease and want to detect it early. I will go and get tested so that, God forbid, I can protect myself, and if, God forbid, there is cancer, I can take control of the situation early."* P13

Perceptions of FIT

Most women expressed embarrassment, and disgust regarding the collection and storage of stool samples, viewing this process unfavorably compared to other types of medical specimen collection. Furthermore, some women expressed concerns about the FIT administration, particularly regarding correctly collecting the stool sample. These concerns were especially pronounced when considering older adults.

> *"If I were to give the test instruments to my father, I'd be doubtful he knows how to do it. My father has a tremor, and he's old. I feel there's no way he would know how to make the correct scratch. so I won't trust the results when they come out."* P1

Several participants expressed reservations about the reliability of the FIT, citing concerns about the potential for false negative or positive results. This led some to state a preference for professional testing in a clinical setting, believing it would yield more accurate and dependable outcomes. Others felt that a colonoscopy, despite its invasive nature, would provide more comprehensive and precise results than FIT.

> *"I feel more comfortable going to the hospital to do it. I feel it will be more accurate. At least if I do it at the hospital, I'm sure the result will be 100% accurate."* P4

> *"If someone is afraid they might have colon cancer, performing a colonoscopy is more accurate and comprehensive, whether there is blood or not."* P1

Despite these concerns, many participants felt the test was convenient and straightforward. The non-invasive nature of FIT was particularly appreciated, as it avoids the physical discomfort, fear, and embarrassment often associated with other screening methods. The ability to perform the test in the privacy of one's home was also highlighted as an advantage. However, one woman expressed a general worry about the physical discomfort associated with screening procedures, which deterred her from participating even before learning about the testing process. These worries were often based on anecdotal experiences shared by others.

> *"Sometimes, fears can prevent you from getting screened. You know, you hear from people that the breast cancer screening is painful and hurts, so now I've just decided to cancel the idea of early screening."* P15

6.4.2.2 Interpersonal level factors

Social support and influence

The experiences and behaviors of individuals within one's social network can potentially shape health behavior decisions. Several women expressed that observing collective participation in CRC screening acts as positive reinforcement, reducing anxiety around the procedure, normalizing the behavior, and ensuring its effectiveness. Others emphasized that personal connections and emotionally impactful experiences motivate individuals to prioritize and participate in health screenings. Without such connections, screening can seem irrelevant.

> *"If you see many people getting tested, you feel encouraged and reassured that the screening is beneficial."*P7

> *"I don't know anyone personally affected by it, and sometimes there are experiences that touch you deeply. This might be one of the reasons why you don't feel the need to get it done."* P6

Additionally, having concerns about family members' health seemed to motivate individuals to seek information and consider preventive screenings. This motivation is often driven by a deep care for loved ones and a strong desire to manage potential health risks within the family.

> *"My husband has Crohn's disease, which affects the intestines. Given that he is among those at increased risk, could it be possible, God forbid, that he might also need to be screened for colon cancer?"* P12

Family context appeared to play a crucial role in shaping personal health decisions, particularly concerning sensitive topics like the stool collection process for CRCS. The degree of openness within the family may influence the support participants receive. For example, one woman expressed her discomfort in discussing such matters with her spouse:

> *"We are now in a formal meeting, but if it's my husband, I would feel shy to say to him let's go to deliver the sample, really I would feel shy."* P14

Open discussions about health concerns within the family seemed to have a dual impact on an individual's healthcare actions. While some participants felt that family involvement often acts as a barrier—discouraging medical visits or downplaying symptoms— others reported that robust family support encouraged them to take proactive health measures.

“Convincing my family that I am going to get this screening is a hurdle. Sometimes they say, No, what for? You don’t need it, you don’t have symptoms, you are fine. Yet, I cannot go without informing them.” P16

“I consult with my husband, and then, yes, I go. He is usually firm and tells me it’s best to see a doctor. I tend to be more relaxed about it.” P5

6.4.2.3 Organizational level factors

Healthcare system factors

Most women acknowledged the critical role of physician recommendations in guiding their health decisions, including their participation in CRCS. They expressed trust in their doctors, especially when there was an established relationship, believing that medical advice was given in their best interests. This trust often extended to familiar healthcare settings, which seemed to enhance adherence to medical advice.

“I want to continue with my doctor and hospital. I don’t want to go to a place where it feels like starting all over again." P14

However, this trust did not universally translate into confidence in the broader healthcare system. Some participants voiced concerns about the system’s reactive nature and questioned whether healthcare providers were adequately informed about preventive measures. These concerns led to calls for systemic changes towards a more holistic and proactive model of care, including integrating CRCS into routine checkups across various specialties.

“Doctors, such as family physicians, general practitioners, or doctors in general, should encourage their patients by saying, "It’s best for you to begin colorectal cancer screening now." Our issue is that we lack a holistic approach.” P17

Most women expressed satisfaction with the primary healthcare services, highlighting that they are free and praising the widespread availability and accessibility of health centers. They believed these qualities positively influence women’s decisions to undergo screening.

“It’s convenient that the health center can receive the samples. It’s a suitable solution because it’s close to home, and one can stop by on their way to or from work.” P16.

However, not all participants viewed the process of seeking healthcare positively. Some women perceived seeking care as burdensome due to transportation challenges, such as long distances and crowded streets. These difficulties potentially discourage regular visits and necessary checkups. Several women also stated frustration with operational inefficiencies at

health centers, particularly noting the crowding and long waiting times. Many women suggested establishing mobile clinics in high-traffic areas such as universities, shopping centers, or workplaces to encourage participation without needing scheduled appointments.

> *"The ease of access was key; I didn't need to go to the hospital or make an appointment. I was heading to the mall and could do it easily when I found it [screening clinic] right before me."* P5

Some women highlighted their mistrust of the protocols and practices that ensure the cleanliness and safety of medical equipment. Concerns about potential contamination from inadequately sterilized tools deterred their acceptance and participation in CRCS.

> *"People are afraid that, God forbid, the tools might not be sterilized, for example, or they fear that the virus could be transmitted to them or something like that."* P7

Many women emphasized the importance of respecting societal values of cleanliness, suggesting the need to create suitable conditions for storing the sample. Providing specialized containers for sample storage and enabling direct delivery to clinics could address hygiene concerns and make the screening process more acceptable.

> *"We are a very clean society; you must create suitable conditions for storing the sample by any means necessary. If there are no alternatives, people could bring it directly to the clinic's location instead of storing it in a home fridge."* P6

Several women highlighted the challenges older adults face in navigating healthcare, including transportation issues and the lack of appropriate equipment for those with physical limitations. They emphasized the need for more flexible healthcare service hours, such as afternoon or evening clinics, to accommodate older adults' varying schedules. Additionally, reliance on digital platforms for scheduling appointments presented another obstacle due to digital literacy barriers. To enhance access for the elderly, several women recommended expanding home-based health services to include CRCS.

> *"Just as you [health institutions] provide services where they [healthcare personnel] go and take the tests at home, take them [CRC test kits] and go to their [the elderly] homes to do it for them."* P10

6.4.2.4 Community Level factors

Cultural and social norms

Women discussed a pervasive mindset within the community that prioritizes reactive health care measures over proactive ones, leading to general neglect of preventive health practices regardless of an individual's educational background or personal knowledge.

> *"We're talking about a community; I'm speaking about the world around me, whether educated or not. We tend to exhibit laziness, neglect, and indifference. Take my husband as an example—he's a well-educated, cultured man who studied abroad. However, when it comes to his health or visiting hospitals, he won't go unless forced. He views regular health checks as an obsession or madness."* P13

Participants emphasized the role of word-of-mouth communication in encouraging screening participation. When a group of individuals undergoes screening, their experiences generate a series of informal discussions that foster public engagement and increase awareness about the screening process and its benefits.

> *"If a certain group, say 20 or 50 people, undergoes the screening, that's enough to create word-of-mouth advertising among the public. They'll talk about it themselves: I did this and got these results. Others will ask, Great, where did you do it? How did you get an appointment? This way, the information spreads."* P10

Many women also emphasized the prominent role of community leaders and social influencers in shaping community norms and practices. They believed these influential figures had the power to encourage screening behaviors to become widely accepted and adopted within the community.

> *"When it [screening behavior] comes from decision-makers, people whose words are heard, or social influencers, it can make an impact."*P6

Several participants discussed religious beliefs and teachings as an essential factor influencing their acceptance of the FIT. Within the framework of Islamic beliefs, which emphasize cleanliness and purity in daily life, handling stool samples is viewed as impure and dirty. This perception seemed to make women more reluctant to engage in the screening.

> *"In our Islamic faith, the concept of purity is significant. We tend to view such things [handling a stool sample] as impure and dirty."* P17

6.4.2.5 Policy Level Factors

Increasing awareness

All participants emphasized the importance of fostering collective CRC awareness within the community, achieved through well-funded and promoted campaigns. They identified the absence of widespread CRC awareness campaigns as a major barrier to screening.

> *"The first thing necessary is knowledge. The more a person understands the importance of the screening and what the results mean, the faster they can decide about undergoing the test."* P2

Many women pointed to the MOH's breast cancer and shingles campaigns as successful efforts that effectively reached and influenced the public. They emphasized the need to adopt similar practices, noted for their extensive reach and use of diverse communication channels.

> *"You don't just decide to go all at once; it has to be multifactorial; it has to speak a language everyone understands, just like with the breast cancer campaign. I see breast cancer awareness as a role model in this regard. It made us all live the experience, and even people who might not be at risk or even of the age of screening still feel like they want to be part of it. All communication channels and media devices have been mobilized for this cause."* P6

Participants deemed education on various aspects of CRC essential. They particularly highlighted the need for information on the test's availability and safety, the economic benefits of early CRC diagnosis compared to treatment costs, the risk factors for the disease, and its prognosis.

> *"There should be an explanation about what the test results will entail. For example, what is the recovery rate? Aside from the recovery and success rates, what might a person face after their results come out, especially if they are positive? What exactly should they do? What are the implications of the result."* P2

Participants voiced the need for ongoing media campaigns across various communication channels to ensure broad demographic appeal and reach. They suggested leveraging traditional media channels like TV, radio, billboards, and newer platforms such as social media to connect with varied audiences. Videos and direct text messaging were also recommended as an effective way to engage older adults. To increase accessibility and visibility further, participants proposed placing informational booths in highly trafficked public areas, including workplaces, shopping centers, and entertainment venues.

> *"Where do we hear about such matters? We hear them in hospitals while sitting in the waiting room, and you might see some educational content on TV. But this doesn't reach us in our homes; it doesn't get to our houses. They need to reach people where they are."* P14

Several women emphasized the importance of disseminating health information through official channels. Government-issued messages, such as those from the MOH, may be perceived as more credible and authoritative due to the Ministry's recognized role in safeguarding public health.

> *"If there were messages from the Ministry of Health, people would accept them more than from other sources."* P12

Most women expressed a preference for communication that is simple, clear, and reassuring yet rich with factual content. They valued directness and transparency about the realities of CRC, emphasizing the importance of tailoring messages to different age groups and varying levels of comprehension or CRC risk.

> *"For me as a person, I'm very data-driven. So, if there were posts that clearly explain how early detection can reduce the incidence and aid in prevention, and if these posts were widespread on social media platforms, that would honestly encourage me a lot."* P3

Some participants highlighted the strong influence of personal stories in health communication. They believed that narratives from individuals who have experienced CRC are particularly effective, resonating deeply and making the message more relatable than traditional methods.

> *" I am drawn to the approach of bringing in people who have gone through or had CRC to talk about their experiences. It may be a bit challenging, but it is indeed impactful. These stories touch people and have a greater impact, resonating more than traditional methods that might not be as engaging."* P13

Enhancing healthcare accessibility

Several women emphasized the need for uniform availability of screening services across all healthcare facilities, not just governmental primary health centers, to increase accessibility and motivate screening participation.

> *"When the screening is available in all hospitals that people frequently visit, no one has an excuse not to get screened."* P2

Some women called for a well-organized health infrastructure that ensures equitable healthcare access for all, regardless of location. They highlighted that navigating healthcare information is challenging in urban areas and even more difficult in remote regions with limited facilities and services.

> *"You hear people saying: "Yes, I really want to do an early screening, but where do I go, to whom?" If this is the case in cities, imagine how much worse it might be in remote areas."* P3

Lastly, women suggested utilizing digital health applications and governmental platforms to enhance CRCS participation by sending automated, personalized reminders to eligible individuals.

> *"Here in Saudi Arabia, I think we should utilize platforms like "Absher" and others because they have our personal data, ages, and everything. They could be used to send reminders."* P3

6.5 Discussion

Our study offers valuable insights into Saudi women's perspectives on CRCS. We discovered a complex interplay of factors influencing women's attitudes and willingness to participate in CRCS, highlighting the need for a multifaceted approach to inform effective public health strategies.

We report a general lack of awareness and knowledge about CRC and its screening among Saudi women, consistent with findings from a recent systematic review on CRC awareness in the region (39). Similar to Middle Eastern and international reports, low awareness of CRC symptoms, risk factors, and screening modalities has been identified as a prominent barrier to screening uptake (31, 40, 41). Despite this limited awareness, we noted a generally positive attitude toward screening, driven by strong beliefs in the benefits of early detection and preventive measures. This aligns with results from a national Saudi survey where 73% of 5720 participants expressed willingness to undergo screening (24). However, competing life demands frequently interfered with prioritizing screening, a barrier also documented in earlier research (23, 31, 42).

Ambivalence about screening decisions and personal risk perceptions was prevalent among participants. Justifications for this ambivalence included the absence of symptoms, lack of family cancer history, misconceptions about risk, and perceptions of good health. These factors, noted in previous studies (41, 42), reflect a crucial misunderstanding: screening is intended to identify at-risk, asymptomatic individuals with no genetic predispositions (40).

Oster et al. explored this phenomenon and its link to procrastination, emphasizing the importance of enhancing screening availability and convenience, particularly for those lacking personal risk perceptions (43).

Negative emotions related to fear of CRC were observed in this study, aligning with findings from diverse international (31, 32) and regional (41) contexts where fear of cancer diagnosis and painful screening procedures are commonly cited barriers to screening. However, in our study, fear appeared to play a dual role in women's decisions regarding CRCS, serving both as a barrier and a motivator. While some individuals avoid screening for fear of bad news, others are driven to take proactive health measures. This complex impact of fear on health behaviors aligns with findings from the UK, where Young et al. observed fear as both an inhibitor and an enabler of screening participation (44). Healthcare professionals emphasize that effectively managing negative fear is crucial for improving CRCS uptake. They suggest that informative conversations with patients, enhanced program publicity, and community acceptance can alleviate patient anxiety (45).

Participants generally accepted the screening procedure, but feelings of disgust, embarrassment, and discomfort with handling the test sample were prevalent. This finding aligns with previous international findings associating these emotions with CRCS avoidance (31, 46). Dressler et al. recommended providing antibacterial wipes and disposable gloves alongside the FIT kit to alleviate these concerns (42). Clear instructions and practical demonstrations were also suggested to address concerns about correctly completing the test, which could potentially increase CRCS uptake (47).

Participants expressed skepticism towards the medical profession's emphasis on preventive screening measures. Previous studies have noted a similar lack of emphasis among Middle Eastern healthcare providers (41). For instance, a survey in Al-Khobar City found that only 10% of patients aged 40 or older reported receiving CRCS recommendations from their physicians (48). Conversely, A recent study in Riyadh City found that most primary healthcare physicians were well-informed and actively engaged in recommending CRCS for asymptomatic patients (49). The variability in physician engagement underscores the need for further investigation into the consistency of CRCS recommendations across Saudi Arabia. The influence of healthcare professionals on screening behavior is well-documented (50-52). We support this association, noting that the extent of influence depends on patients' trust in their doctors and medical institutions. Hoeck et al. reinforced this point by highlighting the critical role of a strong patient-doctor relationship in ensuring adherence to screening recommendations (40). Furthermore, educational programs delivered or endorsed by health professionals have

proven effective in increasing screening participation, likely due to patients' trust in their physicians and their ability to address patient concerns and fears (47).

Our findings emphasize the necessity of increasing awareness and knowledge about CRC and its screening among Saudi women. Participants called for tailored educational interventions that provide balanced, persuasive information through various media channels and community settings, endorsed by trusted entities like the MOH. Educational messages must resonate with the Saudi community, emphasizing the benefits of early detection for asymptomatic individuals, including improved survival rates. Additionally, they should address the specific cultural sensitivities, barriers, and misconceptions identified in this study. Fear appeals in health communication, which highlight the negative outcomes of screening avoidance, are often criticized for provoking defensive behaviors among audiences. Ruiter et al. noted that enhancing perceived screening effectiveness and the individual's confidence in their ability to participate in screening (self-efficacy) is more important than fear arousal (53).

Participants underscored the impact of social influence on screening decisions. Integrating patient stories in awareness campaigns might reduce aversion or ambivalence toward screening and help normalize discussions about CRCS (52). Woudstra and Suurmond highlighted that narratives depicting the screening process and peer experiences can enhance self-efficacy and engagement (54). Similarly, a UK study showed that supplementing standard information with narrative leaflets positively affected screening intentions (55).

Based on the study findings, we recommend implementing family-focused awareness initiatives that emphasize the crucial role of the family in promoting preventive health behaviors. Educational messages should encourage and normalize screening discussions among family members, frame screening as a shared responsibility, and encourage the family's support in decision-making. Family involvement is particularly vital in raising awareness among older adults and assisting them in navigating and accessing healthcare services. Including CRC survivors, community leaders, and social influencers as advocates for screening can also positively impact the public's acceptance and uptake of screening. We also recommend involving religious leaders in awareness initiatives to emphasize Islamic principles supporting disease prevention and to address concerns related to purity.

A recent review in Saudi Arabia found that individuals believe overcoming practical barriers to CRCS is achievable with sufficient motivation and awareness (51). However, Honein-AbouHaidar et al. stress the need for comprehensive strategies addressing logistical challenges, such as scheduling and service delivery issues, and implementing mass media campaigns to raise awareness and enhance participation rates (52). We support the need for

public health efforts addressing both educational and practical barriers to screening. Our findings revealed women's mistrust in various aspects of the healthcare system, underscoring the need to strengthen public confidence in its quality and accessibility. To address this mistrust, we emphasize the importance of clear and transparent communication, using media platforms to educate and reassure the public about CRCS quality and safety standards. Additionally, regular updates on service accessibility, operational improvements, and appointment scheduling are essential to help individuals understand the healthcare system's structure and better navigate care.

Given the myriad factors influencing screening decisions identified in this study, a multi-level intervention approach is essential to strengthen the impact of the CRCS program. Implementing a combination of targeted health promotion efforts can expand program reach, improve engagement, and ultimately enhance patient health outcomes.

6.5.1 Practice implications

The national CRCS program provides free screening to all citizens upon their request. Yet, findings from this study highlight the need for a more structured approach to identify eligible individuals and send invitations and reminders. Women in this study proposed sending reminders through governmental platforms to encourage timely participation in screening programs. Several studies have corroborated the effectiveness of reminder systems in improving patient alertness and increasing screening uptake (47, 56, 57). The program should also incorporate a monitoring system to track screening participation and patient outcomes. Public dissemination of program statistics can facilitate transparent communication, build trust, and motivate participation by demonstrating the program's reach and effectiveness.

To enhance accessibility, the MOH could collaborate with the private healthcare sector to implement the screening program, as women in this study preferred screening in familiar healthcare settings, whether private or public. Additionally, using mobile clinics to reach the public and distribute FIT kits could improve screening access and engender community discussions on CRC screening.

Integrating CRC screening into routine healthcare checkups provided in clinics and home care services can enhance patient awareness and engagement. Furthermore, embedding automated screening prompts in electronic medical records can remind healthcare professionals to discuss and recommend screening. Finally, as healthcare professionals play a crucial role in influencing patient behaviour, established systems should be in place to ensure they receive regular updates on screening guidelines, remain informed about the CRCS program, and proactively recommend screening to eligible patients.

6.5.2 Strengths and limitations

This study represents the first qualitative exploration of CRCS views among Saudi women of diverse ages and educational backgrounds. A key strength of our study lies in our analytical approach, which deviates from traditional methods that categorize findings as either barriers or facilitators. Using the Social Ecological Model, we have explored how certain factors can hinder and promote CRCS, depending on the context. This approach has deepened our understanding, providing a comprehensive framework to grasp the complexities of CRCS decisions for women.

Several limitations in this study should be highlighted. Social desirability bias is a well-documented limitation in qualitative interviews; therefore, we implemented several measures to minimize its impact. We maintained a neutral stance throughout the interviews, avoiding subjective reactions or expressions of judgment to participants' answers. Leading questions were avoided, and participants' confidentiality and anonymity were ensured to encourage honest discussions. Furthermore, there is a potential self-selection bias in the findings, as participants may have had a pre-existing interest in CRC and its screening.

The interviews were exclusively conducted with participants from the Riyadh region, limiting their representativeness across the wider Saudi population. While similar factors influencing screening behaviours have been identified in other regional studies, certain factors may still vary across regions. However, some insights from this study are transferable to women in other Saudi regions, as well as Muslim and Arab women in different countries who share similar cultural values and backgrounds.

Additionally, since most participants had higher education levels, the findings may primarily reflect challenges as perceived by this educational group, potentially leading to a skewed representation with less emphasis on the cultural, practical, and structural barriers encountered by less educated women. Lastly, by focusing exclusively on women, the study did not explore gender differences in screening-related factors, presenting an area for further research.

6.5.3 Conclusion

Our study highlighted the complexity of screening behavior and underscored the need for a multifaceted approach to promote CRCS effectively. Public awareness is crucial, yet it should be part of a broader strategy that includes tailored individual, organizational, and policy-level interventions to meet community needs. Additionally, it is essential to examine the perspectives and challenges of healthcare providers and policymakers who play pivotal roles in

the design and execution of screening programs. Future research should focus on evaluating the implementation of health promotion interventions within the Saudi national screening program and assessing their long-term impact on screening uptake.

Declaration

Acknowledgments: The authors would like to thank all participants who contributed time and insights to this study.

6.6 References

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Chapter 7: Discussion

7.1 Chapter Overview

The main aim of this thesis was to provide robust and reliable evidence on the CRC burden in Saudi Arabia. Five distinct studies were conducted: 1) a systematic review of the literature to describe variations in commonly used incidence measures and assess the quality of reporting incidence methods; 2) a systematic review of studies evaluating incidence trends to describe commonly reported incidence trends measures and evaluate the quality of reporting their methods; 3) a retrospective analysis of SCR data over two decades to examine CRC incidence trends among the Saudi population; 4) a retrospective cohort analysis of 17,541 CRC patients to identify demographic and clinical factors associated with late-stage CRC; and 5) a qualitative exploration of Saudi women's views and perceptions toward CRC screening to determine factors influencing their screening decisions. These studies provide insights that inform current practices, guide future prevention strategies, and identify areas for further exploration.

In this discussion chapter, I summarize the findings of each study and discuss their implications. I conclude by addressing the strengths and limitations of the thesis and highlighting directions for future potential interventions and research.

7.2 Summary of key findings and contribution to the literature

This thesis highlights several key findings regarding the CRC burden in Saudi Arabia. Between 1997 and 2017, CRC incidence rates steadily increased across all ages, sexes, and disease stages. These findings align with global literature indicating a rising incidence among adults under 50. However, in contrast to trends observed in high-income countries, where incidence rates among individuals aged 50 and older have stabilized or declined following the introduction of screening programs, rates in Saudi Arabia among this older age group increased faster than among younger adults. Additionally, incidence trends for distant-stage CRC were often steeper than those for localized or regional tumors across all age and sex groups. Women aged 50–74 years had a higher increase in distant-stage CRC rates compared to their male counterparts. Regarding cancer stage at diagnosis, about one-third of Saudi CRC patients were diagnosed at an advanced stage. Analysis of factors associated with late-stage presentation revealed that young (<50), unmarried women were at a particularly heightened risk.

7.2.1 CRC incidence rate measures and quality of reporting incidence methods

In Study One, I systematically reviewed 165 population-based studies using cancer registries to estimate CRC incidence. I reviewed and described commonly used incidence rate measures and evaluated the quality of reporting incidence. I developed multiple indicators for assessing the quality of reporting incidence methods based on a thorough review of the relevant literature.

The age-standardized incidence rate (ASR) was the most reported measure of incidence, followed by the age-specific incidence rate (ASIR) and the crude rate (CR). Concerning the quality of reporting incidence methods, this review indicated inadequate reporting of registry-data quality control procedures and indicators. Explicit reporting of the CRC definition, the numerator used and denominator data, and population size estimations for the denominator were also limited. There was also inadequate reporting of uncertainty estimates for incidence rates and missing data analysis.

Several recommendations for estimating and reporting incidence were highlighted in this study. The ASR is a valuable estimate for comparative analysis between populations or countries as it adjusts for age structure differences; using it exclusively can obscure important details about incidence. Thus, a comprehensive analysis of incidence should initially focus on examining rates and trends of the ASIR. When calculating the ASR, researchers should justify their choice of standard population and opt for the most updated version of external standards to ensure reliable rates. Additionally, to enhance the comparability of CRC incidence data, the scientific community must establish consensus for CRC anatomical subsite categorizations and definitions. Finally, addressing the identified deficiencies in reporting, ensuring transparency, and acknowledging limitations in methods are essential for accurately reproducing, interpreting, and comparing incidence rates (1).

7.2.1.1 Definition of incidence rate

In Study One, the term “rate” was used interchangeably with “frequency” or “proportion” in some of the reviewed articles. This ambiguity in defining incidence has been documented in previous literature (2), highlighting the importance of explicitly defining the terms and methods used to measure incidence. As explained in Chapter One, when calculating the denominator for incidence rate, estimating person-time at risk is the most reliable method; however, this may not be feasible due to data limitations. Hence, many epidemiological studies use population estimation at one point in time as the denominator.

Spronk et al. argued that when using population estimates to calculate the denominator, the term “incidence proportion” should be used instead of “incidence rate” (2). Yet, IARC has

guided cancer registries to use the term incidence rate even when mid-year population estimates are used to approximate the denominator. According to the IARC, the impact of not estimating person-time at risk is usually minimal for many cancer incidence studies due to the small number of individuals living with a specific cancer type (3). Using and adhering to IARC's recommended terminology aligns with international standards and ensures consistent and standardized incidence reporting across cancer registries and studies.

Most reviewed articles in Study One expressed rates without specifying a time unit— It is unclear whether authors deemed it unnecessary given their estimation methods for the denominator. However, the IARC recommends that incidence rates, even when derived using population estimates as the denominator, be expressed with a time unit, such as whole years or person-time (3). Overall, this study emphasized the need to develop clear guidelines for reporting incidences, which will enhance the clarity and reliability of incidence outputs across the literature and facilitate international comparisons of rates.

7.2.2 Methods for measuring trends in CRC incidence

In Study Two, I conducted a systematic review to summarize the methods used in evaluating incidence trends in population-based studies. I described the reported incidence trends parameters, the software employed, and the quality of reporting trends methods across 145 studies from diverse populations and settings. The methods observed were categorized as either explanatory or modelling approaches. For explanatory methods, most studies used visual summaries along with other methods, such as simple arithmetic calculations of the absolute and relative differences in incidence rates. For statistical modelling, joinpoint regression analysis was the predominant method. Linear regression analysis and generalized linear models, including Poisson regression and age-period-cohort analysis, were also used. In measuring incidence trends, the annual percentage change (APC) in rates was the most reported output, while some studies presented trends as incidence rate ratios. The use of multiple methods in conducting incidence trend analysis was highlighted as a crucial approach to examining CRC trends comprehensively. The analysis software was mostly well-documented, with the joinpoint program—developed by NCI— being the most used.

This review identified inadequate reporting of incidence trends methods, including verification of model assumptions, model fitting methods, and model validity assessment. Definitions and calculations of parameters, such as the APC and average APC (AAPC), often lacked clarity. Additionally, providing justifications for reporting only one of these measures and describing parameter settings within the joinpoint software were inadequate.

Overall, this study provides valuable information about the various incidence trend methods reported in the literature. It supports future researchers in not only selecting parameters that will enhance the comparability of their findings but also in optimizing the reporting of their methods to improve the interpretation and reproducibility of their results (4).

Studies One and Two informed the methodological choices for Study Three in this thesis. Study One findings influenced my analysis approach, as I examined incidence using both the ASIR and ASR measures. I used the 2000 WHO world standard population to standardize rates to ensure that incidence measures would be internationally comparable. Moreover, Study Two results guided my choice to evaluate trends using joinpoint regression analysis and the NCI's joinpoint software (5).

The insights gained from both reviews also enhanced how I reported the methods used in subsequent quantitative studies. I provided a detailed description of the CRC definitions used, methods for estimating the numerator and denominator, uncertainty estimates, the software analysis used, and approaches for assessing and handling missing data in the analysis. Furthermore, I ensured that rates were expressed with a time unit and that the parameters used to examine incidence trends and the parameters set in the joinpoint program were clearly described.

7.2.3 CRC incidence trends in Saudi Arabia

In Study Three, I used SCR data to comprehensively examine CRC incidence trends in Saudi Arabia from 1997 to 2017. Joinpoint regression was used to evaluate trends, a statistical method that identifies points in time where the magnitude and direction of rates significantly shift. These shifts may reflect changes in population health behaviors or practices within the Saudi healthcare system. The analyses also explored rate disparities based on age, sex, and disease stage. The NCI's joinpoint software was used for the analysis. This software calculates the APC and AAPC parameters commonly reported in cancer incidence trends research (4).

I calculated the ASIR for six age groups (<40, 40-49, 50-59, 60-69, 70-79, and 80+). This categorization was chosen to facilitate the examination of trends across different life stages while also increasing the number of cases in each category to enhance the statistical robustness and reliability of incidence rate trends. In addition to the analysis described in Study Three, I conducted a sensitivity analysis by examining the incidence rates across smaller age groups. A detailed breakdown of the ASIR by sex and five-year age intervals is provided in Appendices F.1 and F.2.

To the best of the researcher's knowledge, this study was the first in the Saudi literature to evaluate trends by age and stage at diagnosis, revealing a consistent increase in CRC incidence rates across all ages, sexes, and disease stages over two decades. The overall ASR increased during the study period from 4.0 to 12.9 per 100,000 person-years, reflecting an annual percentage increase of 6.1%. The findings indicated that while the overall CRC incidence increased across all age groups, rates increased at a higher pace among individuals aged 50 and older compared with younger adults. Men in the 50-59 age group had a higher rate increase than their women counterparts. In the 70-79 age group, the AAPC in men doubled that of women. EO-CRC incidence in women rose slightly higher than in men, although no substantial differences in annual ASIRs figures were observed between sexes (6).

Average annual increases in incidence rates for distant CRC were often higher than those for other disease stages across all age groups and sexes. Incidence trends for localized CRC were similar between men and women for all age groups. For regional CRC, trends were often steeper in men. For distant CRC, men and women over 74 had a steeper increase than younger age groups. These trends may be partially attributed to the absence of Saudi screening guidelines for those older than 75. Furthermore, in recent years, women aged 50-74 experienced a faster increase in distant rates than their male counterparts. This trend may indicate potential differences in biological factors or health-seeking behaviours between sexes, highlighting an area for further research (6).

The findings of this thesis are consistent with previous studies noting a temporal increase in CRC incidence across various ages among the Saudi population (7-9). Incidence rates among younger Saudi populations (under 50) were increasing at a pace comparable to the fastest rises in EO-CRC reported in a recent global study (10). According to the IARC, the rates in Saudi Arabia are expected to further increase by 165% between 2022 and 2045 (11). The absence of a national screening program between 1994-2017, improved diagnostic activities, and enhancements in cancer registry operations may have contributed to the observed rise in incidence, particularly compared to the early years. Additionally, the continued increase in CRC rates may reflect the social and economic changes in the country during the past decades that led to the adoption of harmful lifestyles. These lifestyles include smoking, physical inactivity, sedentary behaviours, low fiber intake, and high consumption of fatty and sugar-sweetened foods—all established risk factors for CRC (12).

National surveys reported a high prevalence of risky lifestyles among the Saudi population. Results from the 2019 National Global Adult Tobacco Survey, including 11,381 individuals aged 15 and older, revealed that 30% of men and 4% of women were current tobacco smokers. The average age of initiating smoking was 18 for men and 19 for women (13). Data from the 2019

Saudi World Health Survey also indicated that most respondents (80%) engaged in insufficient physical activity, and 93% reported an inadequate intake of fruits and vegetables (14). Due to the widespread adoption of unhealthy lifestyles and habits, the prevalence of overweight and obesity—biological risk factors linked to CRC development—has substantially increased in Saudi Arabia between 1975 and 2016. Adult obesity rates reached 35.4% in 2016, with rates higher in women than men. Furthermore, in 2016, about one-third of Saudi children and adolescents aged 5-19 years were overweight or obese (15).

Obesity and sedentary behaviors are recognized components of metabolic syndrome (MetS), a cluster of metabolic disorders that also includes high blood pressure, high triglycerides and cholesterol levels, low high-density lipoprotein (HDL) levels, and central obesity (16). The MetS is a well-established risk factor for various health conditions such as cardiovascular diseases and diabetes (17). It has also been associated with an elevated risk of CRC, with recent reports indicating a further link to EO-CRC (18, 19). Choi et al. noted that individuals with either diabetes, dyslipidemia, and/or hypertension had an increased risk of CRC than those without these conditions, with the risk more pronounced in individuals under 40 (20). Moreover, Liu et al. reported a significant association between obesity in early adulthood in women and an increased risk of EO-CRC compared to those with a normal BMI (21).

In Saudi Arabia, studies on the prevalence of MetS among the population have indicated that low HDL levels and impaired glucose metabolism are particularly prevalent (22-24). However, these studies often rely on relatively small, region-specific samples, which may limit the strength and generalizability of the findings. In 2013, Aldaghri et al. found that among 185 Saudi adults in Riyadh (87 males and 98 females) aged 19 to 60 years, MetS prevalence was higher in women than men (55% vs. 24%) (24). Furthermore, a recent cross-sectional study examining MetS risk factors among 172 female adolescents aged 12-19 years identified prevalent factors such as high-fasting plasma glucose (49.%) and high waist circumference (43%) (25). These observations among the Saudi population underscore the critical need for further research with larger, more diverse samples to examine the association between lifestyle and MetS factors and CRC development in Saudi Arabia. Furthermore, interventions to bend these risk factors' figures and mitigate the health and economic burden they impose are imperative.

The current Saudi population is predominantly young; about 88% are under 50. Additionally, the average life expectancy has improved over time, reaching 75 years in 2016, and is projected to increase to more than 80 years by 2050 (26, 27). Given that cancer risk increases with age and the high prevalence of risk factors among the population, a future rise in early and late-onset CRC is anticipated in Saudi Arabia. Hence, developing and implementing primary

and secondary prevention strategies are imperative. Primary prevention of CRC can be achieved through lifestyle modifications (28). Several initiatives under Saudi Arabia's "Vision 2030" target risky behaviors among the population (15), yet changing lifestyles and habits remains a complex and challenging task. Therefore, secondary prevention measures such as screening programs are essential for tackling the disease, enabling early detection and effective treatment.

Study Three findings add to the existing body of evidence in Saudi Arabia, supporting the initiation of CRC screening at age 45. Furthermore, with distant CRC rates increasing more rapidly than other stages, and considering its association with poor prognosis, it is crucial to identify the factors associated with advanced-stage presentation. Such understanding is vital for identifying high-risk groups, developing targeted health promotion interventions, and informing future research to discern factors driving increased risk among specific sub-populations. Study Four examines clinical and demographic characteristics linked to advanced-stage CRC.

7.2.4 Factors associated with advanced stage CRC

In Study Four, I examined clinical and demographic characteristics associated with late-stage CRC using large cohort data from the SCR. For a comprehensive analysis of geographic and sex variations in risk factors, I used different statistical methods, including decision tree analysis and stratified multivariable logistic regression (29).

Results indicated that approximately one-third of CRC cases were diagnosed at an advanced stage. Younger (<50) and unmarried women were identified as having a higher risk of presenting with late-stage disease. The increased risk among these groups was also noted in regions classified by the decision tree analysis as high-risk areas for late-stage CRC, comprising Riyadh, Eastern, Najran, Hail, Qassim, Jouf, Northern, and Tabuk. Additionally, assessment of temporal trends within the models indicated a higher risk of late-stage disease in patients diagnosed after 2001, aligning with trends observed in Study Three and indicating a consistent increase in distant stage-specific CRC incidence over time. These findings support the initiation of screening at 45 and emphasize the need for further examination of the increased late-stage risk among young females.

This study revealed a geographic clustering of low-risk areas in the western and southwestern regions of Saudi Arabia, indicating the need for a deeper investigation into the factors driving these regional disparities. Findings relating to sex disparity in cancer stage at diagnosis align with previous research on CRC and other cancer types, indicating a higher likelihood of late-stage disease among female patients (30-32). This trend has often been attributed to a

combination of biological, socioeconomic, behavioral, and healthcare-related factors, underscoring the need for targeted and multidimensional public health interventions to address this disparity.

This study is the first to examine the association between sex and cancer stage at diagnosis within the Saudi context. In high-risk regions, young females had an increased risk of presenting with advanced disease. Thus, it is essential to explore the factors underpinning this relationship. Understanding women's views and perceptions on CRC and screening is an important aspect that can guide the planning and development of targeted interventions, addressing the needs and concerns of this demographic. Study Five explores this aspect using qualitative interviews.

7.2.5 Factors influencing CRC screening decisions among Saudi women

Study Five explored CRC knowledge and screening perceptions among a sample of Saudi women with diverse ages and educational backgrounds. There was a general lack of awareness about CRC, its symptoms, risk factors, and screening. Most women were unaware of the national CRC early detection program, a finding consistent with a recent study on CRC prevention awareness among Riyadh residents (33). Despite recognizing the benefits of early prevention, decisions to undertake screening were often deterred by competing life demands, absence of symptoms, lack of familial history, misconceptions about risk, and a low perceived personal risk. Fear of cancer diagnosis and family support had a dual influence on screening behavior depending on the individual's beliefs and family dynamics.

The FIT was believed to be simple and convenient, and many women appreciated its availability. Yet, emotional factors such as disgust, embarrassment, and concerns about sample collection and storage were prevalent. Logistical challenges related to the scheduling, accessibility, and delivery of primary healthcare services were also highlighted. Additionally, women suggested implementing a reminder system for CRC screening—operating through governmental platforms— to enhance CRC screening participation.

Study Five results support the need for a multi-component intervention to increase screening uptake among the Saudi population. Tailored health promotion strategies endorsed by the MOH are warranted to raise public awareness and collective screening participation. The influence of word-of-mouth, patient testimonials, and social influencers should be leveraged to motivate screening. Additionally, Study Five highlighted the potential power of healthcare provider endorsement and recommendation in screening uptake, which is further influenced by the quality of the patient-provider relationship.

Study Five used the SEM as a comprehensive framework to categorize and understand the myriad factors influencing CRC screening decisions among Saudi women. This model recognizes human health and behavior as the product of an interaction between multiple levels of influence, including individual, interpersonal, community, organizational, and policy (34). Hence, when examining health issues, this approach deviates from the sole focus on personal-level factors by shedding light on the physical and social-environmental factors that must be addressed. The insights derived from Study Five serve as a valuable blueprint for policymakers and healthcare officials, informing the development of future policies and targeted strategies to improve patient outcomes and lessen the CRC burden in Saudi Arabia.

7.3 Synthesizing the findings

Studies One and Two highlight limitations in the calculations and reporting of incidence measures, providing guidance for researchers on incidence methods commonly reported in the CRC literature and emphasizing the need for transparent reporting practices to enhance the interpretation and reproducibility of their findings.

Studies Three and Four provide valuable insights into the burden of CRC in Saudi Arabia, supporting the need for CRC screening to control the increasing rates and improve patient outcomes. These findings, combined with the fact that most CRC cases are sporadic and the growing prevalence of risky lifestyles among Saudis, support the current recommendation by the national early detection program to initiate CRC screening at age 45. This cutoff age aligns with the latest recommendations from the USPSTF and ACS (35, 36). Modelling studies have shown cost-effectiveness for starting CRC screening at age 45 (37). Furthermore, simulation models evaluating the benefits and harms of screening across various screening modalities and age groups have indicated that annual FIT for average-risk individuals aged 45 to 75 is a sensible option (38).

Between 1997 and 2017, CRC incidence rates in the 45-49 age group increased from 3.7 to 14.2 per 100,000 person-years for females and from 2.1 to 16.7 per 100,000 person-years for males. The ASIR figures for both sexes aged 45-49 in 2017 are comparable to those for the 50-54 age group from less than a decade earlier. Given that the 50-59 age group in both sexes showed the highest incidence trends among screening-targeted age groups, and considering the lag time in the adenoma-carcinoma sequence, initiating screening at age 45 seems reasonable. This approach could also reduce CRC incidence and mortality in individuals over 50. Currently, however, lowering the screening age below 45 is not strongly supported. Although a positive trend was observed in the 40-44 age group, the absolute change in rates was only two points from 1997 to 2017. Furthermore, the age distribution of the Saudi population is currently

skewed toward younger individuals. Lowering the screening age would substantially increase costs and burden the healthcare system, as more individuals would become eligible for screening. This change could potentially divert screening resources from older groups with higher CRC risk. Therefore, monitoring trends and conducting cost-effectiveness analysis for screening in this younger group are warranted to inform future screening recommendations.

Study Four highlights the increased risk of late-stage CRC in specific regions and among young, unmarried women, warranting further investigation into the factors driving these observations. International and Saudi CRC screening guidelines do not provide sex-specific recommendations. The findings of this thesis indicate that younger males and females (aged 40-44) had comparable incidence rates in most years. Therefore, lowering the screening age below 45, particularly for women, cannot be justified based on these findings and is not supported.

Several plausible explanations for the noted sex disparity in late-stage presentations have been discussed in Study Four. The increased prevalence of obesity and MetS among Saudi females could also be contributing factors. Recent studies have linked MetS to EO-CRC (18), worsened stages at presentation, and lower survival rates (39, 40). Further research is needed to establish a clear and robust understanding of the link between late-stage CRC and young women. In the meantime, however, targeted health awareness campaigns are warranted to enhance CRC awareness and encourage screening uptake among this demographic.

It is imperative to note that risk assessment for CRC screening in Saudi Arabia should not only be based on age but also on individual risk factors, such as predisposing health conditions (obesity, MetS, or IBD), the presence of symptoms, genetic factors, history of cancer, or a CRC family history. The American College of Gastroenterology recommends that individuals with a family history of CRC—an affected first-degree relative— should begin screening at the age of 40, or ten years younger than the age at which the youngest relative was diagnosed (41). Additionally, findings from Study Three indicate that CRC rates were rapidly increasing among adults over 79, with men and women over 74 experiencing a steeper rise in distant CRC rates compared to younger age groups. Given the advances in medical interventions and the expected increase in life expectancy in the Saudi population, it may be prudent to consider a personalized approach to CRC screening for those over 75. This approach supports joint decision-making in a clinical setting, taking into account the patient’s current health status, CRC risk factors, screening history, and preferences (37).

This thesis's quantitative and qualitative findings highlight a critical CRC risk among women. In study three, women aged 50-75 had a heightened increase in distant-stage CRC during the later

years of the study period. Study Four revealed that young and unmarried women were at higher risk of presenting with late-stage disease, suggesting potential disparities in health-seeking behaviors or access to screening services. Study Five qualitatively explored CRC screening decisions among Saudi women, revealing a myriad of factors influencing screening behaviors.

The qualitative data indicated a pervasive lack of awareness and numerous misconceptions about CRC risk factors across all age groups. Participants reported a low perceived personal risk and expressed fear of the disease. Feelings of disgust and embarrassment about the sample collection process for screening were common, along with a general mistrust of the healthcare system's safety protocols and preventative programs. Furthermore, the data underscored the crucial role of social and family support in promoting health behaviors. Many women noted the role of these relationships in facilitating their participation in screening by helping them overcome procedural fears and by normalizing and prioritizing health prevention behaviors. This insight helps partially explain the quantitative finding of increased risk among unmarried women, suggesting that the absence of familial support might lead to delayed screening and the detection of disease at a late stage.

Given the recognized role of social and family support in encouraging screening, there is a need for public health awareness and promotional interventions that engage not only individuals within the targeted screening age spectrum (aged 45-75) but also their families. Findings from Study Five confirm this need, indicating a strong demand among Saudi women for an effective targeted CRC screening program and promotional strategies to meet their informational and logistical needs and address their concerns. The use of the SEM in guiding the interpretation of this exploration has emphasized the essential role of employing theoretical frameworks in assessing and planning public health interventions and underscored the need for multi-level intervention to influence human behavior (42). Overall, the insights this thesis provides will support healthcare professionals, public health officials, and decision-makers in developing CRC control efforts informed by understanding the CRC burden and the community's needs within the local context.

7.4 Thesis strengths and limitations

One of the strengths of this thesis is its use of a sequential mixed-methods design, where each study builds upon the findings of the previous one. The combined use of quantitative and qualitative analyses also allowed for a deeper understanding of the CRC burden in Saudi Arabia. The systematic reviews contributed to the international literature by identifying commonly used incidence measures and deficiencies in reporting incidence methods. These

findings highlighted the need for established guidelines to improve the reliability and comparability of incidence data.

Studies Three and Four conducted a retrospective analysis of the longest period of CRC data ever studied in the Saudi literature, providing pivotal insights that strengthen the evidence for CRC screening in Saudi Arabia and inform future CRC control efforts. Additionally, Study Four employed an unconventional approach by utilizing decision tree analysis to identify subpopulations at a higher risk for late-stage CRC. This method deepened our understanding of the data and pinpointed critical areas for further research. The use of decision tree analysis in epidemiological research is beneficial. It facilitates simple and quick visualization and identification of homogenous groups, thereby supporting the development of targeted and tailored interventions.

Lastly, conducting qualitative interviews with Saudi women elucidated and added context to the results observed in the quantitative studies. The generated insights are crucial for developing promotional interventions and enhancing the effectiveness of the screening program.

Several limitations in this thesis must be noted. First, although retrospective registry data can support causal inferences when analyzed with appropriate methods such as Directed Acyclic Graphs (DAGs), the analyses conducted in this thesis were mainly exploratory. The logistic regression analyses presented in Study Four aimed to examine associations between clinical and demographic factors and the likelihood of advanced CRC diagnosis, instead of determining causal relationships. Findings suggested that young and unmarried women were at increased risk for late-stage CRC. Despite the importance of this observation, it should be interpreted with caution, as age, sex, and marital status are inherently complex, and a myriad of factors may influence the observed association. Healthcare provider behaviors, and social-level factors may play roles in these associations. Given the scope of the present thesis, a comprehensive exploration of these relationships was not carried out. Yet, Study Five explored women's views on CRC screening, shedding light on several potential factors impacting women's acceptance and uptake of screening.

The population data obtained from GASTAT, which were used as denominators for calculating incidence rates, were unavailable for certain calendar years. Thus, missing population data were interpolated. While the use of such method is common in epidemiological research, they introduce a degree of uncertainty into incidence rate calculations. Hence, further efforts by GASTAT are needed to provide researchers with complete and accurate population statistics.

Another limitation pertains to the data provided by the SCR. Cancer registry data often have inherent limitations, including missing or incomplete information, coding inaccuracies, and inconsistencies in data collection and reporting processes. These issues are often more pronounced during the early years of a registry's operation when data collection systems and quality control mechanisms are still being developed and improved. In the SCR data used for this thesis, approximately 10% of CRC cases had missing disease stage information. When examining incidence trends by stage, cases with missing stage data were excluded from the analysis, which may have affected the accuracy of trend estimates. A comparison of patient characteristics between those with and without missing stage information revealed a higher proportion of missingness among older adults (aged 80 and above). As a result, incidence trends by disease stage within this age group should be interpreted with caution. Furthermore, when exploring factors associated with late-stage presentation, missing stage data were imputed as part of a sensitivity analysis. Although this approach was employed to assess the robustness of the findings, the imputed values may not be as accurate as having complete and actual stage data. These limitations emphasize the need for improved completeness and quality of CRC stage information within the SCR to enhance the validity of findings in future research efforts. The SCR also lacks information on lifestyle risk factors, comorbidities, and hereditary factors, thus limiting the variables that could be examined for associations with late-stage CRC presentation.

The SCR does not include follow-up data on patient status, such as mortality, nor is it linked to death registries. As a result, calculating cancer-specific mortality rates, mortality-to-incidence ratios, or survival analyses for the cohort studied in this thesis was not feasible. Examining incidence, mortality, and survival rates together would have provided a more comprehensive understanding of the CRC impact and burden in Saudi Arabia. Additionally, given that the data provided by the SCR covered the period between 1997 and 2017, the recorded data do not capture the incidence following the launch of the Saudi national screening program in 2017. Thus, generating insights on the program's impact on CRC incidence was not feasible.

Finally, Study Five's sample included only women from the Riyadh region, informed by insights from Studies Three and Four, which revealed increasing distant CRC rates among women aged 50 to 74 and higher late-stage CRC risks in younger Saudi women. Although this sample does not represent the entire Saudi population, the study findings offer insights that can be transferable to women residing in other Saudi regions and the broader GCC countries. Factors influencing screening decisions may also differ for men, highlighting an area for further investigation.

7.5 Implication of findings

7.5.1 Implications for practice

7.5.1.1 Improving cancer research in Saudi Arabia

The IARC advises countries to prioritize the development of reliable PBCRs to guide their cancer-control efforts and research plans (43-46). In this thesis, information on cancer stage at diagnosis was missing for about 10% of cases. The SCR also lacked follow-up data on patients' outcomes and long-term survival after a CRC diagnosis. Such information is imperative for evaluating the effectiveness of CRC interventions, predicting the future cancer burden on healthcare services and expenditures, and determining future research priorities. Hence, it is essential for the Saudi Health Council, as the governing authority of the SCR, to make the necessary efforts to collect stage and follow-up data (such as vital status) and ensure its completeness and quality. Collaborating with a regional IARC hub can provide the required training and guidance to optimize the quality and comprehensiveness of the SCR. Additionally, linking the SCR with mortality data from death registries would facilitate understanding the impact of the stage at diagnosis on survival rates within Saudi Arabia, providing evidence to support targeted health promotion activities to improve early detection.

As part of the Saudi Vision 2030 goals to improve scientific research and innovations, the Saudi National Institute for Health (SNIH) was recently established to support health research, build research capacity, and provide funding. However, cancer research in Saudi Arabia still faces major barriers, including the absence of a regulatory body for cancer research, a national research strategy, and well-defined priorities. Additionally, limited funding opportunities and access to cancer data are persisting challenges. Accessibility issues are often due to complex and bureaucratic application procedures and the involvement of multiple official entities in data governance (47). Alessay et al. recently assessed cancer research capacity in the country, highlighting the need for a more regulated and transparent procedure to access cancer data and an established plan for research priorities. The Saudi National Cancer Institute, operating under the Saudi Health Council, was suggested to lead the development of research priorities. Furthermore, creating additional funding opportunities within the SNIH was recommended (47). Indeed, improving cancer research capacity and overcoming the challenges researchers face are essential steps toward improving cancer research outputs in the country.

7.5.1.2 An organized and effective CRC screening program

The current CRC screening approach introduced by the MOH can be considered semi-organized. Participants are expected to take the initiative to request screening, which is

offered free of charge through primary healthcare centers. A system is in place to refer Individuals with abnormal FIT to follow-up examinations. Despite removing barriers related to testing and caring costs, relying on patients to request screening may lead to lower participation rates, reducing the program's effectiveness. Studies across various populations have shown that implementing organized screening resulted in increased screening participation and a substantial decrease in CRC incidence and mortality (48-51).

In 2022, the IARC published a consensus statement defining 16 essential and eight desirable criteria for organized cancer screening programs. Essential criteria included developing a protocol that specifies the target population, screening methods, and referral processes; implementing a system to identify and invite eligible individuals for screening; evaluating the program's performance and publishing the results regularly; and developing a system for notifying results, monitoring follow-up, and sending reminders. Additionally, IARC emphasized the importance of establishing an information system that integrates data from population databases, cancer registries, and screening records to facilitate a comprehensive evaluation of the screening program. The authors of this report, however, suggested that labeling programs as organized or non-organized should preferably be avoided due to the diversity in organization across screening programs and the complexities in their implementation. Instead, they proposed using the identified criteria to guide quality improvement and resource distribution (52).

For the Saudi national screening program to effectively prevent and detect CRC early, the identified criteria by the IARC should be employed to strengthen the quality and implementation of the program. One of the essential components currently missing from the Saudi program is an established system for inviting participation. Findings from Study Five highlight this gap, with women suggesting the development of reminder systems within governmental platforms to systematically identify and actively engage eligible individuals, thereby enhancing participation rates.

According to European guidelines for CRC screening, a minimum uptake rate of 45% is considered acceptable, with a target of at least 65% (53). D'Andrea et al. indicated that the level of adherence to screening substantially impacts CRC incidence and mortality. They proposed that to match colonoscopy benefits, stool-based tests' adherence rates should exceed 65-70% (54). Similarly, a consensus statement by the US Multi-Society Task Force on FIT application recommends achieving a 60% or higher FIT completion rate and a colonoscopy completion rate of at least 80% for patients with a positive FIT result (55). Despite these recommendations, screening uptake remains suboptimal in many populations (56). Increasing the acceptance and uptake of CRC screening among the Saudi population requires

multicomponent interventions that target multiple levels of influence, including the individual, community, and healthcare systems and policies. Key strategies include raising awareness through targeted health promotion campaigns directed at healthcare providers and the general population and addressing logistical and structural barriers hindering healthcare system access and navigation. Previous reports supported the effectiveness of such a multi-component approach in increasing participation rates (57, 58).

The current Saudi CRC screening program also requires two samples for the FIT, in contrast to the recommended single sample in many available FITs (59). This discrepancy could deter participation, as potential participants may perceive collecting two samples as burdensome. Although requiring two samples may aim to increase diagnostic accuracy, existing evidence suggests that an annual one-sample FIT regimen is as effective as a multi-sample approach (55). Furthermore, the US Multi-Society Task Force recommends a cut-off value of less than 20 mgHb/g of stool for a positive FIT test, as it offers optimal diagnostic accuracy (55). Thus, to enhance screening accuracy and uptake, revisiting the Saudi screening protocol to reduce the number of required samples and conducting local studies to determine the optimal cut-off value for a positive FIT among the Saudi population should be considered.

Additionally, individuals who are non-compliant with the FIT could be offered alternative options, such as the SEPT9 DNA blood-based test, which detects methylated DNA specific to colorectal cancer in a patient's blood (60). A systematic review and meta-analysis of 19 studies assessing the effectiveness of this test for early detection indicated high specificity and moderate sensitivity for CRC, making it a viable screening option (60). Additionally, as strong patient preference and adherence to the SEPT9 test have been reported (54), including the test in annual regular checkups may be a practical strategy to increase screening participation.

Lastly, integrating an individualized approach into the screening program, in which risk assessments based on personal risk factors guide screening recommendations, can enhance the program's effectiveness. The role of healthcare providers in encouraging screening was strongly emphasized in the literature (51), and findings from Study Five confirm the importance of provider recommendations in motivating screening participation among Saudi women. Providers have an essential role in risk assessment for CRC screening by leveraging their knowledge of patients' health history and risk factors to inform screening recommendations. Therefore, prioritizing the collection of patients' lifestyle habits and personal/family cancer history is crucial. Additionally, notification systems should be established to enhance provider involvement, prompting them to recommend screening to eligible individuals.

7.5.1.3 Effective CRC screening promotional interventions

Study Five findings and recommendations align with Behavioral Economics (BE) principles to understand human decision-making processes. BE-based interventions often leverage automatic human responses (System 1 thinking) rooted in heuristics. These interventions also employ nudges—subtle changes in the decision-making environment— to encourage participation in cancer screening programs (61-63).

Leveraging BE concepts such as judgment, decision-making, and choice architecture in promoting cancer screening enhanced screening uptake. The judgment principle emphasizes the importance of increasing an individual's perceived risk by providing personally relevant messages that contain accurate and memorable information on cancer risk. The decision-making concept underscores the influence of message framing on screening adherence. For example, framing messages to address perceived barriers, costs, and risk factors, while emphasizing benefits such as mortality reduction and the specificity of screening tests positively impacted screening decisions. Messages framed positively in terms of the emotional and physical gains of screening were more recommended than those highlighting the potential costs and losses from non-participation. Additionally, aligning screening messages with social and cultural norms by portraying screening as a common practice among peers enhanced intentions to participate (64).

Choice architecture involves "organizing the context in which people make decisions", which can be achieved by framing messages to elicit positive views on screening while making screening the default option, allowing people to opt-out. This principle also supports using technology, incentives, reminders, flexible scheduling, and testing options to enhance screening uptake (64).

A recent systematic review and meta-analysis on the effectiveness of BE-based interventions in increasing CRC screening uptake revealed a positive influence. Interventions that allow individuals to opt-out showed the largest impact, followed by navigation strategies that provide a healthcare navigator to assist patients in overcoming barriers and making informed decisions (61). Taylor et al. also showed that default-based interventions that involved mailing test kits with an invitation letter endorsed by a general practitioner effectively promoted screening (62). Regarding BE messages, Gorini et al. reported that social norm messages, indicating that non-respondents are part of a "minority group", improved CRC screening behavior (63). In Saudi Arabia, a recent trial reported increased screening uptake by nudging participants through motivational and positively framed invitation messages, in which the test was labeled "GIT safety" (65).

Overall, integrating BE principles with the SEM framework, as identified in Study Five, for planning and tailoring communication styles and strategies in CRC screening interventions will potentially enhance the uptake and adherence to cancer screening recommendations among the Saudi population.

7.5.1.4 Healthcare system preparedness

This thesis highlights a steady increase in CRC incidence rates across all ages and stages, and the burden is expected to increase in the foreseeable future. Such trends underscore the need for a well-prepared healthcare system to address the growing burden effectively. Recent transformative changes within the Saudi healthcare system have prioritized disease prevention and providing high-quality care. Developing cancer control efforts were emphasized among these priorities, and a CRC screening program was established. Efforts to promote the program have been implemented. As the outreach and coverage of the program improve, a surge in CRC cases is anticipated, impacting healthcare service demands. Hence, equipping and strengthening the healthcare system is vital.

Main priorities for the healthcare system should include ensuring adequate infrastructure, workforce, and supplies to support the screening program's implementation and sustainability. Ensuring equal access to primary healthcare services across all regions of the country, including rural areas, is also imperative. Periodic revisions of screening guidelines are necessary to incorporate emerging evidence relating to CRC incidence, risk factors, and etiology. Updates to guidelines should be well-communicated to healthcare providers and integrated into clinical practice. Additionally, providers should actively promote screening by leveraging their interactions with patients to raise awareness and encourage participation.

Women interviewed in Study Five preferred continuing care with familiar healthcare providers and settings. Given that the private sector and other governmental organizations deliver 40% of healthcare services in the country (66), a joint effort between the MOH and other healthcare sectors to promote and implement CRC screening could enhance the program's reach and effectiveness.

7.5.1.5 Effective monitoring of behavioral risk factors

The Saudi Arabian government has implemented numerous policies and strategies to address the obesity and smoking epidemics. To combat obesity, initiatives coordinated by various governmental agencies have targeted behavioral risk factors such as dietary habits and physical activity. These initiatives include implementing a sugar-sweetened beverages tax (50%), mandating nutrition facts labeling on food and drink packages and calorie menu labeling,

regulating school canteens, and introducing physical activity programs. Additionally, mass media campaigns were implemented to raise public awareness about the harmful effects of obesity and the benefits of healthy eating and physical activity. However, despite these measures, monitoring of implementation compliance and evaluating the effectiveness of these obesity prevention strategies remains inadequate (15).

In 2017, the government implemented a strict policy to address the smoking epidemic, enacting a 100% excise duty on tobacco products and fining commercial entities violating regulatory policies. The MOH has also joined efforts to combat smoking by launching awareness campaigns, publishing educational materials, and establishing 542 anti-smoking clinics by 2019. These clinics provide free consultations and medical services to individuals seeking help to quit smoking. Similar to obesity-related prevention efforts, the impact of these anti-smoking interventions on tobacco control within the country has not been evaluated (67).

One method of evaluating the impact of public health interventions is through Behavioral Risk Factor Surveillance Systems (BRFSS). These systems play a critical role in continuously collecting and interpreting data on the prevalence of chronic health conditions and behavioral risk factors (68). They are also vital for informing and guiding public health strategies and policies (69). Currently, the only behavioral risk factor surveys available in Saudi Arabia are the 2013 Saudi Health Interview and the 2019 World Health Survey (14, 70). These surveys vary in terms of tools used and reported variables; age-distributed data for many factors is also lacking. Moreover, nationally representative figures on childhood obesity are currently unavailable (15). Given the role of modifiable risk factors and comorbid conditions in CRC etiology, establishing a robust and standardized system to monitor chronic diseases and behavioral risk factors among the Saudi population should be prioritized to effectively guide future public health planning and interventions.

7.5.2 Implications for future research

In this thesis, I identified several gaps in the Saudi literature that warrant further research. Ensuring the quality of registry data is essential for producing reliable and valid evidence on the magnitude of the cancer burden. Although annual reports from the SCR indicate that quality control procedures are in place, published independent studies assessing SCR data quality are limited. A study conducted in 2003 evaluated the completeness and validity of cancer data reported in 1994 by a major public hospital, identifying substantial deficiencies in data quality (71). Given that the SCR began operating in 1994, such findings are expected, and it is reasonable to assume that data quality has improved over the last 30 years. Hence,

updated quality assessment studies are essential to confirm these improvements and identify any deficiencies that require further attention.

Findings from Study Two suggested that using various methods and estimate measures to examine incidence trends can provide a more in-depth understanding of the CRC burden. Future research in Saudi Arabia could use age-period cohort modelling (APCM) to analyze CRC trends more thoroughly. Given that CRC is a disease with multifactorial etiology, examining the independent and simultaneous effect of age, calendar period, and birth cohort on incidence rates can reveal critical insights into how these factors contribute to CRC incidence trends (72). In APCM analysis, age effects are a surrogate for the biological aging processes. Period effects are related to seasonal factors that affect all age groups simultaneously at a specific time, and cohort effects are variations attributable to exposures within a specific generation (72, 73). Several International reports observed increased CRC incidence with successive periods and birth cohorts, particularly a heightened risk among younger populations, suggesting a strong cohort effect for EO-CRC (74, 75). An examination of SCR data using APCM analysis can corroborate the findings of this thesis and elucidate the driving factors in CRC etiology among Saudi patients.

Study Three examined changes in the magnitude and direction of CRC across all ages, sexes, and stages at diagnoses. In addition to this analysis, similar analytical approaches (such as joinpoint regression and age-specific trend analysis) could be applied to regional data to explore geographic variations in CRC incidence. This type of analysis would offer valuable insights, guide prevention efforts, and inform future research to explore the underlying factors driving any observed variations in trends. Additionally, recent studies have indicated an association between CRC anatomical location and its prognostic features (76). Therefore, further research is essential to analyze CRC incidence trends by cancer subsite (colon, rectum) and stage at diagnosis. This can be achieved using joinpoint regression analysis, applying the same age categorization used for CRC stage trends in this thesis. Such analysis will enhance our understanding of CRC etiology by site and inform screening strategies and programs. To explore factors underlying the rising CRC incidence, future research efforts in Saudi Arabia could include cross-sectional studies involving patients diagnosed with CRC. These studies could use surveys to collect information on various factors, including lifestyle and healthcare-seeking behaviors, awareness of screening, and family history. The collected data can then be analyzed to explore the distribution of risk factors among individuals diagnosed with CRC.

In Study Four, young and unmarried women in certain regions had an increased risk for late-stage CRC. This observation warrants further investigation to pinpoint potential underlying causes. Examining lifestyle factors, health conditions, genetic markers, and healthcare

access—including referral pathways and diagnostic timelines— among high-risk subpopulations can inform targeted interventions and tailored strategies to improve their outcomes. This can be achieved through a combination of quantitative and qualitative research approaches.

Cross-sectional surveys administered to female CRC patients could be used to assess the prevalence of potential risk factors. The collected data could also be analyzed using multiple logistic regression to identify factors associated with late-stage presentation. A practical approach to collecting such information in the future could involve integrating risk factor surveys within the national screening program. Individuals could be invited to complete a brief questionnaire when receiving the screening kit, capturing information on sociodemographic characteristics, health-related behaviors, awareness levels, existing health conditions, and family history. Such an approach would facilitate the routine collection of valuable data to understand CRC risk factors within the Saudi population.

In-depth qualitative studies involving interviews with women diagnosed with distant-stage CRC, followed by thematic analysis, could provide valuable insights into individual, cultural, and structural barriers that delay diagnosis. Additionally, it is essential to employ qualitative methods to explore further the public's awareness of CRC and their acceptance and uptake of screening across the country's 13 regions. Such investigations will help partially understand the observed regional variations in late-stage risk and guide targeted public health policies and interventions in reducing the economic and health burden of late-stage diagnoses.

Future research should also investigate clinical and pathological differences between early and late-onset CRC among Saudi patients. Global studies have noted distinctions between the two groups in terms of CRC anatomical site, histopathological features, and stage at presentation (37, 77). Such examination will build on existing CRC research in the country, enhancing our understanding of CRC etiology and informing screening protocols.

Findings from Study Five provided foundational knowledge necessary for developing a comprehensive, multifaceted intervention to raise awareness and increase CRC screening uptake among women. Future research should explore factors affecting screening decisions among a broader demographic, including men and residents of other regions in Saudi Arabia. Moreover, it is crucial to investigate healthcare providers' and policymakers' roles and perspectives regarding the national CRC screening program's implementation, reach, and current challenges.

Concerning health promotion interventions, evaluating the effectiveness of these activities in terms of public engagement and increased screening participation is integral for identifying

areas for improvement, sharing learned lessons, and planning future promotional efforts. Finally, ongoing research should focus on monitoring the CRC burden among the Saudi population, identifying variations in rates among specific groups, and indirectly gauging the effectiveness of the CRC screening program in reducing the incidence and improving patient outcomes.

7.6 Conclusions

This thesis offers valuable guidance on measuring CRC incidence and provides substantial evidence on the burden of CRC in Saudi Arabia. Incidence rates increased steadily across all ages and sexes from 1997 to 2017. Presentation with a distant stage increased at a higher rate than other stages. Young and unmarried women had a heightened risk of presenting with late-stage CRC. There was a general lack of awareness among women about CRC screening and the national screening program. Willingness to undergo screening was influenced by a myriad of variables, including personal, social, community, and logistical factors.

Cancer control is a primary goal of Saudi Vision 2030; thus, ongoing public health and policy-level efforts to tackle the growing CRC burden are warranted. This thesis supports the national screening program's recommendation to screen average-risk individuals starting at age 45. Yet, measures to strengthen the quality and implementation of the screening program should be adopted. Organized and multicomponent interventions are crucial to raising public awareness, addressing barriers, and augmenting participation in the CRC screening program. Future research should focus on discerning risk factors contributing to CRC development and late-stage diagnosis in the Saudi population. Ongoing research is needed to gauge the impact of screening on CRC burden and to develop effective CRC-control strategies.

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Appendix A: Study One supplementary materials

Appendix A.1: Search strategies for systematic review

Database: MEDLINE

In steps:

#	Exposures	Hits
1	exp Colorectal Neoplasms/	199011
2	(colorect* or rect* or colon* or bowel).tw,kw.	821785
3	(cancer* or neoplas* or tumo?r* or malignan* or carcinoma* or adeno*).tw,kw.	3493361
4	2 and 3	329291
5	1 or 4	369542
6	Incidence/	258624
7	incidence.tw,kw.	740036
8	Trend*.tw,kw.	391905
9	6 or 7 or 8	844856
10	exp Registries/	94470
11	(cancer adj3 regist*).tw,kw.	23493
12	10 or 11	107181
13	5 and 9 and 12	3318
14	limit 13 to english language	3130
15	limit 14 to yr="2010 -Current"	**1787**

Database: Embase

In steps:

#	Exposures	Hits
1	(colorect* or rect* or colon* or bowel).tw,kw.	925983
2	(cancer* or neoplas* or tumo?r* or malignan* or carcinoma* or adeno*).tw,kw.	3825267
3	1 and 2	429033
4	exp colon tumor/	280525
5	exp rectum tumor/	229465
6	3 or 4 or 5	494055
7	Incidence/	376884
8	Cancer incidence/	67144
9	incidence.tw,kw.	885965
10	Trend*.tw,kw.	502568
11	7 or 8 or 9 or 10	1460125
12	Cancer registry/	33889
13	Register/	108956
14	(cancer adj3 regist*).tw,kw.	33651

15	12 or 13 or 14	150261
16	6 and 11 and 15	4657
17	limit 16 to english language	4444
18	Limit 17 to conference abstract	1440
19	17 NOT 18	3004
20	limit 19 to yr="2010 -Current"	**1977**

Database: Web of science

In steps:

#	Exposures	Hits
1	(TS=(cancer* or neoplas* or tumor* or tumours or malignan* or carcinoma* or adeno*)) AND LANGUAGE: (English) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=2010-2020	2,126,653
2	(TS=(colorect* or rect* or colon* or bowel)) AND LANGUAGE: (English) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=2010-2020	667,363
3	1 and 2	235,826
4	(TS=(incidence or trend*)) AND LANGUAGE: (English) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=2010-2020	883,278
5	(TS=(registry or registries)) AND LANGUAGE: (English) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=2010-2020	104,506
6	3 and 4 and 5	**1584**

Appendix A.2: Title/Abstract screening inter-reviewer agreement rate calculation (κ statistic)

	Reviewer (AA)			
		Included	Excluded	Total
Reviewer (NA)	Included	234 (a)	5 (b)	239
	Excluded	15 (c)	2652(d)	2667
	Total	249	2657	2906

$$p_0 = \frac{(a+d)}{a+d+b+c} = \frac{(234+2649)}{2906} = 99\%$$

$$p_e = \left[\left({}^{a+b}/_{n}\right) * \left({}^{a+c}/_{n}\right)\right] + \left[\left({}^{c+d}/_{n}\right) * \left({}^{b+d}/_{n}\right)\right] =$$

$$\left[\left({}^{239}/_{2906}\right) * \left({}^{249}/_{2906}\right)\right] + \left[\left({}^{2667}/_{2906}\right) * \left({}^{2657}/_{2906}\right)\right] = 84\%$$

$$\kappa = \frac{(p_0 - p_e)}{(1-p_e)} = \frac{(99\% - 84\%)}{(1-84\%)} = 94\%$$

Appendix A.3: Description of characteristics of included studies

Study characteristics	
Country	***N (% out of 165)***
The United States of America	66 (40.0)
Europe	38 (23.0)
Asia	36 (21.8)
Oceania	7 (4.2)
Canada	5 (3.0)
Africa	5 (3.0)
Multi-country	6 (3.6)
Central and South America	2 (1.2)
Main outcomes *(presented here the three most common outcomes reported in the included studies)*	***N (% out of 165)***
Incidence	165 (100.0)
Mortality	41 (24.8)
Survival	36 (21.8)
Type of cancer	***N (% out of 165)***
Colorectal cancer (CRC)	160 (96.9)
Colon cancer	3 (1.8)
Rectum cancer	2 (1.2)
Observation period	***N (% out of 165)***
A single year	5 (3.0)
Less than 10 years	32 (19.4)
10-19 years	61 (36.9)
20 years or more	69 (41.8)
Reported incidence rate measures	
Type of measures used for reporting incidence (Some studies reported more than one incident measure)	***N (% out of 165)***
Age-standardized incidence rate (ASR)	132 (80.0)
Age-specific incidence rate (ASIR)	50 (30.3)
Crude incidence rate (CR)	31 (18.8)
Cumulative incidence rate	3 (1.8)

Cumulative risk	7 (4.2)
Truncated ASR	3 (1.8)
Delay adjusted rate	4 (2.4)
Incidence rate • Derived from modelling. • Reported as the frequency of new cases. • Reported as the percentage of CRC cases among various groups.	18 (10.9) 4 (2.4) 2 (1.2) 2 (1.2)
Risk adjusted rate	1 (0.6)
Only ASR	74 (44.8)
Only ASIR	9 (5.5)
Only CR	4 (2.4)
Only ASR + ASIR	28 (16.9)
Only ASR + CR	14 (8.5)
Only ASR +ASIR + CR	12 (7.3)
Only ASIR + CR	1 (0.6)
The standard population used in estimating the ASR	***N (% out of 127 studies that reported the standard population)***
Study employed a local reference population	64 (50.4)
Study employed an external reference population	71 (55.9)
Study employed both a local and an external standard population	4 (3.1)
Used standard population according to study aim	***N (% out of studies with a specific aim (13,114))***
Study conducted international comparisons (all used an external reference): • Used same external reference population. • Used different external reference populations.	13 10 (76.9) 3 (23.1)
Study assessed only local incidence rates and trends: • Used a local reference. • Used an external reference.	114 62 (54.4) 52 (45.6)
Stratification of CRC incidence rate by anatomical site	***N (% out of 160 studies that reported CRC incidence)***
According to CRC anatomical site	86 (53.8)

Anatomical sites chosen for reporting CRC incidence: (some studies used a combination of the below sites)	***N (% out of 86 studies that reported incidence stratified by anatomical site)***
• Colon/Rectum.	77 (89.5)
• Proximal/Distal colon.	33 (38.4)
• Right-sided/Left-sided tumours.	11 (12.8)
• Colon, not otherwise specified (NOS).	7 (8.1)
• Appendix.	6 (6.9)
• Overlapping lesion of the colon.	2 (2.3)
• Rectosigmoid junction.	6 (6.9)
• Anus.	4 (4.7)
• Multiple anatomical sites in the colon.	7 (8.1)
Study reported only site-specific incidence rate without total CRC rate	29 (33.7% out of 86)
Quality of reporting incidence	
Quality of cancer registry data	***N (% out of 165)***
Study cited a reference for previously conducted research as evidence of cancer registry data quality: • Study referenced other studies or reports including validation or completeness assessments. • Study referenced similar epidemiological studies conducted in the same data source.	10 (6.1) 8 (4.8) 2 (1.2)
Study assessed and reported specific validity indicators	5 (3.0)
Study reported specific validity indicators that were identified in an external reference	3 (1.8)
Study reported that a cancer registration program checked data quality	6 (3.6)
Study indicated that the registration quality is being audited and certified regularly by a certification body	9 (5.5)
Study indicated that the cancer registry is meeting or utilizing standards for data quality set by national or international agencies	7 (4.2)

Study indicated complete case ascertainment of cancer data without providing a reference study	1 (0.6)
Definition of colorectal cancer	***N (% out of the indicated number)***
Classification system	
Study reported the use of a classification system	120 (72.7% out of 165)
• ICD-O	78 (65.0% out of 120)
○ 1st edition	2 (1.7% out of 120)
○ 2nd edition	7 (5.8% out of 120)
○ 3rd edition	63 (52.5% out of 120)
○ No edition specified	6 (5.0% out of 120)
• ICD	53 (44.2% out of 120)
○ 7th edition	1 (0.8% out of 120)
○ 8th edition	1 (0.8% out of 120)
○ 9th edition	8 (6.7% out of 120)
○ 10th edition	40 (33.3% out of 120)
○ No edition specified	3 (2.5% out of 120)
Study reported a classification system but without describing CRC codes	23 (13.9% out of 165)
Study did not report a classification system:	45 (27.3% out of 165)
• No reporting of the classification system and CRC codes.	32 (19.4% out of 165)
• No reporting of classification system but providing CRC site codes.	5 (3.0% out of 165)
• No reporting of classification system but describing only CRC sites.	8 (4.8% out of 165)
CRC codes	
Study did not report CRC codes	63 (38.2% out of 165)
Study reported CRC codes	102 (61.8% out of 165)
Study reported morphology codes only	6 (3.6% out of 165)
Study reported topography codes only	85 (51.5% out of 165)
Study reported morphology and topography codes	11 (6.7% out of 165)
Tumour behaviour	

Study explicitly indicated tumour behaviour (malignant/ in situ, other)	28 (16.9% out of 165)
Type of cancer	
Study specified the included cancer type (primary/secondary)	31 (18.8% out of 165)
Definition of numerator and denominator data	***N (% out of 165)***
Numerator	
Study explicitly explained excluding certain CRC cases from the numerator	20 (12.1)
Study excluded cases with unknown sites of primary tumours, or disease stage, or survival time	3 (1.8)
Study excluded in situ cancers	5 (3.0)
Study excluded cases with family history, hereditary syndromes, and IBD	3 (1.8)
Study excluded cases identified by only death certificate	4 (2.4)
Study excluded non-microscopically confirmed cases	8 (4.8)
Study excluded cases with incomplete address information	1 (0.6)
Study provided information about considerations for secondary CRC (synchronous and metachronous cancer cases) in incidence calculation	5 (3.0)
Denominator	
Study reported the data source for population statistics	65 (39.4)
Study reported the estimation of annual mid-year population	1 (0.6)
Study reported census years used for population size estimation	24 (14.5)
Study reported the method used to estimate yearly population counts (i.e., interpolation, extrapolation)	10 (6.1)
Study explicitly explained the population size estimation procedure for calculating average incidence rates (over the study period):	5 (3.0)

• Person-time at risk was calculated by creating closed cohorts of the population on various census nights and following them over time.	1 (0.6)
• Population size was estimated by multiplying the population count in a particular census year by the number of years included in the study.	3 (1.8)
• Population size was calculated by averaging population counts of two censuses conducted at the beginning and near the end of the study period.	1 (0.6)
Estimation of the age-standardized rate	***N (% out of 132)***
Study reported the method of standardization:	36 (27.3)
• Direct.	36 (27.3)
• Indirect.	0
Study reported the standard population used for standardization	127 (96.2)
Study did not report the standard population used for standardization	5 (3.8)
Study justified the chosen standard population	5 (3.9% out of 127)
Time interval for measuring incidence (e.g., annual, overall average)	***N (% out of 165)***
Time interval was clearly reported	62 (37.6)
Time interval was not clearly reported	103 (62.4)
Study reported an overall incidence measure for a specific observation period	90 (54.5)
Presentation of incidence rates	***N (% out of 165)***
Incidence rate was expressed with a time unit (whole years or person-time)	43 (26.1)
Incidence rate was expressed without a time unit	119 (72.1)
Age band for measuring incidence	***N (% out of 165)***
Age bands were clearly reported.	131 (79.4)
Number of age bands	
○ 1	12 (7.3)

○ 2	19 (11.5)
○ 3	23 (13.9)
○ 4	15 (9.1)
○ 5-10 age bands	35 (21.2)
○ 11-15 age bands	13 (7.9)
○ 16-20 age bands	12 (7.3)
○ 30-33	2 (1.2)
Estimation of uncertainty of incidence estimates	***N (% out of 165)***
Study reported a confidence interval for the incidence rate	33 (20.0)
Analysis of missing data	***N (% out of 165)***
Study reported handling of missing data in the analysis:	9 (5.5)
• Study excluded cases with missing values from incidence calculation.	5 (3.0)
• Study estimated missing data via joinpoint regression or multiple imputation.	2 (1.2)
• Study assumed missing data to be missing at random.	1 (0.6)
• Study corrected rates for missing data.	1 (0.6)
Study reported the type of missing data	8 (4.8)
Study indicated the amount of missing data	2 (1.2)
Study justified assumption on the reasons for the missing data	0
Statistical software	***N (% out of 165)***
Study reported software information for incidence rate analysis	110 (66.7)
<u>Software reported for estimating incidence rate:</u>	***N (% out of 110)***
• SEER	40 (36.4)
• SAS	19 (17.3)
• STATA	18 (16.4)
• SPSS	17 (15.5)
• Microsoft Excel	9 (8.2)

• R	8 (7.3)
• Can Reg4/CanReg-5	2 (1.8)
• Joinpoint	6 (5.5)
• Microsoft Fox Pro	1 (0.9)
• WinBUGS	1 (0.9)
• Open-Source Epidemiologic Statistics for Public Health software (OpenEpi)	1 (0.9)
• Statistica	1 (0.9)
• Rapid Inquiry Facility	1 (0.9)
• DevCan	1 (0.9)

Appendix A.4: Types of standard populations employed for the calculation of age-standardized rates (ASR)

	Reference Population	N (% out of 132 studies reported ASR)	Countries
1	2000 US standard population	52 (39.4)	United States of America, United Kingdom
2	WHO world standard population	27 (20.5)	Iran, Malaysia, seven high-income countries, France, Brunei Darussalam, Cyprus, Jordan, Israel, Izmir, Turkey, Italy, Tunisia, Sri- Lanka, Poland, Finland, New-Zealand, Luxembourg, Hong Kong, Korea, Japan, Taiwan, Estonia
3	Segi's world population	11 (8.3)	Pakistan, Iran, China, Central and South America, Shanghai, Korea
4	Segi's standard world population (modified by Doll)	5 (3.8)	China, Hong Kong, Thailand, Iran, Saudi Arabia
5	Ferlay's modified world population	1 (0.8)	Lebanon
6	European standard population	13 (9.8)	Portugal, New Zealand, United Kingdom, Ireland, Germany Sweden, Scotland, Italy, Spain, Netherlands
7	The 2001 European standard population	1 (0.8)	Italy
8	The 2000 European standard population	1 (0.8)	Italy
9	The 2013 European standard Population	2 (1.5)	United Kingdom, Italy
10	The 1976 European standard population	6 (4.5)	New Zealand, Ireland, United Kingdom, Netherlands, Germany, Ireland
12	The 2000 Chinese population	2 (1.5)	China
13	The Italian populations	2 (1.5)	Italy
14	The 2001 Canadian population	1 (0.8)	Canada
15	The 1991 Canadian population	2 (1.5)	Canada
16	The 2000 Swedish population	2 (1.5)	Sweden
17	The 2001 Australian population	1 (0.8)	Australian
18	The 2000 Korean population	1 (0.8)	Korea
19	The 2001 New South Wales (NSW) population	1 (0.8)	Wales

Appendix A.5: Quality appraisal checklist

Item	Yes	No	Unclear
1) Were the aims/objectives of the study clear? *			
2) Was the study design appropriate for the stated aim(s)? *			
3) Was the sample size adequate? §			
4) Were the study subjects and setting described in detail? §			
5) Were valid methods used for the identification of the condition? §			
6) Were the risk factor and outcome variables measured correctly using instruments/measurements that had been trialed, piloted, or published previously?*			
7) Was there an appropriate statistical analysis? §			
8) Is it clear what was used to determine statistical significance and/or precision estimates? (e.g., p values, CIs)? *			
9) Were the methods (including statistical methods) sufficiently described to enable them to be repeated? *			
10) Were the limitations of the study discussed? *			

§ Item from the Joanna Briggs Institute Prevalence Critical Appraisal Tool.

*Item from the AXIS tool.

Appendix A.6: Quality assessment. Studies are sorted in order from highest to lowest quality

First author and year	Clear aim and objectives	Appropriate study design	Adequate sample size	Description of study subjects and setting	Valid methods to identify the condition*	Outcome variables were measured correctly using instruments/measurements that had been published previously	Appropriate statistical analysis*	Determine precision estimates	Methods sufficiently described to enable them to be repeated	limitations of the study discussed	Total
Steinbrecher 2012	√	√	√	√	√	√	√	√	√	√	10
Danos 2018	√	√	√	√	√	√	√	X	√	√	9
Stern 2016	√	√	√	√	X	√	√	√	√	√	9
Crosbie 2018	√	√	√	√	√	√	X	√	X	√	8
Jayarajah 2020	√	√	√	√	√	√	X	√	X	√	8
Katsidzira 2016	√	√	√	√	√	√	√	X	X	√	8
Shafqat 2015	√	√	√	√	√	√	X	√	X	√	8
Safaee 2012	√	√	√	√	√	√	X	√	X	√	8
Shah 2012	√	√	√	√	√	√	√	X	X	√	8
Patel 2016	√	√	√	√	√	√	X	√	X	√	8
Siegel 2019	√	√	√	√	√	√	X	√	X	√	8
Wu 2018	√	√	√	√	√	√	√	X	X	√	8

Young 2015	√	√	√	√	√	√	X	√	X	√	8
Abdifard 2016	√	√	√	√	√	√	√	X	X	X	7
Abualkhair 2020	√	√	√	√	√	√	X	X	X	√	7
Araghi 2019	√	√	√	√	√	√	X	X	X	√	7
Austin 2014	√	√	√	√	√	√	X	X	X	√	7
Aziz 2015	√	√	√	√	√	√	X	X	X	√	7
Boyce 2016	√	√	√	√	√	√	X	X	X	√	7
Brenner 2016	√	√	√	√	√	√	X	X	X	√	7
Brouwer 2018	√	√	√	√	√	√	X	X	X	√	7
Caldarella 2013	√	√	√	√	√	√	X	X	X	√	7
Carroll 2019	√	√	√	√	√	√	X	X	X	√	7
Chambers 2020	√	√	√	√	√	√	X	X	X	√	7
Cheng 2011	√	√	√	√	√	√	X	X	X	√	7
Chernyavskiy 2019	√	√	√	√	X	√	X	X	√	√	7
Chittleborough 2020	√	√	√	√	X	√	X	√	X	√	7
Dehghani 2019	√	√	√	√	√	√	√	X	X	X	7
Edwards 2010	√	√	√	√	√	√	X	X	X	√	7

Enayatrad 2018	√	√	√	√	√	√	X	X	X	√	7
Exarchakou 2019	√	√	√	√	√	√	X	X	X	√	7
Feletto 2019	√	√	√	√	X	√	X	√	X	√	7
Martinsen 2016	√	√	√	√	√	√	X	X	X	√	7
Giddings 2012	√	√	√	√	√	√	X	X	X	√	7
Loomans-Kropp 2019	√	√	√	√	√	√	X	X	X	√	7
Gandhi 2017	√	√	√	√	X	√	X	√	X	√	7
Lopez 2019	√	√	√	√	√	√	X	X	X	√	7
Lopez-Abente 2010	√	√	√	√	√	√	X	X	X	√	7
McClements 2012	√	√	√	√	√	√	X	X	X	√	7
Ladabaum 2014	√	√	√	√	√	√	X	X	X	√	7
Liu 2015	√	√	√	√	√	√	√	X	X	X	7
Fournel 2016	√	√	√	√	X	√	X	√	X	√	7
Lee 2019	√	√	√	√	√	√	X	X	X	√	7
Khiari; Ben Ayoube 2017	√	√	√	√	√	√	X	√	X	X	7
Jandova 2016	√	√	√	√	√	√	X	X	X	√	7

Li; Lin 2017	√	√	√	√	√	√	X	X	X	√	7
Meza 2010	√	√	√	√	√	√	X	X	X	√	7
Jafri 2013	√	√	√	√	√	√	X	X	X	√	7
Meyer 2010	√	√	√	√	X	√	X	√	X	√	7
Garcia 2018	√	√	√	√	X	√	X	√	X	√	7
Fournel 2012	√	√	√	√	X	√	X	√	X	√	7
Brenner 2019	√	√	√	√	√	√	X	X	X	√	7
Fedewa 2019	√	√	√	√	X	√	X	√	X	√	7
Domati 2014	√	√	√	√	X	√	√	√	X	X	7
Vuik 2019	√	√	√	√	√	√	X	X	X	√	7
Singh 2018	√	√	√	√	√	√	X	X	X	√	7
Nfonsam 2015	√	√	√	√	√	√	X	X	X	√	7
Sammour 2009	√	√	√	√	X	√	√	X	X	√	7
Sheneman 2017	√	√	√	√	√	√	X	X	X	√	7
Murphy 2011	√	√	√	√	√	√	X	X	X	√	7
Siegel; Fedewa 2017	√	√	√	√	√	√	X	X	X	√	7
Siegel 2012	√	√	√	√	√	√	X	X	X	√	7

Sierra 2016	√	√	√	√	√	√	X	X	X	√	7
Oliveira 2016	√	√	√	√	√	√	X	X	X	√	7
Reggiani-Bonetti 2013	√	√	√	√	X	√	√	√	X	X	7
Phipps 2012	√	√	√	√	√	√	X	X	X	√	7
Innos 2018	√	√	√	√	√	√	X	X	X	√	7
Sia 2014	√	√	√	√	√	√	X	X	X	√	7
Stock 2012	√	√	√	√	√	√	X	X	X	√	7
Sun 2020	√	√	√	√	√	√	X	X	X	√	7
Tawadros 2015	√	√	√	√	√	√	X	X	X	√	7
Thirunavukarasu 2010	√	√	√	√	√	√	X	X	X	√	7
Troeung 2017	√	√	√	√	√	√	X	X	X	√	7
Veruttipong 2012	√	√	√	√	X	√	X	√	X	√	7
Wang 2017	√	√	√	√	√	√	X	X	X	√	7
Wang; de Grubb 2017	√	√	√	√	√	√	X	X	X	√	7
Wang 2019	√	√	√	√	√	√	X	X	X	√	7

Wessler 2010	√	√	√	√	√	√	X	X	X	√	7
Yoon 2015	√	√	√	√	√	√	X	X	X	√	7
Zheng 2014	√	√	√	√	√	√	√	X	X	X	7
Zhou 2015	√	√	√	√	√	√	X	X	X	√	7
Zhu 2013	√	√	√	√	√	√	X	X	X	√	7
Zorzi 2019	√	√	√	√	√	√	X	X	X	√	7
Zorzi 2015	√	√	√	√	√	√	X	X	X	√	7
Abdifard 2013	√	√	√	√	√	√	X	X	X	X	6
Abreu 2010	√	√	√	√	√	√	X	X	X	X	6
Araghi 2018	√	√	√	√	X	√	X	X	X	√	6
Ashktorab 2016	√	√	√	√	X	√	X	X	X	√	6
Baniasadi 2015	√	√	√	√	X	√	√	X	X	X	6
Bhurgri 2011	√	√	√	√	√	√	X	X	X	X	6
Winther 2016	√	√	√	√	√	√	X	X	X	X	6
Chatterjee 2015	√	√	√	√	X	√	X	X	X	√	6
Alsanea 2015	√	√	√	√	X	√	X	X	X	√	6
Chauvenet 2011	√	√	√	√	√	√	X	X	X	X	6

Chen 2012	√	√	√	√	X	√	X	X	X	√	6
Chong 2015	√	√	√	√	X	√	X	X	X	√	6
Clarke 2014	√	√	√	√	√	√	X	X	X	X	6
Ellis 2018	√	√	√	√	X	√	X	X	X	√	6
Eser 2018	√	√	√	√	√	√	X	X	X	X	6
May 2017	√	√	√	√	X	√	X	X	X	√	6
Koblinski 2018	√	√	√	√	X	√	X	X	X	√	6
Missaoui 2011	√	√	√	√	√	√	X	X	X	X	6
Kelly 2012	√	√	√	√	√	√	X	X	X	X	6
Gan 2019	√	√	√	√	X	√	X	X	X	√	6
Fowler 2018	√	√	√	√	X	√	X	X	X	√	6
Meester 2019	√	√	√	√	X	√	X	X	X	√	6
Li 2017	√	√	√	√	X	√	X	X	X	√	6
Khiari 2017	√	√	√	√	√	√	X	X	X	X	6
Shadmani 2017	√	√	√	√	X	√	X	X	X	√	6
Merrill 2011	√	√	√	√	√	√	X	X	X	X	6
McDevitt 2017	√	√	√	√	√	√	X	X	X	X	6

Khachfe 2019	√	√	√	√	X	√	X	X	X	√	6
Brenner 2017	√	√	√	√	√	√	X	X	X	X	6
Augustus 2018	√	√	√	√	X	√	X	X	X	√	6
Davis 2011	√	√	√	√	X	√	X	X	X	√	6
Siegel 2017	√	√	√	√	√	√	X	X	X	X	6
Savijarvi 2019	√	√	√	√	X	√	X	X	X	√	6
Van Beck 2018	√	√	√	√	X	√	X	X	X	√	6
Russo 2019	√	√	√	√	√	√	X	X	X	X	6
Oliphant 2011	√	√	√	√	X	√	X	X	X	√	6
Perdue 2014	√	√	√	√	X	√	X	X	X	√	6
Murphy 2017	√	√	√	√	X	√	X	X	X	√	6
Siegel 2020	√	√	√	√	√	√	X	X	X	X	6
Shin 2012	√	√	√	√	√	√	X	X	X	X	6
Murphy 2018	√	√	√	√	X	√	X	X	X	√	6
Sung 2019	√	√	√	√	X	√	X	X	X	√	6
Rafiemanesh 2016	√	√	√	√	√	√	X	X	X	X	6
Nowicki 2018	√	√	√	√	√	√	X	X	X	X	6

Oppelt 2019	√	√	√	√	X	√	X	X	X	√	6
Murphy 2019	√	√	√	√	X	√	X	X	X	√	6
Siegel 2014	√	√	√	√	√	√	X	X	X	X	6
Rejali 2018	√	√	√	√	√	√	X	X	X	X	6
Sarakarn 2017	√	√	√	√	√	√	X	X	X	X	6
Keum 2014	√	√	√	√	X	√	X	X	X	√	6
Singh 2014	√	√	√	√	X	√	X	X	X	√	6
Sjostrom 2018	√	√	√	√	X	√	X	X	X	√	6
Stromberg 2019	√	√	√	√	X	√	X	X	X	√	6
Thuraisingam 2017	√	√	√	√	X	√	X	X	X	√	6
Ugarte 2012	√	√	√	√	√	√	X	X	X	X	6
Ullah 2018	√	√	√	√	X	√	X	X	X	√	6
Wan Ibrahim 2020	√	√	√	√	X	√	X	X	X	√	6
Wen 2018	√	√	√	√	√	√	X	X	X	X	6
Yee 2010	√	√	√	√	√	√	X	X	X	X	6
Yeo 2017	√	√	√	√	X	√	X	X	X	√	6
Zhang 2018	√	√	√	√	X	√	X	X	X	√	6

Ohri 2020	√	√	√	√	X	√	X	X	X	√	6
Hassan 2016	√	√	√	√	x	√	X	X	X	X	5
Al Dahhan 2018	√	√	√	√	X	√	X	X	X	X	5
Bailey 2015	√	√	√	√	X	√	X	X	X	X	5
Crocetti 2010	√	√	√	√	X	√	X	X	X	X	5
Hasanpour-Heidari 2019	√	√	√	√	X	√	X	X	X	X	5
Lemmens 2010	√	√	√	√	X	√	X	X	X	X	5
Fusco 2010	√	√	√	√	X	√	X	X	X	X	5
Klugarova 2019	√	√	√	√	X	√	X	X	X	X	5
Klimczak 2011	√	√	√	√	X	√	X	X	X	X	5
Koblinski 2019	√	√	√	√	X	√	X	X	X	X	5
Purim 2013	√	√	√	√	X	√	X	X	X	X	5
Rahman 2015	√	√	√	√	X	√	X	X	X	X	5
Mosli 2012	√	√	√	√	X	√	X	X	X	X	5
Mosli 2012	√	√	√	√	X	√	X	X	X	X	5
Pakzad 2016	√	√	√	√	X	√	X	X	X	X	5

Pescatore 2013	√	√	√	√	X	√	X	X	X	X	5
Palmieri 2013	√	√	√	√	X	√	X	X	X	X	5
Paquette 2015	√	√	√	√	X	√	X	X	X	X	5
Zhabagin 2015	√	√	√	√	X	√	X	X	X	X	5

***Explanation of indicators:**

- **Valid methods to identify the condition**: This indicator assessed if the study clearly reported the classification system used to assess colorectal cancer and the site codes included in the analysis.
- **Appropriate statistical analysis**: This indicator assessed if the study clearly reported the numerator and denominator data in incidence calculation and described the analytical methods employed in detail.

Appendix A.7: Characteristics of included studies, measures of incidence, and chosen anatomical site for reporting incidence (Form A)

	First author and year	Country	Cancer type	Main outcomes	Observation period	Measure/s of incidence	Anatomical site stratification
1	Abdifard 2016	Iran	CRC	Incidence	2000–2009	ASR, ASIR	CRC
2	Abdifard 2013	Iran	CRC	Incidence	2000–2005	ASR	CRC
3	Abreu 2010	Portugal	Rectal	Incidence, survival	1995–2004	Sex and Age standardized incidence rate, CR, Cumulative risk	Rectum
4	Hassan 2016	Malaysia	CRC	Incidence, mortality	2008–2013	ASR	CRC
5	Abualkhair 2020	USA	CRC	Incidence	2000–2015	ASR	(Colon, rectum, CRC)
6	Al Dahhan 2018	Iraq	CRC	Incidence	2002–2011	CR	CRC
7	Araghi 2018	USA	CRC	Incidence, projection	1973–2014	ASR	CRC
8	Araghi 2019	Seven high income countries	CRC	Incidence	2008–2012/2009–2013/ 2010–2014	ASR	(Colon, rectum)
9	Ashktorab 2016	USA	CRC	Incidence	2000–2012	ASR, ASIR	CRC
10	Austin 2014	USA	CRC	Incidence	1998–2009	ASR	(Proximal/distal colon, rectum, CRC)[A]

11	Aziz 2015	USA	CRC	Incidence	1995–2010	Mean incidence from modelling	CRC
12	Bailey 2015	USA	CRC	Incidence	1975–2010	ASR	(Colon, right/left colon, rectosigmoid and rectum, colon (NOS))
13	Baniasadi 2015	Iran	CRC	Incidence	2003–2013	ASR, ASIR	CRC
14	Bhurgri 2011	Pakistan	CRC	Incidence, gender and clinical distribution	1995–1997/ 1998–2002	CR, ASR, ASIR	(Colon, rectum and anus, CRC)
15	Boyce 2016	Australia	CRC	Incidence, clinical and demographic features, survival	2001–2008	ASR, ASIR	CRC
16	Winther 2016	Denmark	CRC	Incidence, prevalence, survival, mortality	1980–2012	ASIR	(Colon, rectum and anus)
17	Brenner 2016	Germany	CRC	Incidence, mortality	2003–2012	ASR, Cumulative risk	CRC
18	Brouwer 2018	Netherlands	CRC	Incidence, mortality, treatment, survival	1989–2014	ASR	(Colon, rectum)
19	Caldarella 2013	Italy	CRC	Incidence	1985–2005	ASR, ASIR	(Proximal/distal colon, rectum, CRC)[A]
20	Carroll 2019	USA	CRC	Incidence, survival	1973–2013	Incidence rate from Poisson modelling	CRC

21	Chambers 2020	United Kingdom	CRC	Incidence	1974–2015	ASR, ASIR	(Proximal/distal colon, CRC)[B4]
22	Chatterjee 2015	USA	CRC	Incidence, screening practices, CRC risk factors	2000–2009	ASR	CRC
23	Alsanea 2015	Saudi Arabia	CRC	Incidence, survival, demographic features	1994–2010	ASR	CRC
24	Chauvenet 2011	France	CRC	Incidence	1976–2005	ASR, Cumulative risk	(Right/left colon, sigmoid, rectum, CRC) [C]
25	Chen 2012	Taiwan	CRC	Incidence	1988–2007	ASIR	(CRC, left/right colon, colon, rectum)[D]
26	Cheng 2011	USA	CRC	Incidence	1976–2005	ASR	(Proximal/distal colon, rectum) [A]
27	Chernyavskiy 2019	USA	CRC	Incidence	2000–2014	Incidence rate from modelling	(Colon, rectum)
28	Chittleborough 2020	New Zealand, Sweden, and Scotland	CRC	Incidence	1995–2012/1970–2014/ 1990–2014	ASR	(Rectum, colon, distal/proximal colon, CRC)[A]
29	Chong 2015	Brunei Darussalam	CRC	Incidence	1991 and 2014	ASR, ASIR	(Rectum, colon, CRC)
30	Clarke 2014	Ireland	CRC	Incidence, age and stage distribution, treatment, mortality, survival	1994–2010	ASR	(Colon, rectum, CRC)
31	Crocetti 2010	Italy	CRC	Incidence	1985–2005	ASR	CRC

32	Crosbie 2018	USA	CRC	Incidence, demographic and clinical features	1979–2014	ASR	(Proximal/distal colon, rectum, CRC)[A1]
33	Danos 2018	USA	CRC	Incidence	2008–2012	CR	CRC
34	Dehghani 2019	Iran	CRC	Incidence	2003–2010	CR, ASIR	CRC
35	Edwards 2010	USA	CRC	Incidence, mortality, survival, projection	1975–2006	ASR, ASIR	CRC
36	Ellis 2018	USA	CRC	Incidence	1990–2014	ASR	CRC
37	Enayatrad 2018	Iran	CRC	Incidence	2009	ASR	CRC
38	Eser 2018	Cyprus, Jordan, Israel, and İzmir/Turkey	CRC	Incidence	2005–2010	ASR, CR	(Colon, rectum, CRC)
39	Exarchakou 2019	England	CRC	Incidence	1971–2014	ASR, ASIR, CR	(Right/left colon, rectum, colon (NOS), CRC)[F]
40	Feletto 2019	Australia	CRC	Incidence	1982–2014	ASIR	(Colon, rectum)
41	Hasanpour-Heidari 2019	Iran	CRC	Incidence	2004–2013	ASR, ASIR, CR	(Colon, rectum, CRC)
42	Lemmens 2010	Netherlands	CRC	Incidence, stage distribution, treatment, mortality, survival	1975–2007	ASR	(Colon, rectum, ascending colon, transverse colon, descending and sigmoid colon)

43	May 2017	USA	CRC	Incidence, stage distribution	1975–2012	ASR	CRC
44	Fusco 2010	Italy	CRC	Incidence, mortality, survival, clinical and demographic features	2000–2005	ASR, CR, ASIR, Cumulative risk	CRC
45	Klugarova 2019	Czech Republic	CRC	Incidence, prevalence, mortality, treatment, survival	1982–2016	Incidence rate	CRC
46	Koblinski 2018	USA	CRC	Incidence	2000–2010	Incidence rate	CRC
47	Martinsen 2016	USA	CRC	Incidence, mortality, survival	1990–2012	ASR	(Distal/proximal colon, CRC)[B]
48	Giddings 2012	USA	CRC	Incidence	1988–2007	ASR	CRC
49	Missaoui 2011	Tunisia	CRC	Incidence	1993–2007	ASR, CR, ASIR	CRC
50	Kelly 2012	USA	CRC	Incidence	2005–2009	ASR, ASIR	(Colon, proximal/distal colon, rectum, CRC)[A]
51	Loomans-Kropp 2019	USA	CRC	Incidence, mortality	1980–2016	ASR	(Rectum, colon, proximal/distal colon)[A1]
52	Gandhi 2017	New Zealand	CRC	Incidence	1995–2012	ASR, CR	(Proximal/distal colon, rectum, CRC)[A]
53	Lopez 2019	France	CRC	Incidence, management, recurrence, survival	1982–2011	ASR	CRC

54	Lopez-Abente 2010	Spain	CRC	Incidence, mortality	1975–1993/2000–2004	ASR	CRC
55	McClements 2012	United Kingdom	CRC	Incidence, stage distribution, mortality	1982–2006	ASIR	CRC
56	Gan 2019	USA	CRC	Incidence, screening practices, survival	2011–2016	Incidence rate (defined as number of CRC cases)	CRC
57	Ladabaum 2014	USA	CRC	Incidence	1990–2004	ASR	CRC
58	Fowler 2018	USA	CRC	Incidence, mortality	1991–2010	ASR	CRC
59	Meester 2019	USA	CRC	Incidence, stage distribution	1975–2015	ASR	CRC
60	Li 2017	China	CRC	Incidence	1998–2012	ASR, CR	(Colon, rectum, CRC, proximal/ distal colon)[A]
61	Liu 2015	China	CRC	Incidence, mortality	2011	ASR, ASIR, CR, Truncated ASR (35-64), Cumulative incidence rate	CRC
62	Jayarajah 2020	Sri Lanka	CRC	Incidence, clinical features	2001–2010	ASR, ASIR	CRC

63	Katsidzira 2016	Zimbabwe	CRC	Incidence, demographic and clinical features	2003–2012	ASR, ASIR	CRC
64	Fournel 2016	France	CRC	Incidence	1995–2002	Sex and Age standardized incidence rate	CRC
65	Lee 2019	Taiwan	CRC	Incidence, survival, mortality	1984–2013	ASIR	CRC
66	Khiari 2017	Tunisia	CRC	Incidence, age and clinical distribution	2007–2009	ASR, CR	(Colon, rectum, CRC)
67	Shadmani 2017	Iran	CRC	Incidence	2008	ASR, CR	CRC
68	Merrill 2011	USA	CRC	Incidence	2005–2007	ASR, Risk-adjusted incidence rate	CRC
69	Klimczak 2011	Poland	CRC	Incidence, prevalence	1999–2008	ASR	(Colon, rectum)
70	Khiari; Ben Ayoube 2017	Tunisia	CRC	Incidence, projection	1994–2009	ASR	(CRC, colon, proximal/distal colon, rectum)[A]
71	Jandova 2016	USA	CRC	Incidence, mortality, demographic and clinical features	1995–2011	Incidence rate	CRC
72	Li; Lin 2017	China	CRC	Incidence	2010–2014	ASR, CR	CRC
73	Meza 2010	United Kingdom and USA	CRC	Incidence	1973–2006	ASR	(Proximal/distal colon, rectum)[B]

74	Jafri 2013	USA	CRC	Incidence, survival	1993–2007	ASR, ASIR	(CRC, Cecum, ascending colon, hepatic flexure, transverse colon, splenic flexure, descending colon, sigmoid colon, Rectosigmoid junction, rectum, and large intestine (NOS))
75	McDevitt 2017	Ireland	CRC	Incidence, mortality, survival, anatomical site and stage distribution	1994–2012	ASR	(Colon, proximal/distal colon, overlapping and colon (NOS), rectosigmoid junction and rectum, CRC)[B1]
76	Khachfe 2019	Lebanon	CRC	Incidence	2005–2015	ASR, ASIR	CRC
77	Meyer 2010	USA	CRC	Incidence	1973–2005	ASR	(Rectum, rectosigmoid junction, sigmoid colon, descending colon, colon excluding rectum)
78	Garcia 2018	USA	CRC	Incidence	2001–2014	ASR, ASIR	(Proximal/distal colon, rectum, CRC)[A1]
79	Fournel 2012	France	CRC	Incidence, stage distribution	1990–1999	Sex and Age standardized incidence rate, CR	CRC

80	Brenner 2017	Canada	CRC	Incidence	1971–2012	ASIR	(Colon, rectum)
81	Brenner 2019	Canada	CRC	Incidence	1971–2015	ASR, ASIR	(Colon, rectum)
82	Fedewa 2019	USA	CRC	Incidence, colonoscopy rate	2000–2015	Delay-adjusted incidence rate	CRC
83	Augustus 2018	USA	CRC	Incidence	2000–2014	ASR	(Proximal/distal colon, CRC)[B3]
84	Davis 2011	USA	CRC	Incidence, age and anatomical site distribution	1987–2006	ASIR	(Colon, CRC, cecum, appendix, ascending colon, hepatic flexure, transverse colon, splenic flexure, descending colon, sigmoid colon, rectosigmoid junction, rectum)
85	Domati 2014	Italy	CRC	Incidence, survival, clinical features	1986–2008	CR	CRC
86	Koblinski 2019	USA	CRC	Incidence, demographic and clinical features	2000–2010	Incidence rate	CRC
87	Purim 2013	USA	CRC	Incidence, survival, stage distribution	2002–2006	ASR, ASIR	(Rectum, colon)
88	Vuik 2019	Europe	CRC	Incidence, mortality	1990–2016	ASR, ASIR	(CRC, colon, rectum)

89	Shafqat 2015	USA	CRC	Incidence, survival, management	2000–2011	ASR	CRC
90	Safaee 2012	Iran	CRC	Incidence	2005–2009	ASR	(Colon, rectum, rectosigmoid junction, anus, anal canal, CRC)
91	Siegel 2017	USA	CRC	Incidence, mortality, survival, stage distribution, screening prevalence	2009–2013	ASR	(Proximal/distal colon, rectum, appendix/ unspecified subsite, CRC)[A]
92	Singh 2018	Canada	CRC	Incidence	1985–2012	Sex and Age standardized incidence rate	(CRC, proximal/distal colon)[B1]
93	Savijarvi 2019	Finland	CRC	Incidence	1976–2014	ASR	(Colon, proximal/distal colon, rectum, CRC)[B1]
94	Rahman 2015	USA	CRC	Incidence, survival	1992–2009	ASR	CRC
95	Nfonsam 2015	USA	CRC	Incidence, mortality, stage distribution	1995–2010	Incidence rate	CRC
96	Van Beck 2018	USA	CRC	Incidence, mortality	1976–2015	ASR	CRC
97	Sammour 2009	New Zealand	Colon	Incidence, mortality, survival, anatomical site and stage distribution	1996–2003	ASR	Colon
98	Mosli 2012	Saudi Arabia	CRC	Incidence, clinical features	2001–2006	Incidence (presented as percentage)	(Colon, rectum, CRC)

99	Mosli 2012	Saudi Arabia	CRC	Incidence, clinical features	2000–2006	Incidence (presented as percentage)	CRC
100	Russo 2019	Italy	CRC	Incidence	1999–2015	ASIR	(Colon, rectum, CRC)
101	Sheneman 2017	USA	CRC	Incidence, survival	1992–2013	ASR, ASIR	(Left/right colon, CRC)
102	Oliphant 2011	United Kingdom	CRC	Incidence	1999–2007	ASR	CRC
103	Perdue 2014	USA	CRC	Incidence, mortality	2005–2009	ASR	CRC
104	Murphy 2017	USA	CRC	Incidence	1975–2013	ASR	(CRC, proximal/distal colon, rectum)[A1]
105	Shah 2012	New Zealand	CRC	Incidence	1981–2004	ASR	(Right/left colon, rectum)[D]
106	Siegel 2020	USA	CRC	Incidence, mortality, screening prevalence, survival, stage distribution	2012–2016/1995–2016	ASR, Delay-adjusted incidence rate	(Colon, rectum, CRC, proximal/distal colon, appendix, large intestine (NOS), CRC including appendix)[A]
107	Murphy 2011	USA	CRC	Incidence	1992–2006	ASR	(Proximal/distal colon, rectum)[A]
108	Shin 2012	Korea	CRC	Incidence	1999–2009	ASR	(CRC, proximal/distal colon, rectum)[B1]
109	Patel 2016	Canada	CRC	Incidence, CRC risk factors	1969–2010	ASR	(CRC, colon, rectum and rectosigmoid)

110	Pakzad 2016	Iran	CRC	Incidence, spatial distribution	2009	ASR	CRC
111	Siegel; Fedewa 2017	USA	CRC	Incidence	1974–2013	ASR, ASIR, Delay-adjusted incidence rate,	(Colon, rectum, proximal/distal colon)[A1]
112	Pescatore 2013	Luxembourg	CRC	Incidence, survival, stage distribution	1990–2009	ASR, CR, ASIR	CRC
113	Murphy 2018	USA	CRC	Incidence	1975–2014	ASR, ASIR	(CRC, proximal/distal colon, rectum)[A1]
114	Siegel 2012	USA	CRC	Incidence	1992–2008	ASR	(Right/left colon)[D1]
115	Siegel 2019	USA	CRC	Incidence, CRC risk factors	1995–2015	ASR	(Colon, rectum, CRC)
116	Sung 2019	Hong Kong, Korea, Japan, and Taiwan	CRC	Incidence	1995–2014	ASR	(Colon, rectum)
117	Rafiemanesh 2016	Iran	CRC	Incidence, clinical features	2003–2008	ASR, CR	CRC
118	Sierra 2016	Central and South America	CRC	Incidence, mortality	2003–2007	ASR, CR	CRC
119	Oliveira 2016	Brazil	CRC	Incidence, mortality	1988–2008	ASR	(Colon, rectum)
120	Palmieri 2013	Italy	CRC	Incidence, mortality, survival, demographic and clinical features	1992–2010	ASR, CR, ASIR, Cumulative risk	CRC

121	Paquette 2015	USA	CRC	Incidence	2000–2011	ASR, ASIR	(Colon, rectum, CRC)
122	Reggiani-Bonetti 2013	Italy	CRC	Incidence, clinical features	1986–2008	ASR, CR	(Colon, rectum, CRC)
123	Nowicki 2018	Poland	CRC	Incidence, morbidity, survival	2006–2011	CR (refers to the frequency of new cases reported for the first time in a given year)	(Colon, rectosigmoid junction, rectum)
124	Phipps 2012	USA	CRC	Incidence, mortality	1975–2007	ASR	(Proximal/distal colon, CRC)[A2]
125	Oppelt 2019	Germany	CRC	Incidence	2008–2014	ASR	CRC
126	Murphy 2019	USA	CRC	Incidence, survival	1992–2014	ASR	(Proximal/distal colon, rectum, appendix/unspecifie) [A1]
127	Innos 2018	Estonia	CRC	Incidence, survival	1995–2014	ASR, ASIR	(Colon, rectum, right/left colon, colon other, anus and anal canal)[F]
128	Siegel 2014	USA	CRC	Incidence, survival, mortality, anatomical site and stage distribution	1975–2010	ASR, Delay-adjusted incidence rate	(Proximal/distal colon, rectum, colon other, CRC)[A]

129	Sia 2014	Australia	CRC	Incidence, anatomical site and histopathology distribution	2000–2010	Incidence rate (defined as number of CRC cases)	(Colon, rectum, CRC)
130	Rejali 2018	Iran	CRC	Incidence	2000–2011	ASR, Truncated ASR (at 25)	CRC
131	Sarakarn 2017	Thailand	CRC	Incidence	1989–2012	ASR	CRC
132	Keum 2014	USA	CRC	Incidence, mortality	1975–2009	ASR, ASIR	CRC
133	Singh 2014	USA	CRC	Incidence	1988–2009	ASIR	(CRC, proximal/distal colon, rectum)[A]
134	Sjostrom 2018	Sweden	CRC	Incidence, mortality, survival	2007–2013	ASR	(Colon, rectum)
135	Steinbrecher 2012	USA	CRC	Incidence, mortality	1998–2002	ASR	(CRC, right/left colon, rectum)[F]
136	Stern 2016	USA	CRC	Incidence, demographic and clinical features	1995–2011	ASR	CRC
137	Stock 2012	USA	CRC	Cumulative risk	1978–2007	Cumulative incidence rates, Cumulative risk	(CRC, colon, rectum, proximal/distal colon)[A3]
138	Stromberg 2019	Sweden	CRC	Incidence, mortality	2008–2016	Incidence rate from Poisson modelling	CRC

139	Sun 2020	Sweden	CRC	Incidence, survival	1960–2014	Age standardized-sex-specific incidence rate	(Right/left colon, rectum)[E]
140	Tawadros 2015	USA	Rectal	Incidence, clinical features	1980–2010	Incidence rate	Rectum
141	Thirunavukarasu 2010	USA	CRC	Incidence, survival, clinical and demographic features	1973–2006	Incidence rate	CRC
142	Thuraisingam 2017	USA	Colon	Incidence	2000–2012	Incidence rate	Colon
143	Troeung 2017	Australia	CRC	Incidence, mortality, colonoscopy history	1982–2007	ASR, ASIR	CRC
144	Ugarte 2012	Spain	CRC	Incidence	1990–2005	ASR, ASIR	CRC
145	Ullah 2018	Ireland	CRC	Incidence, stage distribution	1994–2012	ASR	CRC
146	Veruttipong 2012	Egypt	CRC	Incidence, clinical and demographic features	1999–2007	ASR, ASIR	(Colon, rectum, CRC)
147	Wan Ibrahim 2020	Malaysia	CRC	Incidence, mortality, survival, clinical and demographic features	2007–2017	ASR, CR	CRC
148	Wang 2017	USA	CRC	Incidence, survival, stage distribution	1995–2010	ASR	(CRC, right/left colon)[D1]
149	Wang; de Grubb 2017	USA	CRC	Incidence	1994–2013	ASR	(Proximal/distal colon, rectum, CRC)[A]

150	Wang 2019	USA	CRC	Incidence, factors associated with cancer-specific death	1988–2013	ASR	CRC
151	Wen 2018	China	CRC	Incidence	2012/2000–2015	ASR, ASIR, CR, Cumulative incidence rate	CRC
152	Wessler 2010	Norfolk, Suffolk, Cambridgeshire (NSC) (East of England)	CRC	Incidence	1971–2005	ASR, ASIR, CR	(CRC, proximal/distal colon, colon, rectum)[A]
153	Wu 2018	Shanghai	CRC	Incidence, mortality	1975–2013	ASR, CR	(CRC, colon, rectum)
154	Yee 2010	Hong Kong	CRC	Incidence	1983–2006	ASR, CR, Incidence rate	CRC
155	Yeo 2017	USA	CRC	Incidence, clinical and demographic features	2000–2011	ASR	(Cecum, ascending colon, hepatic flexure, transverse colon, splenic flexure, descending colon, sigmoid, rectosigmoid junction, rectum)
156	Yoon 2015	Korea	CRC	Incidence, mortality, fatality, screening rate	1999–2012	ASR, ASIR	CRC
157	Young 2015	Canada	CRC	Incidence	1998–2009	ASR	(Colon, rectum, CRC)
158	Zhabagin 2015	Kazakhstan	CRC	Incidence, mortality	2004–2013	Incidence rate	(Colon, rectum, CRC)

159	Zhang 2018	Hong Kong	CRC	Incidence	1983–2012	ASR	(Colon, rectum)
160	Zheng 2014	China	CRC	Incidence, mortality	2010	ASR, CR, ASIR, Cumulative risk, Truncated ASR (35-64)	CRC
161	Zhou 2015	China/Guangzhou	CRC	Incidence, age and anatomical site distribution	2000–2011	ASR, CR, ASIR	(CRC, ascending colon, transverse colon, descending colon, sigmoid colon, rectum)
162	Zhu 2013	USA	Colon	Incidence	1973–2008	Age standardized-sex-specific incidence rate, ASIR	(Cecum, appendix, ascending colon, hepatic flexure, transverse colon, splenic flexure, descending colon, sigmoid colon, overlapping lesion of colon, colon (NOS))
163	Zorzi 2019	Italy	CRC	Incidence, mortality	2003–2014	ASR	(Colon, rectum, CRC)
164	Zorzi 2015	Italy	CRC	Incidence	2000–2008	ASR	(CRC, colon (NOS), proximal/distal colon, rectum)[B2]
165	Ohri 2020	USA	CRC	Incidence	2000–2014	ASR	CRC

Abbreviations: CRC: Colorectal cancer, USA: United States of America, ASR: Age-standardized incidence rate, ASIR: Age-specific incidence rate, CR: Crude incidence rate, NOS: Not otherwise specified.

Definitions of proximal/distal, right/left tumors:

- A: Proximal colon: cecum, ascending colon, hepatic flexure, transverse colon, and splenic flexure. Distal colon: descending colon and sigmoid colon.
- A1: Same as (A) but splenic flexure is in the distal colon.
- A2: Same as (A) but rectosigmoid junction and rectum are in the distal colon.
- A3: Proximal colon: cecum, ascending colon, hepatic flexure, transverse colon. Distal colon: splenic flexure, descending colon, sigmoid colon, rectosigmoid junction, and rectum.
- B: Proximal colon: cecum, appendix, ascending colon, hepatic flexure, transverse colon. Distal colon: splenic flexure, descending colon, sigmoid colon.
- B1: Same as (B) but splenic flexure is in the proximal colon.
- B2: Same as (B) but overlapping lesion of the colon is in the distal colon.
- B3: Same as (B) but rectosigmoid junction and rectum are in the distal colon.
- B4: Proximal colon: cecum, appendix, ascending colon, hepatic flexure, transverse colon, splenic flexure, descending colon. Distal colon: sigmoid colon, rectosigmoid junction, and rectum.
- C: Right colon: cecum, ascending colon, hepatic flexure, transverse colon. Left colon: splenic flexure and descending colon.
- D: Right colon: cecum, ascending colon, hepatic flexure, transverse colon, and splenic flexure. Left colon: descending colon, sigmoid colon, rectosigmoid junction, and rectum.
- D1: Same as (D) but splenic flexure is in the left colon.
- E: Right colon: cecum, ascending colon, transverse colon, and splenic flexure. Left colon: descending colon and sigmoid colon.
- F: Right colon: cecum, appendix, ascending colon, hepatic flexure, and transverse colon. Left colon: splenic flexure, descending colon, and sigmoid colon.

Appendix A.8: Criteria for assessing the quality of reporting incidence (Form B)

First author and year	Definition of CRC	Quality assessment of registry data	Definition of numerator	Definition of denominator	Time interval for incidence calculation	Presentation of incidence rates with a time unit	Age-standardized rates(Method/ standard population)	Age bands	Assessment of uncertainty	Assessment of missing data	Software information
Abdifard 2016	ICD: site codes provided.	Not reported	CRC cases	C3/C4/C5	Not clear (mostly annual)	Whole years	(Direct /WHO world standard population)	Seven	Not reported	Not reported	STATA
Abdifard 2013	ICD-O-2: site codes provided.	Not reported	CRC cases	C4/C5	Not clear (mostly annual)	Whole years	(Direct /WHO world standard population)	Nine	Not reported	Not reported	STATA
Abreu 2010	ICD-O-3	Not reported	Rectal cancer cases	C4/C5	Not clear (mostly average)	No time unit	(Not reported/ European standard population)	Five	CI for incidence trends	Not reported	SPSS
Hassan 2016	Not reported	Not reported	CRC cases/B6	C5	Not clear (mostly average)	No time unit	(Direct/ New WHO world standard population)*	Thirteen	Not reported	Not reported	SPSS
Abualkhair 2020	ICD-O-3: site codes for primary CRC provided.	A1.1	CRC cases	Not reported	Average	No time unit	(Not reported/ 2000 US standard population)	Thirty	CI for incidence rate and trends	Not reported	SEER
Al Dahhan 2018	ICD-O-3	Not reported	CRC cases	C5	Not clear (mostly annual)	No time unit	Not applicable	Not reported	Not reported	Not reported	Not reported
Araghi 2018	CRC site codes provided.	Not reported	CRC cases	Not reported	Not clear (mostly annual + average)	No time unit	(Not reported/ 2000 US standard population)	Twelve	Not reported	Not reported	Not reported
Araghi 2019	ICD-10: site codes for primary CRC provided.	Not reported	CRC cases	Not reported	Not clear (mostly annual + average)	Person-time	(Not reported/ WHO world standard population)	Three	Not reported	Not reported	Not reported

Ashktorab 2016	ICD-O-3: site description without codes.	Not reported	CRC cases	Not reported	Annual+ Average	No time unit	(Not reported/ 2000 US standard population)	One	Not reported	Not reported	SEER
Austin 2014	ICD-O-3: site codes provided.	Not reported	CRC cases	Not reported	Annual	No time unit	(Not reported/ 2000 US standard million population)	Two	CI for incidence trends	Not reported	STATA
Aziz 2015	ICD-O-3: morphological codes provided. Conversion of codes not stated.	Not reported	CRC cases	Not reported	Not clear (mostly annual)	No time unit	Not applicable	Two/ Four	Not reported	Not reported	SAS
Bailey 2015	Not reported	Not reported	CRC cases	Not reported	Annual	Whole years	(Not reported/ 2000 US standard population)	Four	CI for incidence trends	Not reported	SEER
Baniasadi 2015	Not reported	Not reported	CRC cases	C3/C4	Not clear (mostly annual)	Whole years	(Not reported/ WHO world standard population)	Seven	Not reported	Not reported	Microsoft Excel
Bhurgri 2011	ICD-O-3: site codes provided.	A4/ A6	CRC cases/B6	C4/C5	Average	Whole years	(Direct/ 1960 Segi's world population)	Seven	Not reported	Not reported	SPSS
Boyce 2016	ICD-10, Australian modification (AM) and ICD-O-3: site codes provided.	Not reported	CRC cases	Not reported	Not clear (mostly annual)	No time unit	(Not reported/ NSW population at 2001)	Two	CI for incidence trends	Not reported	STATA, SAS
Winther 2016	ICD-10: site codes provided. Conversion of	Not reported	CRC cases	Not reported	Annual + Average	Person-time	Not applicable	Four	Not reported	Not reported	Not reported

	codes not stated.										
Brenner 2016	ICD-10: site codes provided.	Not reported	CRC cases	Not reported	Annual	No time unit	(Not reported/ European standard population)	Three	Not reported	Not reported	Not reported
Brouwer 2018	ICD-O: site codes for primary CRC provided.	Not reported	CRC cases/B1	Not reported	Annual	Person-time	(Not reported/ 1976 European standard population)	Not reported	CI for incidence trends	Not reported	STATA, SAS, SPSS
Caldarella 2013	ICD-O-3: site codes provided. Conversion of codes not stated.	Not reported	CRC cases	Not reported	Average+ Annual (not clear)	Person-time	(Not reported/ 2000 European standard population)	Fourteen	CI for incidence trends	Not reported	Not reported
Carroll 2019	ICD-10: site codes provided. Conversion of codes not stated	Not reported	CRC cases	C5	Not clear (mostly annual)	Not reported	Not applicable	Not reported	Not reported	Not reported	Not reported
Chambers 2020	ICD-9: site codes provided. ICD-10: site codes provided.	Not reported	CRC cases	C5	Not clear (mostly annual)	Person-time	(Direct/ 2013 European standard population)	Four	CI for incidence trends	Not reported	Not reported
Chatterjee 2015	Not reported	Not reported	CRC cases	C5	Annual + Average	Whole years	(Not reported/ 2000 US standard population)	Four	Not reported	Not reported	Not reported
Alsanea 2015	Not reported	Not reported	CRC cases	Not reported	Not clear (mostly annual)	No time unit	(Not reported/ Segi's world population - modified by Doll)	Eight	Not reported	Not reported	Not reported

Chauvenet 2011	ICD-O-3: site codes provided. Conversion of codes not stated.	A5	CRC cases	C5	Not clear (mostly average)	No time unit	(Direct/ WHO world standard population)*	Not reported	CI for incidence trends	Not reported	STATA
Chen 2012	ICD-9- Clinical Modification (CM): site codes for primary and secondary CRC provided.	Not reported	CRC cases/B1	C5	Average	No time unit	Not applicable	Twenty/ Four	Not reported	Not reported	SPSS
Cheng 2011	ICD-O-3: site codes for primary, in situ and invasive CRC provided. Conversion of codes not stated.	Not reported	CRC cases	Not reported	Not clear (mostly average)	Person-time	(Not reported/ 2000 US standard population)	Five	CI for incidence rate	Not reported	SEER
Chernyavskiy 2019	Not reported	Not reported	CRC cases	Not reported	Average	Person-time	Not applicable	Two	CI for incidence rate and trends	Not reported	R
Chittleboroug-h 2020	CRC sites are described without codes.	Not reported	CRC cases	Not reported	Annual + Average (not clear)	Whole years	(Not reported/ European standard population)*	Three	CI for incidence rate and trends	Not reported	R
Chong 2015	Not reported	Not reported	CRC cases/B6	C4/C5	Not clear (mostly average)	No time unit	(Not reported/ WHO world standard population)	Fifteen	Not reported	Not reported	SPSS
Clarke 2014	ICD-10: site codes for primary, invasive CRC provided.	A1.1	CRC cases	Not reported	Not clear (mostly annual)	No time unit	(Direct/ European standard population)	Not reported	CI for incidence trends	Not reported	Not reported

Crocetti 2010	Invasive CRC.	Not reported	CRC cases	Not reported	Not clear (mostly annual)	No time unit	(Not reported/ European standard population)	Two	CI for incidence trends	Not reported	Not reported
Crosbie 2018	ICD-O-3: site codes for primary CRC provided. Excluded specific morphological codes. Conversion of codes not stated.	Not reported	CRC cases	Not reported	Annual (reported as annual rates in methods, but average rates were presented in results)	No time unit	(Not reported/ 2000 US standard population)	Three	CI for incidence rate and trends	D1/D5	SEER
Danos 2018	ICD-O-3: site codes for invasive primary CRC provided. Excluded specific morphological codes.	Not reported	CRC cases/B2/B3	C1.2/C4/C5	Average	No time unit	Not applicable	Four	Not reported	Not reported	SAS
Dehghani 2019	ICD-O-2: site codes provided.	Not reported	CRC cases	C3/C4	Not clear (mostly annual)	Person-time	Not applicable	Seven	Not reported	Not reported	Not reported
Edwards 2010	ICD-O-3: site codes for first primary CRC provided. Conversion of codes not stated.	A6	CRC cases/B5	C5	Annual + Average	No time unit	(Not reported/ 2000 US standard population)	Three	Not reported	Not reported	SEER
Ellis 2018	Site codes provided for invasive and in situ CRC.	Not reported	CRC cases	C3/C4	Annual + Average	No time unit	(Not reported/ 2000 US standard population)	Three	CI for incidence rate and trends	Not reported	SEER

Enayatrad 2018	ICD-O-2: site codes provided.	Not reported	CRC cases	Not reported	2009	No time unit	(Direct/ WHO world standard population)	Not reported	Not reported	Not reported	SPSS
Eser 2018	ICD-O-3: site codes for invasive CRC provided.	Not reported	CRC cases	Not reported	Not clear (mostly annual + average)	No time unit	(Direct/New WHO world standard population)	Not reported	CI for incidence rate	Not reported	SAS
Exarchakou 2019	ICD-8/9/10: site codes for first primary, invasive CRC provided.	A1.1	CRC cases	Not reported	Annual	No time unit	(Not reported/ European standard population)	Eight	CI for incidence trends	Not reported	Not reported
Feletto 2019	CRC site codes provided.	Not reported	CRC cases	C5	Annual	No time unit	Not applicable	Eleven	CI for incidence trends	Not reported	Not reported
Hasanpour-Heidari 2019	ICD-O-3. Primary CRC.	A2	CRC cases	C5	Not clear (mostly annual + average)	Person-time	(Direct/ 1960 Segi's world population)	Not reported	CI for incidence trends	Not reported	CanReg-5
Lemmens 2010	Site codes for primary CRC provided.	A1.1	CRC cases/B2	Not reported	Average	Person-time	(Not reported/ European standard population)	Not reported	Not reported	Not reported	Not reported
May 2017	ICD-O-3. Conversion of codes not stated.	Not reported	CRC cases/B6	Not reported	Not clear (mostly annual + average)	No time unit	(Not reported/ 2000 US standard population)	Not reported	Not reported	Not reported	SEER
Fusco 2010	ICD-O-3: invasive CRC.	Not reported	CRC cases/B1/B3	Not reported	Not clear (mostly average)	Whole years	(Not reported/ World, European and Italian standard populations)	Eight	Not reported	Not reported	STATA
Klugarova 2019	ICD-10-Clinical Modification (CM). Conversion of	Not reported	CRC cases	Not reported	Not clear (mostly	No time unit	Not applicable	Eighteen	Not reported	Not reported	Not reported

	codes not stated.				annual + average)						
Koblinski 2018	CRC sites are described without codes.	Not reported	CRC cases	C5	Not clear (mostly annual)	No time unit	Not applicable	Two	Not reported	Not reported	SPSS
Martinsen 2016	ICD-O-3: site codes for invasive CRC provided. Excluded specific morphological codes.	Not reported	CRC cases/B3/B6	Not reported	Not clear (mostly annual)	No time unit	(Not reported/ 2000 US standard population)	Four	Not reported	Not reported	SEER
Giddings 2012	ICD-O-3: site codes provided. Excluded specific morphological codes. Conversion of codes not stated.	A6	CRC cases	C3/C4/C5	Average + Annual (not clear)	No time unit	(Not reported/ 2000 US standard population)	Two	CI for incidence trends	Not reported	SEER
Missaoui 2011	ICD-10: site codes provided.	Not reported	CRC cases	C5	Not clear (mostly annual + average)	Person-time	(Direct/ New WHO world standard population)	Fourteen	CI for incidence trends	Not reported	Not reported
Kelly 2012	ICD-O-2 &3: site codes provided.	Not reported	CRC cases	C5	Average	No time unit	(Direct/ 2000 US standard population)	Seven	Not reported	Not reported	Not reported
Loomans-Kropp 2019	ICD-O-3: site codes provided. Conversion of codes not stated.	Not reported	CRC cases	Not reported	Not clear (mostly annual)	No time unit	(Not reported/ 2000 US standard population)	Nine	CI for incidence trends	Not reported	SEER

Gandhi 2017	CRC sites are described without codes.	Not reported	CRC cases	Not reported	Not clear (mostly annual)	No time unit	(Not reported/ 1976 European standard population)	Three	CI for incidence rate and trends	Not reported	Not reported
Lopez 2019	ICD-O-3: site codes for invasive CRC provided. Conversion of codes not stated.	A5	CRC cases/B1/B4	C5	Not clear (mostly average)	No time unit	(Direct/ WHO world standard population)	Three	Not reported	Not reported	Not reported
Lopez-Abente 2010	ICD-9: site codes provided. ICD-10: site codes provided.	Not reported	CRC cases	C5	Not clear (mostly average)	No time unit	(Direct/ European standard population)	Not reported	CI for incidence trends	Not reported	Not reported
McClements 2012	ICD-10: site codes provided. Conversion of codes not stated.	Not reported	CRC cases	C5	Not clear (mostly annual)	No time unit	Not applicable	One	Not reported	Not reported	SPSS, STATA
Gan 2019	ICD-9 & 10. First primary, invasive CRC.	A5	CRC cases/B5	Not reported	Not clear	Not reported	Not applicable	Four	Not reported	Not reported	SAS
Ladabaum 2014	ICD-O-3: site codes for primary invasive CRC provided. Excluded specific morphological codes.	Not reported	CRC cases	C3/C4/C5	Not clear (mostly annual + average)	No time unit	(Not reported/ 2000 US standard population)	Not reported	CI for incidence rate and trends	Not reported	SEER
Fowler 2018	ICD-O-3	Not reported	CRC cases	C5	Annual + Average (not clear)	Person-time	(Not reported/ 2000 US	Not reported	CI for incidence rate	Not reported	SAS

							standard population)				
Meester 2019	Not reported	Not reported	CRC cases	Not reported	Not clear (mostly annual)	No time unit	(Not reported/ 2000 US standard population)	One	CI for incidence trends	Not reported	Joinpoint
Li 2017	ICD-10: CRC sites are described without codes.	A6	CRC cases	Not reported	Annual	Person-time	(Not reported/ 1960 Segi's world population)	Four	CI for incidence trends	Not reported	Not reported
Liu 2015	ICD-10: site codes for invasive CRC provided.	A2	CRC cases	C3/C4/C5	2011	No time unit	(Not reported/2000 Chinese population and 1960 Segi's world population)	Eighteen	Not reported	Not reported	SAS
Jayarajah 2020	ICD-10: site codes provided.	Not reported	CRC cases	Not reported	Annual	No time unit	(Not reported/ New WHO world standard population) *	Ten	CI for incidence rate and trends	Not reported	Not reported
Katsidzira 2016	ICD-O-3: site and morphological codes provided.	A4	CRC cases	C3/C4/C5	Annual	No time unit	(Not reported/ Not reported)	Thirteen	CI for incidence trends	Not reported	STATA, CanReg- 4
Fournel 2016	First primary, invasive CRC.	A5	CRC cases/B4/B7	Not reported	Not clear (mostly average)	No time unit	(Direct/ New WHO world standard population)	Not reported	CI for incidence rate	Not reported	Not reported
Lee 2019	ICD-10: site codes provided. Conversion of codes not stated.	Not reported	CRC cases	Not reported	Not clear (mostly average)	Person-time	Not applicable	Eleven	CI for incidence trends	Not reported	SAS, WinBUGS

Khiari 2017	ICD-O-1 & 3: site codes provided.	A4	CRC cases	C5	Not clear (mostly average)	No time unit	(Direct/ Not reported)	Nine	Not reported	Not reported	SPSS
Shadmani 2017	ICD-O	Not reported	CRC cases	Not reported	2008	Person-time	(Not reported/ Segi's world population - modified by Doll)	Eighteen	Not reported	Not reported	Microsoft Excel
Merrill 2011	ICD-O-2: site codes for primary and secondary malignant CRC provided.	Not reported	CRC cases	C5	Not clear (mostly average)	No time unit	(Not reported/ 2000 US standard population)	Six	Not reported	Not reported	SEER, DevCan
Klimczak 2011	Not reported	Not reported	CRC cases	Not reported	Not clear (mostly annual)	No time unit	(Not reported/ WHO world standard population)	Not reported	Not reported	Not reported	Not reported
Khiari; Ben Ayoube 2017	ICD-O-1: site codes provided. ICD-O-3: site codes provided.	A4	CRC cases	C5	Not clear (mostly annual)	No time unit	(Not reported/ WHO world standard population)	Not reported	CI for incidence rate and trends	Not reported	R
Jandova 2016	ICD-O-3: Morphological codes provided.	Not reported	CRC cases	Not reported	Not clear (mostly annual)	No time unit	Not applicable	Not reported	Not reported	D1/D5	SPSS
Li; Lin 2017	ICD-10: site codes provided.	Not reported	CRC cases	C4/C5	Not clear (mostly annual)	No time unit	(Not reported/ 1964 Segi's world population)	Not reported	CI for incidence trends	Not reported	Microsoft Excel
Meza 2010	ICD-O-3: site codes provided. Conversion of codes not stated.	Not reported	CRC cases	C5	Not clear (mostly annual)	No time unit	(Not reported/ 2000 US standard population)	Eighteen	Not reported	Not reported	Not reported

Jafri 2013	ICD-O: site and morphological codes provided.	A1.2	CRC cases	Not reported	Annual (reported as annual, but average rates were presented)	Person-time	(Not reported/ 2000 US standard population)	Six	CI for incidence rate	Not reported	SAS
McDevitt 2017	ICD-O-3: site codes for primary, invasive CRC provided.	A1.1	CRC cases	Not reported	Not clear (mostly average)	No time unit	(Not reported/ 1976 European standard population)	Not reported	CI for incidence trends	D2/D5/D6	Not reported
Khachfe 2019	ICD-O-3. Primary CRC.	Not reported	CRC cases	Not reported	Annual + Average	No time unit	(Not reported/ Ferlay's modified world population)	Sixteen	CI for incidence trends	Not reported	Not reported
Meyer 2010	CRC sites are described without codes.	Not reported	CRC cases	Not reported	Not clear (mostly annual + average)	No time unit	(Not reported/ 2000 US standard population)	One	CI for incidence rate and trends	Not reported	SEER
Garcia 2018	ICD-O-3: CRC sites are described without codes.	Not reported	CRC cases	Not reported	Not clear (mostly annual + average)	No time unit	(Not reported/ 2000 US standard population)	Six	CI for incidence rate	D1/D5	SEER
Fournel 2012	ICD-O-2: morphological codes for first primary, invasive CRC provided.	A5	CRC cases/B4	C3/C4	Not clear (mostly average)	Person-time	(Direct / New WHO world standard population)	Not reported	CI for incidence rate	Not reported	STATA
Brenner 2017	ICD-O-3: site codes provided. Conversion of codes not stated.	Not reported	CRC cases	Not reported	Not clear (mostly annual)	No time unit	Not applicable	Eleven	Not reported	Not reported	Joinpoint, Age-Period-Cohort web tool (NCI)

Brenner 2019	ICD-10: site codes provided. Conversion of codes not stated.	Not reported	CRC cases	Not reported	Not clear (mostly annual)	No time unit	(Not reported/Not reported)	Two	Not reported	Not reported	Joinpoint, Age-Period-Cohort web tool (NCI)
Fedewa 2019	Not reported	Not reported	CRC cases	Not reported	Annual	No time unit	Not applicable	Three	CI for incidence rate and trends	Not reported	SEER
Augustus 2018	ICD-O-3	Not reported	CRC cases	Not reported	Not clear (mostly annual)	No time unit	(Not reported/ 2000 US standard population)	Three	Not reported	Not reported	SEER
Davis 2011	Not reported	Not reported	CRC cases	C5	Annual	No time unit	Not applicable	Eighteen	Not reported	Not reported	SEER
Domati 2014	ICD-10. Conversion of codes not stated.	Not reported	CRC cases	C4	Not clear (mostly annual)	Person-time	Not applicable	One	CI for incidence trends	Not reported	Joinpoint
Koblinski 2019	CRC sites are described without codes.	Not reported	CRC cases	C5	Not clear (mostly annual)	No time unit	Not applicable	Two	Not reported	Not reported	SEER
Purim 2013	Malignant CRC.	Not reported	CRC cases/B6	Not reported	Not clear (mostly average)	No time unit	(Not reported/ 2000 US standard population)	Eight	Not reported	Not reported	Not reported
Vuik 2019	ICD-O-3: site codes provided.	A2	CRC cases	Not reported	Average + Annual (not clear)	No time unit	(Not reported/ Population numbers for each country (not clear))	Three	Not reported	Not reported	Not reported
Shafqat 2015	ICD-O-3: morphological codes for	A4	CRC cases/B2/B3/B5/B6	Not reported	Not clear (mostly annual + average)	Person-time	(Not reported/ 2000 US standard population)	Not reported	CI for incidence rate and trends	Not reported	STATA

	invasive CRC provided.										
Safaee 2012	ICD-O-3: site codes provided.	Not reported	CRC cases	C4/C5	Not clear (mostly average)	No time unit	(Direct/ WHO world standard population)	Four	CI for incidence rate	D1/D5	SPSS, OpenEpi
Siegel 2017	ICD-O-3: site codes provided.	Not reported	CRC cases	Not reported	Average	No time unit	(Not reported/ 2000 US standard population)	Three	Not reported	Not reported	SEER
Singh 2018	ICD-9- Clinical Modification (CM): site codes provided. ICD-10-CA: site codes provided.	A5	CRC cases	C5	Annual + Average (not clear)	No time unit	(Not reported/ 2001 Canadian population)	Eight	Not reported	Not reported	Not reported
Savijarvi 2019	CRC site codes provided.	Not reported	CRC cases	C5	Average	No time unit	(Not reported/ WHO world standard population)	One	CI for incidence trends	D1/D5	Not reported
Rahman 2015	Not reported	Not reported	CRC cases	C5	Not clear (mostly annual + average)	No time unit	(Not reported/ 2000 US standard population)	Two	Not reported	D3	SEER
Nfonsam 2015	ICD-O-3: morphological codes provided. Conversion of codes not stated.	A6	CRC cases	C5	Not clear (mostly annual)	No time unit	Not applicable	Not reported	Not reported	Not reported	SAS
Van Beck 2018	Not reported	Not reported	CRC cases	Not reported	Not clear (mostly annual)	No time unit	(Not reported/ 2000 US standard population)	Two	CI for incidence trends	Not reported	Joinpoint

Sammour 2009	Not reported	Not reported	Colon cancer cases	C1.3/C4	Not clear (mostly average)	Whole years	(Direct/ New WHO world standard population)	Not reported	Not reported	Not reported	SPSS
Mosli 2012	Not reported	Not reported	CRC cases	Not reported	Not clear (mostly annual + average)	No time unit	Not applicable	Eighteen	Not reported	Not reported	Microsoft Excel
Mosli 2012	Not reported	Not reported	CRC cases	Not reported	Annual	No time unit	Not applicable	Two	Not reported	Not reported	Microsoft Excel
Russo 2019	ICD-O-3: site codes provided. Excluded specific morphological codes.	Not reported	CRC cases	Not reported	Not clear (mostly annual)	No time unit	Not applicable	Seven	CI for incidence trends	Not reported	Not reported
Sheneman 2017	ICD-O-3: site codes provided.	A5	CRC cases	Not reported	Average + Annual (not reported)	Person-time	(Direct/ 2000 US standard population)	Two	Not reported	Not reported	Microsoft Excel
Oliphant 2011	ICD-10: site codes provided.	Not reported	CRC cases	C5	Average + Annual (not reported)	No time unit	(Direct/ 1976 European Standard Population)	Not reported	CI for incidence rate	Not reported	STATA
Perdue 2014	ICD-O-3	Not reported	CRC cases	C5	Not clear (mostly average)	No time unit	(Direct/ 2000 US standard population)	Three	Not reported	Not reported	SEER
Murphy 2017	ICD-O-3: CRC sites are described without codes. Conversion of codes not stated.	Not reported	CRC cases	Not reported	Not clear (mostly average)	No time unit	(Not reported/ 2000 US standard population)	Nine	Not reported	Not reported	SEER

Shah 2012	ICD-10: site codes provided. Conversion of codes not stated.	Not reported	CRC cases	C1.1/C4	Not clear (mostly average)	Person-time	(Direct/ New WHO world standard population)	Two	CI for incidence rate and trends	Not reported	SAS
Siegel 2020	ICD-O-3: site codes provided.	Not reported	CRC cases	C4/C5	Average + Annual (not reported)	No time unit	(Not reported/ 2000 US standard population)	Three	Not reported	Not reported	SEER
Murphy 2011	ICD-O-3: site codes provided.	Not reported	CRC cases	Not reported	Not clear (mostly average)	Person-time	(Not reported/ 2000 US standard population)	Nine	Not reported	Not reported	STATA
Shin 2012	ICD-10: site codes provided.	Not reported	CRC cases	Not reported	Not clear (mostly annual)	No time unit	(Not reported/ 2000 Korean population)	Six	CI for incidence trends	Not reported	STATA
Patel 2016	ICD-O-3: site codes provided. Conversion of codes not stated.	Not reported	CRC cases	Not reported	Not clear (mostly annual)	No time unit	(Not reported/ 1991 Canadian population)	Three	CI for incidence trends	Not reported	Not reported
Pakzad 2016	ICD-O	Not reported	CRC cases	Not reported	2009	No time unit	(Direct/ WHO world standard population)	Not reported	Not reported	Not reported	Microsoft Excel
Siegel; Fedewa 2017	ICD-O-3: site codes provided. Conversion of codes not stated.	Not reported	CRC cases	Not reported	Not clear (mostly annual)	Person-time	(Not reported/ 2000 US standard population)	Eleven	CI for incidence trends	Not reported	SEER
Pescatore 2013	Nor clear	Not reported	CRC cases	Not reported	Annual	No time unit	(Direct/ WHO world standard population)	Sevent-een	Not reported	Not reported	Not reported

Murphy 2018	CRC sites are described without codes.	Not reported	CRC cases	Not reported	Average	No time unit	(Not reported/ 2000 US standard population)	Six	Not reported	Not reported	SEER
Siegel 2012	ICD-O-3: site codes provided.	Not reported	CRC cases	Not reported	Not clear (mostly annual)	No time unit	(Not reported/ 2000 US standard population)	One	CI for incidence trends	Not reported	SEER
Siegel 2019	ICD-O-3: site codes provided.	Not reported	CRC cases	Not reported	Not clear (mostly average)	Person-time	(Not reported/ 2000 US standard population)	One	CI for incidence rate and trends	Not reported	SEER
Sung 2019	Colon and rectal cancers were classified according to medical records.	Not reported	CRC cases	Not reported	Not clear (mostly annual)	No time unit	(Not reported/ New WHO world standard population)	One	CI for incidence trends	Not reported	Not reported
Rafiemanesh 2016	ICD-O-3: site and morphological codes provided.	Not reported	CRC cases	Not reported	Not clear (mostly annual)	No time unit	(Direct/ WHO world standard population)	Not reported	CI for incidence trends	Not reported	Not reported
Sierra 2016	ICD-10: site codes provided.	A3	CRC cases	Not reported	Not clear (mostly average)	Person-time	(Direct/1960 Segi's world population)	Not reported	Not reported	Not reported	STATA
Oliveira 2016	ICD-10: site codes provided. Conversion of codes not stated.	Not reported	CRC cases	C5	Not clear (mostly annual)	No time unit	(Not reported/ 1960 Segi's world population)	Not reported	Not reported	Not reported	R
Palmieri 2013	Not reported	Not reported	CRC cases	Not reported	Not clear (mostly average)	Whole years	(Not reported/ European standard population)	Sevent-een	Not reported	Not reported	Not reported

Paquette 2015	CRC sites are described without codes.	Not reported	CRC cases	Not reported	Not clear (mostly average)	No time unit	(Not reported/ 2000 US standard population)	Thirty-three	Not reported	Not reported	SEER
Reggiani-Bonetti 2013	ICD-O	Not reported	CRC cases	C4	Not clear (mostly average)	Whole years	(Not reported/ Italy, Europe, World standard population)	Not reported	CI for incidence trends	Not reported	Joinpoint
Nowicki 2018	ICD-10: site codes for malignant CRC provided.	Not reported	CRC cases	Not reported	Not clear (mostly annual)	No time unit	Not applicable	Not reported	Not reported	Not reported	Statistica, Microsoft Excel
Phipps 2012	ICD-O-3: site codes for invasive CRC provided. Conversion of codes not stated.	Not reported	CRC cases/B3	Not reported	Annual	No time unit	(Not reported/ 2000 US standard population)	Three	CI for incidence trends	Not reported	Not reported
Oppelt 2019	ICD-10 German modification (GM).	A6	CRC cases	Not reported	Annual	No time unit	(Not reported/ 1976 European standard population)	Not reported	Not reported	Not reported	SAS
Murphy 2019	CRC sites are described without codes.	A1.1	CRC cases	Not reported	Not clear (mostly average)	No time unit	(Not reported/ 2000 US standard population)	One	Not reported	Not reported	SEER
Innos 2018	ICD-10: site codes provided.	A2	CRC cases	Not reported	Not clear (mostly annual)	No time unit	(Not reported/ WHO world standard population)	Four	CI for incidence trends	Not reported	Not reported
Siegel 2014	ICD-O-3: site codes provided. Conversion of	Not reported	CRC cases	Not reported	Not clear (mostly average)	No time unit	(Not reported/ 2000 US standard population)	Three	Not reported	Not reported	SEER

	codes not stated.										
Sia 2014	ICD: site codes provided.	Not reported	CRC cases	C5	Not clear (mostly annual)	No time unit	Not applicable	Two	CI for incidence trends	Not reported	Not reported
Rejali 2018	ICD-O-3: site codes for first primary CRC provided.	Not reported	CRC cases	C5	Annual	No time unit	(Direct/ 2000 US standard population)	Not reported	CI for incidence rate and trends	D4/D5/D6	STATA
Sarakarn 2017	ICD-O: site codes provided.	Not reported	CRC cases	Not reported	Annual	No time unit	(Direct/ Segi's world population - modified by Doll)	Four	Not reported	Not reported	Not reported
Keum 2014	Invasive cancers.	Not reported	CRC cases	Not reported	Not clear (mostly annual)	No time unit	(Not reported/ 2000 US standard population)	Three	Not reported	Not reported	SEER
Singh 2014	ICD-O-3: morphological codes for malignant CRC provided. Conversion of codes not stated.	A7	CRC cases	C5	Average + Annual	No time unit	Not applicable	Seven	CI for incidence rate	Not reported	SAS
Sjostrom 2018	ICD	Not reported	CRC cases	C5	Not clear (mostly average)	Person-time	(Not reported/ 2000 Swedish population)	Four	Not reported	Not reported	R
Steinbrecher 2012	ICD-O-2: site codes for first primary, invasive CRC provided.	Not reported	CRC cases	C1.2/C4/C5	Not clear (mostly average)	No time unit	(Not reported/ 2000 US standard population)	One	CI for incidence rate	Not reported	SEER

Stern 2016	ICD-O-3	Not reported	CRC cases	C1.2/C4/C5	Not clear (mostly average)	No time unit	(Not reported/ 2000 US standard population)	Not reported	CI for incidence rate	Not reported	Not reported
Stock 2012	ICD-O-3: site codes provided. Conversion of codes not stated.	Not reported	CRC cases	Not reported	Not clear (mostly average)	Not applicable	Not applicable	Five	CI for incidence rate	Not reported	Not reported
Stromberg 2019	First primary CRC.	Not reported	CRC cases	C5	Average	Whole years	Not applicable	Twelve	Not reported	Not reported	Rapid Inquiry Facility, R, SPSS
Sun 2020	ICD-7: site codes for first primary CRC provided.	Not reported	CRC cases	Not reported	Not clear (mostly average)	Person-time	(Direct/ 2000 Swedish population)	Two	CI for incidence trends	Not reported	SAS
Tawadros 2015	ICD-9: site codes provided.	Not reported	Rectal cancer cases	Not reported	Not clear (mostly annual)	No time unit	Not applicable	Two	Not reported	Not reported	SEER
Thirunavu-karasu 2010	ICD-O-3: morphological code for malignant CRC provided. Conversion of codes not stated.	Not reported	CRC cases	Not reported	Average + Annual (not clear)	No time unit	Not applicable	Five	CI for incidence rate	Not reported	SPSS
Thuraisingam 2017	Not reported	Not reported	Colon cancer cases	Not reported	Not clear (mostly annual)	No time unit	Not applicable	Not reported	Not reported	Not reported	SPSS
Troeung 2017	ICD-9-Clinical Modifications (CM): site codes for first primary CRC provided. ICD-	Not reported	CRC cases	C5	Average	No time unit	(Direct/ 2001 Australian population)	Five	CI for incidence trends	Not reported	Not reported

	10- Australian Modification (AM): site codes for first primary CRC provided.										
Ugarte 2012	ICD-10: site codes provided. Conversion of codes not stated.	Not reported	CRC cases	C5	Not clear (mostly annual + average)	No time unit	(Not reported/ European standard population)	Three	Not reported	Not reported	R
Ullah 2018	Not reported	A1.1	CRC cases/B6	C5	Not clear (mostly annual)	No time unit	(Not reported/ 1976 European standard population)	Seven	Not reported	Not reported	Not reported
Veruttipong 2012	Not reported	A5	CRC cases	C5	Not clear (mostly average)	No time unit	(Not reported/ Not reported)	Nineteen	CI for incidence rate	Not reported	SAS
Wan Ibrahim 2020	Not reported	Not reported	CRC cases	C5	Not clear (mostly annual + average)	No time unit	(Not reported/ New WHO world standard population)	Two	Not reported	Not reported	R
Wang 2017	ICD-O-3: site and morphological codes for primary, invasive CRC provided.	A6	CRC cases	Not reported	Not clear (mostly annual + average)	No time unit	(Direct/ 2000 US standard population)	Four	CI for incidence trends	Not reported	SEER
Wang; de-Grubb 2017	ICD-O-3: site codes provided	Not reported	CRC cases	Not reported	Annual + Average (not clear)	Person-time/ Whole years	(Not reported/ 2000 US Standard population)	Five	CI for incidence rate and trends	Not reported	SEER, SPSS
Wang 2019	ICD-O-3: site codes for primary CRC provided.	Not reported	CRC cases	Not reported	Annual	No time unit	(Not reported/ 2000 US	One	Not reported	Not reported	SAS

	Conversion of codes not stated.						standard population)				
Wen 2018	ICD-10: site codes provided.	A5	CRC cases	C5	Annual	No time unit	(Not reported/ Segi's world population - modified by Doll)	Eighteen	Not reported	Not reported	Not reported
Wessler 2010	ICD-10: site codes provided. Conversion of codes not stated.	A1.1/ A3	CRC cases	C5	Not clear (mostly average)	Person-time	(Direct/ European standard population)	Twelve	CI for incidence trends	Not reported	STATA
Wu 2018	ICD-10: site codes provided. Conversion of codes stated.	Not reported	CRC cases	C2/C3/C5	Not clear (mostly average)	No time unit	(Direct/ 1960 Segi's world population)	Eleven	CI for incidence trends	Not reported	Not reported
Yee 2010	ICD-10: site codes provided. Conversion of codes not stated.	A4	CRC cases	C5	Average + Annual (not clear)	No time unit	(Not reported/ WHO world standard population)	Six	Not reported	Not reported	Not reported
Yeo 2017	First primary CRC.	Not reported	CRC cases	Not reported	Not clear (mostly annual)	No time unit	(Not reported/ 2000 US standard population)	Two	Not reported	Not reported	SEER, STATA
Yoon 2015	ICD-10: site codes provided.	Not reported	CRC cases	C5	Not clear (mostly annual)	No time unit	(Not reported/ 1960 Segi's world population)*	Fourteen	Not reported	Not reported	Not reported
Young 2015	ICD-O-3: site codes for primary,	Not reported	CRC cases	C4/C5	Not clear (mostly average)	No time unit	(Direct/ 1991 Canadian population)	Three	CI for incidence rate	Not reported	SEER

	invasive CRC provided.										
Zhabagin 2015	First primary CRC.	Not reported	CRC cases	C5	Average + Annual (not clear)	No time unit	Not applicable	Six	Not reported	Not reported	Not reported
Zhang 2018	Not reported	Not reported	CRC cases	C5	Annual + Average	Person-time	(Direct/ Segi's world population - modified by Doll)	Three	CI for incidence trends	Not reported	Not reported
Zheng 2014	ICD-10: site codes provided.	A2	CRC cases	C5	2010	No time unit	(Not reported/ 2000 Chinese standard population and 1960 Segi's world population)	Fourteen	Not reported	Not reported	Microsoft FoxPro, Microsoft Excel, SAS
Zhou 2015	ICD-10: site codes provided.	Not reported	CRC cases	C5	Annual	No time unit	(Not reported/ 1960 Segi's world population)	Three	Not reported	Not reported	SAS
Zhu 2013	ICD-O-3: site codes for primary, in situ and invasive colon cancer provided. Conversion of codes not stated.	Not reported	colon cancer cases	Not reported	Not clear (mostly average)	No time unit	(Not reported/ 2000 US standard population)	Nine	Not reported	Not reported	SEER
Zorzi 2019	ICD-10: site codes provided.	A1.2/A3	CRC cases	Not reported	Not clear (mostly annual)	No time unit	(Not reported/ 2013 European standard population)	Three	CI for incidence trends	D2/D5	Not reported
Zorzi 2015	ICD-10: site codes for primary and	Not reported	CRC cases/B1/B5	Not reported	Annual	No time unit	(Not reported/ 2001 European population)	Six	CI for incidence trends	Not reported	Not reported

	secondary CRC provided.										
Ohri 2020	Not reported	Not reported	CRC cases	Not reported	Annual + Average (not clear)	Whole years	(Not reported/ 2000 US standard population)	Ten	CI for incidence rate	Not reported	SEER

*Study justified the chosen standard population

Abbreviations: ICD: International classification of disease, ICD-0: International classification of disease for oncology, CRC: Colorectal cancer, CI: Confidence interval, NCI: National cancer institute.

Quality assessment of registry data. A1: Study cited a reference for previously conducted research as evidence of cancer registry data quality: A1.1: Study referenced other studies or reports including validation or completeness assessments, A1.2: Study referenced similar epidemiological studies conducted in the same data source; A2: Study assessed and reported certain validity indicators; A3: Study reported specific validity indicators from external resources; A4: Study reported that a cancer registration program checked data quality; A5: Study indicated that the registration quality is being audited and certified regularly by a certification body; A6: Study indicated that cancer registry is meeting or utilizing standards for data quality set by national or international agencies; A7: Study indicated complete case ascertainment of cancer data without providing a reference.

Definition of the numerator. B1: Information provided about considerations for synchronous and metachronous CRC cases in incidence calculation; B2: Exclude cases with an unknown site of the primary tumour or disease stage or survival time; B3: Excluded In situ cancers; B4: Exclude cases with family history, hereditary syndromes, and IBD; B5: Exclude cases identified by only death certificate; B6: Exclude non-microscopically confirmed cases; B7: Exclude cases with incomplete address information.

Definition of the denominator. C1: Explicit explanation of population size estimation: C1.1: The study calculated person-time at risk by creating closed cohorts of the population on various census nights and following them over time, C1.2: Population size was estimated by multiplying the population count in a particular census year by the number of years included in the study, C1.3: The denominator size was calculated by averaging population counts of two censuses conducted at the beginning and near the end of the study period. C2: The annual mid-year population is estimated by averaging the populations at the end of the adjacent years. C3: Yearly population counts are interpolated and extrapolated. C4: Reporting of census years that were used for population size estimation. C5: Data source of the general population is reported.

Assessment of missing data. D1: Study excluded cases with missing values from incidence calculation; D2: Study estimated missing data; D3: Study assumed missing data to be missing at random; D4: Study corrected rates for missing data; D5: Study reported type of missing data; D6: Study indicated the amount of missing data

Appendix B: Study Two supplementary materials

Appendix B.1: Search strategy

Database: MEDLINE

In steps:

#	Exposures	Hits
1	exp Colorectal Neoplasms/	199011
2	(colorect* or rect* or colon* or bowel).tw,kw.	821785
3	(cancer* or neoplas* or tumo?r* or malignan* or carcinoma* or adeno*).tw,kw.	3493361
4	2 and 3	329291
5	1 or 4	369542
6	Incidence/	258624
7	incidence.tw,kw.	740036
8	Trend*.tw,kw.	391905
9	6 or 7 or 8	844856
10	exp Registries/	94470
11	(cancer adj3 regist*).tw,kw.	23493
12	10 or 11	107181
13	5 and 9 and 12	3318
14	limit 13 to english language	3130
15	limit 14 to yr="2010 -Current"	**1787**

Database: Embase

In steps:

#	Exposures	Hits
1	(colorect* or rect* or colon* or bowel).tw,kw.	925983
2	(cancer* or neoplas* or tumo?r* or malignan* or carcinoma* or adeno*).tw,kw.	3825267
3	1 and 2	429033
4	exp colon tumor/	280525
5	exp rectum tumor/	229465
6	3 or 4 or 5	494055
7	Incidence/	376884
8	Cancer incidence/	67144
9	incidence.tw,kw.	885965
10	Trend*.tw,kw.	502568
11	7 or 8 or 9 or 10	1460125
12	Cancer registry/	33889
13	Register/	108956
14	(cancer adj3 regist*).tw,kw.	33651

15	12 or 13 or 14	150261
16	6 and 11 and 15	4657
17	limit 16 to english language	4444
18	Limit 17 to conference abstract	1440
19	17 NOT 18	3004
20	limit 19 to yr="2010 -Current"	**1977**

Database: Web of science

In steps:

#	Exposures	Hits
1	(TS=(cancer* or neoplas* or tumor* or tumours or malignan* or carcinoma* or adeno*)) AND LANGUAGE: (English) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=2010-2020	2,126,653
2	(TS=(colorect* or rect* or colon* or bowel)) AND LANGUAGE: (English) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=2010-2020	667,363
3	1 and 2	235,826
4	(TS=(incidence or trend*)) AND LANGUAGE: (English) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=2010-2020	883,278
5	(TS=(registry or registries)) AND LANGUAGE: (English) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=2010-2020	104,506
6	3 and 4 and 5	**1584**

Appendix B.2: Quality assessment

Quality appraisal checklist			
Item	**Yes**	**No**	**Unclear**
1) Were the aims/objectives of the study clear? *			
2) Was the study design appropriate for the stated aim(s)? *			
3) Was the sample size adequate? §			
4) Were the study subjects and setting described in detail? §			
5) Were valid methods used for the identification of the condition? §			
6) Were the risk factor and outcome variables measured correctly using instruments/measurements that had been trialed, piloted, or published previously?*			
7) Was there an appropriate statistical analysis? §			
8) Is it clear what was used to determine statistical significance and/or precision estimates? (e.g., p values, CIs)? *			
9) Were the methods (including statistical methods) sufficiently described to enable them to be repeated? *			
10) Were the limitations of the study discussed? *			

§ Item from the Joanna Briggs Institute Prevalence Critical Appraisal Tool
*Item from the Appraisal tool for Cross-Sectional Studies

Appendix B.3: Descriptive summary of statistical modelling methods commonly used to measure incidence trends in 2010-2020

Modelling method:

Joinpoint regression

In evaluating incidence trends, joinpoint (segmented) regression analysis identifies the points in time where rates change in direction (joinpoints) and the magnitude of the incidence rate change. It estimates the percentage change using a permutation test-the most common technique reported in cancer incidence- to fit a series of joined straight lines to the natural logarithm of observed rates (1). The join point regression analysis starts with the minimum number of joinpoints (0 join points, which is a straight line) and tests whether more joinpoints are statistically significant and should be added to the model. When the joinpoint model is fixed on zero joinpoints, the conventional annual percentage change (cAPC) is estimated. The cAPC assumes that incidence trends are linear and change at a constant rate over the study's entire period (2). This assumption might not hold when investigating long-term trends or when trends are suspected to be non-linear. Therefore, the sensible approach to analyzing trends in this scenario is by employing a segmented regression analysis wherein more joinpoints are added to the model. This analysis estimates rate changes for different time partitions, known as the segmented annual percentage change (sAPC) (1, 2). For segmented analysis, the percentage of change in incidence rates is assumed constant over specific time intervals defined by joinpoints; yet it might fluctuate over different time partitions. The joinpoint program users' guide (3) provides recommendations for the maximum number of joinpoints that could be added to the model based on the number of years covered. The joinpoint program will select a final model with the optimal number of joinpoints. Yet, the program allows the user to view the results of the other less parsimonious models with a different number of joinpoints.

Linear regression

Linear regression models assume a linear relationship between a dependent variable (continuous) and an independent variable (continuous or categorical). Several approaches could be used to fit linear regression models, such as the least-squares and maximum-likelihood estimation techniques (4). Linear regression assumes the dependent variable to have a conditional normal error structure (5). In measuring time trends, the incidence rate is regressed on time, and the slope of this model is transformed through a specific formula $((e^b - 1)x100)$ to calculate the annual percentage change (APC)(2).

Generalized linear models (GLM)

GLM is a class of modelling that generalizes linear regression models allowing for different types of dependent variables like binary, ordinal, nominal, or count data. It also assumes that the errors in the dependent variable have other than a normal distribution, such as binomial or Poisson distribution (5). Parameters in these models are estimated by the maximum likelihood method. GLM doesn't assume a linear relationship between the dependent and predictor variable. Yet, it allows the transformation of the dependent variable (through the link function), which can linearize the relationship (5).

Poisson regression

Poisson regression is a type of GLM used to model count data by assuming that the dependent variable has a Poisson distribution. In this type of modelling, a regression line is fitted to the dependent variable's natural logarithm (6). In measuring trends, diagnosis year is included in the Poisson regression model as a regressor (independent) variable. The regression coefficient of time represents the incidence rate ratio and could be transformed to present the annual percentage change in incidence rates using the formula $((e^b - 1)x100)$ (5). A main characteristic of the Poisson distribution is that the mean and variance are assumed equal, a condition known as "equidispersion". When the variance is larger than the mean, "overdispersion" occurs (7). Overdispersion is common and can result in small standard errors and confidence limits, large test statistics, and overestimated significance. Among the most common methods for adjusting overdispersion are the overdispersed Poisson model and the negative binomial model (5).

Age-period-cohort modelling

Age-period-cohort modelling is another type of GLM that further investigates incidence trends by describing the simultaneous and independent effect of age (biological processes of aging), birth cohorts (exposures/experiences that vary from one generation to the next), and period (external factors that affect all age groups similarly at a specific calendar time) on cancer incidence (8). Period and cohort effects are usually presented as incidence rate ratios, calculated by comparing the age-specific incidence rate of a given period or cohort group with an arbitrarily chosen referent group. This modelling technique also generates a variety of other parameters providing a comprehensive examination of trends (9).

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Appendix B.4: Title/Abstract screening inter-reviewer agreement rate calculation (κ statistic)

		Reviewer (AA)		
		Included	Excluded	Total
Reviewer (NA)	Included	234 (a)	5 (b)	239
	Excluded	15 (c)	2652(d)	2667
	Total	249	2657	2906

$$p_0 = \frac{(a+d)}{a+d+b+c} = \frac{(234+2649)}{2906} = 99\%$$

$$p_e = \left[\left({}^{a+b}/_{n}\right) * \left({}^{a+c}/_{n}\right)\right] + \left[\left({}^{c+d}/_{n}\right) * \left({}^{b+d}/_{n}\right)\right] =$$

$$\left[\left({}^{239}/_{2906}\right) * \left({}^{249}/_{2906}\right)\right] + \left[\left({}^{2667}/_{2906}\right) * \left({}^{2657}/_{2906}\right)\right] = 84\%$$

$$\kappa = \frac{(p_0 - p_e)}{(1-p_e)} = \frac{(99\% - 84\%)}{(1-84\%)} = 94\%$$

Appendix B.5: Data extraction sheet

	First author and year	Country	Main outcomes	Observation period	Method(s) for calculating incidence trends	Reporting model fit statistics (Yes/NR/NA)	Software
1	Abdifard 2016 *(16)*	Iran	Incidence	2000-2009	Visual summary + Poisson regression [P2]	NR	Stata
2	Abdifard 2013 *(17)*	Iran	Incidence	2000–2005	Visual summary + Poisson regression [P2]	NR	Stata
3	Abreu 2010 *(18)*	Portugal	Incidence, survival	1995–2004	Visual summary + Poisson regression [P1]	NR	SPSS
4	Al Dahhan 2018 *(19)*	Iraq	Incidence	2002–2011	Visual summary	NA	Not reported
5	Araghi 2018 *(20)*	USA	Incidence, projection	1973–2014	Visual summary + Age-period-cohort modelling [APC7,10]	NR	R (Nordpred)
6	Araghi 2019 *(21)*	Seven high income countries	Incidence	2008–2012/2009–2013/ 2010–2014	Visual summary + Join point regression +Age-period-cohort modelling [APC7,9,10]	Yes (method only)[M1,3]	APCfit in Stata
7	Ashktorab 2016 *(22)*	USA	Incidence	2000–2012	Visual summary + Poisson Regression [P1]	NR	Not reported
8	Austin 2014 *(23)*	USA	Incidence	1998–2009	visual summary + Linear regression analysis (weighted-least squares method, log-linear model)[L1]	NR	Stata
9	Aziz 2015 *(24)*	USA	Incidence	1995–2010	Visual summary + Linear regression analysis [L1]	NR	SAS
10	Bailey 2015 *(25)*	USA	Incidence	1975–2010	Visual summary + Linear regression analysis (weighted-least squares method, log- model) [L1]	NR	SEER Stat

11	Baniasadi 2015 *(26)*	Iran	Incidence	2003–2013	Visual summary + Linear regression analysis [L3]	NR	MINITAB
12	Bhurgri 2011 *(27)*	Pakistan	Incidence, gender and clinical distribution	1995–1997/ 1998–2002	Visual summary	NA	SPSS
13	Boyce 2016 *(28)*	Australia	Incidence, clinical and demographic features, survival	2001-2008	Visual summary + Poisson regression [(P1)]	NR	STATA/SAS
14	Winther 2016 *(29)*	Denmark	Incidence, prevalence, survival, mortality	1980–2012	Visual summary + Relative change	NA	Not reported
15	Brenner 2016 *(30)*	Germany	Incidence, mortality	2003–2012	Visual summary + Relative change	NA	Not reported
16	Brouwer 2018 *(31)*	Netherlands	Incidence, mortality, treatment, survival	1989–2014	Visual summary + Average annual percentage of change analysis (method not specified)	NR	STATA/SAS/SPSS
17	Caldarella 2013 *(32)*	Italy	Incidence	1985–2005	Visual summary+ Linear regression analysis (weighted-least squares method) [L1]	NR	Not reported
18	Carroll 2019 *(33)*	USA	Incidence, survival	1973–2013	Poisson regression [(P1)]	NR	Not reported
19	Chambers 2020 *(34)*	United Kingdom	Incidence	1974–2015	Visual summary + Join point regression + Age-period-cohort modelling [(APC2,7)]	Yes (method and assessment results)[M1,4]	Joinpoint, Age-Period-Cohort web tool (NCI)
20	Chatterjee 2015 *(35)*	USA	Incidence, screening prevalence, CRC risk factors	2000–2009	Visual summary + Annual percentage of change analysis (method not specified)	NR	Not reported
21	Alsanea 2015 *(36)*	Saudi Arabia	Incidence, survival, demographic features	1994–2010	Visual summary	NA	Not reported

22	Chauvenet 2011 *(37)*	France	Incidence	1976–2005	Visual summary + Poisson regression[(P1)] + Age-cohort modelling [(APC1,12)]	NR	Stata
23	Chen 2012 *(38)*	Taiwan	Incidence	1988–2007	Visual summary	NA	SPSS
24	Cheng 2011 *(39)*	USA	Incidence	1976–2005	Visual summary + Relative change + Annual percentage of change analysis (method not specified)	NR	SEER Stat
25	Chernyavskiy 2019 *(40)*	USA	Incidence	2000–2014	Age-period-cohort modelling [(APC1,2,7)]	Yes (method and assessment results)[M6]	R (Brms)
26	Chittleborough 2020 *(41)*	New Zealand, Sweden, and Scotland	Incidence	1995–2012/1970–2014/ 1990–2014	Visual summary + Poisson regression [(P1)] + Linear regression analysis [L2]	NR	R
27	Chong 2015 *(42)*	Brunei Darussalam	Incidence	1991 and 2014	Visual summary	NA	SPSS
28	Clarke 2014 *(43)*	Ireland	Incidence, age and stage distribution, treatment, mortality, survival	1994-2010	Visual summary + Join point regression	Yes (method only)[M1]	Joinpoint
29	Crocetti 2010 *(44)*	Italy	Incidence	1985–2005	Visual summary + regression	NR	Joinpoint
30	Crosbie 2018 *(45)*	USA	Incidence, demographic and clinical features	1979–2014	Visual summary + Join point regression	Yes (method only)[M1]	Joinpoint
31	Dehghani 2019 *(46)*	Iran	Incidence	2003–2010	Visual summary + Poisson regression [(P3)]	NR	Microsoft Excel
32	Edwards 2010 *(47)*	USA	Incidence, mortality, survival, projection	1975–2006	Visual summary + Join point regression	Yes (method only)[M1]	Joinpoint

33	Ellis 2018 *(48)*	USA	Incidence	1990–2014	Visual summary + Join point regression	Yes (method and assessment results) [M1]	Joinpoint
34	Eser 2018 *(49)*	Cyprus, Jordan, Israel, and İzmir,Turkey	Incidence	2005–2010	Visual summary + Join point regression	NR	Joinpoint
35	Exarchakou 2019 *(50)*	England	Incidence	1971–2014	Visual summary + Join point regression	Yes (method only)[M1]	Joinpoint
36	Feletto 2019 *(51)*	Australia	Incidence	1982–2014	Visual summary + Join point regression + Age-period-cohort modelling [(APC2,7)]	Yes (method only)[M1]	Joinpoint, Age-Period-Cohort web tool (NCI)
37	Hasanpour-Heidari 2019 *(52)*	Iran	Incidence	2004–2013	Visual summary + Join point regression	Yes (method only)[M1]	Joinpoint
38	Lemmens 2010 *(53)*	Netherlands	Incidence, stage distribution, treatment, mortality, survival	1975–2007	Visual summary	NA	Not reported
39	May 2017 *(54)*	USA	Incidence, stage distribution	1975–2012	Visual summary + Join point regression	Yes (method only)[M1]	Joinpoint
40	Klugarova 2019 *(55)*	Czech Republic	Incidence, prevalence, mortality, treatment, survival	1982–2016	Visual summary	NA	Not reported
41	Koblinski 2018 *(56)*	USA	Incidence	2000–2010	Visual summary + Linear regression analysis [L1]	NR	SPSS
42	Martinsen 2016 *(57)*	USA	Incidence, mortality, survival	1990–2012	Visual summary + Join point regression	NR	Joinpoint
43	Giddings 2012 *(58)*	USA	Incidence	1988–2007	Visual summary + Join point regression	NR	Joinpoint
44	Missaoui 2011 *(59)*	Tunisia	Incidence	1993–2007	Visual summary + Linear regression analysis (log-linear model) [L1]	NR	Not reported

45	Kelly 2012 *(60)*	USA	Incidence	2005–2009	Visual summary	NA	Not reported
46	Loomans-Kropp 2019 *(61)*	USA	Incidence, mortality	1980–2016	Visual summary + Join point regression	Yes (method only)[M1]	Joinpoint
47	Gandhi 2017 *(62)*	New Zealand	Incidence	1995–2012	Visual summary + Poisson regression [(P1)]	Yes (method and assessment results)[M2]	Not reported
48	Lopez-Abente 2010 *(63)*	Spain	Incidence, mortality	1975–1993/2000–2004	Visual summary + Poisson regression[(P1)] (Change-point model/ Age-period-cohort modelling[(APC1,9)])	NR	R
49	McClements 2012 *(64)*	United Kingdom	Incidence, stage distribution, mortality	1982–2006	Visual summary	NA	SPSS + STATA
50	Ladabaum 2014 *(65)*	USA	Incidence	1990–2004	Visual summary + Join point regression	Yes (method only)[M1]	Not reported
51	Fowler 2018 *(66)*	USA	Incidence, mortality	1991–2010	Visual summary + LOESS method to generate nonparametric local regression smoothing	NR	SAS
52	Meester 2019 *(67)*	USA	Incidence, stage distribution	1975–2015	Visual summary + Join point regression	NR	Joinpoint
53	Li 2017 *(68)*	China	Incidence	1998–2012	Visual summary + Join point regression	NR	Joinpoint
54	Jayarajah 2020 *(69)*	Sri Lanka	Incidence, clinical features	2001–2010	Visual summary + Join point regression	Yes (assessment results only)	Joinpoint
55	Katsidzira 2016 *(70)*	Zimbabwe	Incidence, demographic and clinical features	2003–2012	Visual summary + Join point regression	NR	Joinpoint
56	Lee 2019 *(71)*	Taiwan	Incidence, survival, mortality	1984–2013	Visual summary + Poisson regression [(P1)] + Age-period-cohort modelling[(APC2,11)]	NR	SAS, WinBUGS

57	Merrill 2011 *(72)*	USA	Incidence	2005–2007	Relative change	NA	Not reported
58	Klimczak 2011 *(73)*	Poland	Incidence, prevalence	1999–2008	Visual summary	NA	Not reported
59	Khiari 2017 *(74)*	Tunisia	Incidence, projection	1994–2009	Visual summary + Join point regression	NR	Joinpoint
60	Jandova 2016 *(75)*	USA	Incidence, mortality, demographic and clinical features	1995–2011	Visual summary + Relative change	NA	SPSS
61	Li; Lin 2017 *(76)*	China	Incidence	2010–2014	Visual summary + Join point regression	NR	Joinpoint
62	Meza 2010 *(77)*	United Kingdom and USA	Incidence	1973–2006	Visual summary + Poisson regression[(P1)] (Age-period-cohort modelling[(APC7)]	NR	Not reported
63	Jafri 2013 *(78)*	USA	Incidence, survival	1993–2007	Visual summary + Poisson regression [(P1)] + Linear regression analysis (weighted-least squares method) [L1]	NR	SAS
64	McDevitt 2017 *(79)*	Ireland	Incidence, mortality, survival, anatomical site and stage distribution	1994–2012	Join point regression	Yes (method only)[M1]	Not reported
65	Khachfe 2019 *(80)*	Lebanon	Incidence	2005–2015	Visual summary + Join point regression	Yes (assessment results only)	Joinpoint
66	Meyer 2010 *(81)*	USA	Incidence	1973–2005	Visual summary + Join point regression + Linear regression analysis (weighted-least squares method) [L1]	NR	SEER Stat + Joinpoint
67	Garcia 2018 *(82)*	USA	Incidence	2001–2014	Visual summary + Absolute and relative change	NA	Not reported

68	Brenner 2017 *(83)*	Canada	Incidence	1971–2012	Visual summary + Join point regression + Age-period-cohort modelling[(APC7)] + Interrupted time-series regression analysis	Yes (method only)[M1]	Joinpoint, Age-Period-Cohort web tool (NCI)
69	Brenner 2019 *(84)*	Canada	Incidence	1971–2015	Visual summary + Join point regression+ Age-period-cohort modelling[(APC7)]	Yes (method only)[M1]	Joinpoint, Age-Period-Cohort web tool (NCI)
70	Fedewa 2019 *(85)*	USA	Incidence/ colonoscopy rate	2000–2015	Visual summary + Join point regression +Incidence rate ratios	NR	Joinpoint
71	Melnitchouk 2018 *(86)*	Ukraine	Incidence, mortality, treatment, stage distribution	2000 –2014	Visual summary + Join point regression	Yes (method only)[M1]	Joinpoint
72	Nooyi 2011 *(87)*	India	Incidence	1968–2002	Visual summary + Mean annual percentage change (MAPC) + Poisson regression [(P1)]	NR	SAS
73	Siegel 2019 *(88)*	Global	Incidence	2008–2012	Visual summary + Join point regression	Yes (method only)[M1]	Not reported
74	Al-Zalabani 2020 *(89)*	Saudi Arabia	Population attributable fraction (PAF), Incidence, projection	1994–2015	Visual summary + Join point regression	Yes (method and assessment results)[M1]	Joinpoint
75	Augustus 2018 *(90)*	USA	Incidence	2000–2014	Visual summary + Join point regression	NR	Joinpoint, R
76	Davis 2011 *(91)*	USA	Incidence, age and anatomical site distribution	1987–2006	Visual summary + Relative change	NA	Microsoft Excel
77	Domati 2014 *(92)*	Italy	Incidence, survival, clinical features	1986–2008	Visual summary + Join point regression	Yes (method only)[M1]	joinpoint

78	Koblinski 2019 *(93)*	USA	Incidence, demographic and clinical features	2000–2010	Visual summary + linear regression analysis [L1]	NR	SPSS
79	Vuik 2019 *(94)*	Europe	Incidence, mortality	1990–2016	Visual summary + Join point regression	NR	Joinpoint
80	Shafqat 2015 *(95)*	USA	Incidence, survival, management	2000–2011	Visual summary + Join point regression	NR	Joinpoint
81	Siegel 2017 *(96)*	USA	Incidence, mortality, survival, stage distribution, screening prevalence	2009–2013	Visual summary + Join point regression	NR	Joinpoint
82	Savijarvi 2019 *(97)*	Finland	Incidence	1976–2014	Visual summary + Poisson regression [(P1)]	NR	Not reported
83	Rahman 2015 *(98)*	USA	Incidence, survival	1992–2009	Visual summary + Join point regression	NR	Not reported
84	Nfonsam 2015 *(99)*	USA	Incidence, mortality, stage distribution	1995–2010	Visual summary	NA	SAS
85	Van Beck 2018 *(100)*	USA	Incidence, mortality	1976–2015	Visual summary+ join point regression	NR	Joinpoint
86	Wong 2020 *(101)*	39 countries	Incidence, mortality	1980–2016	Visual summary + Join point regression	NR	Not reported
87	Mosli 2012 *(102)*	Saudi Arabia	Incidence, clinical features	2001–2006	Visual summary	NA	Microsoft Excel
88	Mosli 2012 *(103)*	Saudi Arabia	Incidence, clinical features	2000–2006	Visual summary	NA	Microsoft Excel
89	Russo 2019 *(104)*	Italy	Incidence	1999–2015	Visual summary + Join point regression + Age-period-cohort modelling[(APC7,8,9)]	NR	Joinpoint, R(macro)
90	Sheneman 2017*(105)*	USA	Incidence, survival	1992–2013	Visual summary + linear regression analysis (log-linear model) [L1]	NR	Microsoft Excel

91	Oliphant 2011 *(106)*	United Kingdom	Incidence	1999 –2007	Visual summary	NA	STATA
92	Perdue 2014 *(107)*	USA	Incidence, mortality	2005–2009	Join point regression	Yes (method only)[M1]	joinpoint
93	Murphy 2017 *(108)*	USA	Incidence	1975–2013	Visual summary + Relative change	NA	Not reported
94	Shah 2012 *(109)*	New Zealand	Incidence	1981–2004	Visual summary + Linear regression analysis (weighted-least squares method) [L1] + Relative change	NR	SAS
95	Siegel 2020 *(110)*	USA	Incidence, mortality, screening prevalence, survival, stage distribution	2012–2016/1995–2016	Visual summary + Join point regression	NR	joinpoint
96	Shin 2012 *(111)*	Korea	Incidence	1999–2009	Visual summary + Linear regression analysis (log-linear model) [L1]	NR	R
97	Patel 2016 *(112)*	Canada	Incidence, CRC risk factors	1969–2010	Visual summary + Join point regression	Yes (method only)[M1]	Joinpoint
98	Vardanjani 2018 *(113)*	Iran	Incidence, prevalence, projection	2003–2012	Join point regression	NR	Joinpoint
99	Siegel; Fedewa 2017 *(114)*	USA	Incidence	1974–2013	Visual summary + Join point regression + Age-period-cohort modelling[(APC1-7,9)]	Yes (method and assessment results)[M1,5]	Joinpoint, Age-Period-Cohort web tool (NCI)
100	Pescatore 2013 *(115)*	Luxembourg	Incidence, survival, stage distribution	1990–2009	Visual summary	NA	Not reported
101	Murphy 2018 *(116)*	USA	Incidence	1975–2014	Visual summary + Age-period-cohort modelling[(APC7,10)]	NR	Age-Period-Cohort web tool (NCI)

102	Siegel 2012 *(117)*	USA	Incidence	1992–2008	Visual summary + Join point regression	Yes (method only)[M1]	joinpoint
103	Siegel; Medhanie 2019 *(118)*	USA	Incidence, CRC risk factors	1995–2015	Join point regression	Yes (method only)[M1]	joinpoint
104	Sung 2019 *(119)*	Hong Kong, Korea, Japan, and Taiwan	Incidence	1995–2014	Visual summary + Join point regression	Yes (method only)[M1]	joinpoint
105	Rafiemanesh 2016 *(120)*	Iran	Incidence, clinical features	2003–2008	Join point regression	NR	joinpoint
106	Sierra 2016 *(121)*	Central and South America	Incidence, mortality	2003–2007	Visual summary +Annual percentage of change analysis (method not specified)	NR	STATA
107	Zhu 2017 *(122)*	China	Incidence, mortality, projection	2003–2011	Visual summary	NA	SPSS
108	Palmieri 2013 *(123)*	Italy	Incidence, mortality, survival, demographic and clinical features	1992–2010	Visual summary	NA	Not reported
109	Reggiani-Bonetti 2013 *(124)*	Italy	Incidence, clinical features	1986–2008	Visual summary + Join point regression	Yes (method only)[M1]	Joinpoint
110	Nowicki 2018 *(125)*	Poland	Incidence, morbidity, survival	2006–2011	Visual summary	NA	Statistica, Microsoft Excel
111	Phipps 2012 *(126)*	USA	Incidence, mortality	1975–2007	Visual summary + Join point regression	Yes (method only)[M1]	Joinpoint
112	Oppelt 2019 *(127)*	Germany	Incidence	2008–2014	Visual summary	NA	SAS
113	Murphy 2019 *(128)*	USA	Incidence, survival	1992–2014	Relative and absolute change	NA	Not reported

114	Innos 2018 *(129)*	Estonia	Incidence, survival	1995–2014	Visual summary + Join point regression	NR	Joinpoint
115	Siegel 2014 *(130)*	USA	Incidence, survival, mortality, anatomical site and stage distribution	1975–2010	Visual summary + Join point regression	NR	Joinpoint
116	Sia 2014 *(131)*	Australia	Incidence, anatomical site and histopathology distribution	2000–2010	Visual summary + Join point regression + Poisson regression [P1]	NR	Joinpoint, Stata
117	Rejali 2018 *(132)*	Iran	Incidence	2000–2011	Visual summary + Join point regression	Yes (method only)[M1]	Joinpoint
118	Sarakarn 2017 *(133)*	Thailand	Incidence	1989–2012	Visual summary + Join point regression	Yes (method only)[M1]	Joinpoint
119	Keum 2014 *(134)*	USA	Incidence, mortality	1975–2009	Visual summary + Join point regression	NR	Joinpoint
120	Singh 2014 *(135)*	USA	Incidence	1988–2009	Join point regression	NR	Not reported
121	Stock 2012 *(136)*	USA	Cumulative risk	1978–2007	Visual summary+ Relative change	NA	Not reported
122	Sun 2020 *(137)*	Sweden	Incidence, survival	1960–2014	Visual summary + Join point regression	Yes (method only)[M1]	Joinpoint
123	Tawadros 2015 *(138)*	USA	Incidence, clinical features	1980–2010	Visual summary + Linear regression analysis (weighted-least squares method) [L1]	NR	Not reported
124	Thirunavukarasu 2010 *(139)*	USA	Incidence, survival, clinical and demographic features	1973–2006	Visual summary	NA	SPSS
125	Thuraisingam 2017 *(140)*	USA	Incidence	2000–2012	Visual summary+ Relative change	NA	SPSS

126	Troeung 2017 *(141)*	Australia	Incidence, mortality, colonoscopy history	1982–2007	Visual summary + Join point regression	Yes (method and assessment results)[M1]	Joinpoint
127	Ugarte 2012 *(142)*	Spain	Incidence	1990–2005	Visual summary + Bayesian analysis of spatio-temporal conditional autoregressive models	NR	R
128	Ullah 2018 *(143)*	Ireland	Incidence, stage distribution	1994–2012	Visual summary + Linear regression analysis [L1]	NR	SPSS
129	Wan Ibrahim 2020 *(144)*	Malaysia	Incidence, mortality, survival, clinical and demographic features	2007–2017	Visual summary + Time-series regression analysis	NR	R
130	Wang 2017 *(145)*	USA	Incidence, survival, stage distribution	1995–2010	Visual summary + Annual percentage of change analysis (method not specified)	NR	SEER Stat
131	Wang; de Grubb 2017 *(146)*	USA	Incidence	1994–2013	Visual summary + Linear regression analysis (weighted-least squares method) [L1]	NR	SEER Stat + SPSS
132	Wang 2019 *(147)*	USA	Incidence, factors associated with cancer-specific death	1988–2013	Visual summary	NA	SAS
133	Wen 2018 *(148)*	China	Incidence	2012/2000–2015	Visual summary + Join point regression	NR	Joinpoint
134	Wessler 2010 *(149)*	Norfolk, Suffolk, Cambridgeshire (NSC) (East of England)	Incidence	1971–2005	Visual summary + Poisson regression [(P1)] (Age-period-cohort modelling) [(APC1,7)]	Yes (method and assessment results)[M2,3]	STATA
135	Wu 2018 *(150)*	Shanghai	Incidence, mortality	1975–2013	Visual summary + Join point regression + Age-period-cohort modelling[(APC2,3,7)]	Yes (method only)[M1]	Joinpoint, Age-Period-Cohort web tool (NCI)

136	Yee 2010 *(151)*	Hong Kong	Incidence	1983–2006	Visual summary + Relative change	NA	Not reported
137	Yeo 2017 *(152)*	USA	Incidence, clinical and demographic features	2000–2011	Visual summary + Linear regression analysis (least squares method) [L1]	NR	STATA
138	Yoon 2015 *(153)*	Korea	Incidence, mortality, fatality, screening rate	1999–2012	Visual summary	NA	Not reported
139	Zhabagin 2015 *(154)*	Kazakhstan	Incidence, mortality	2004–2013	Visual summary	NA	Not reported
140	Zhang 2018 *(155)*	Hong Kong	Incidence	1983–2012	Visual summary + Join point regression + Age-period-cohort modelling[(APC1-3,7)]	Yes (method only)[M1]	Joinpoint, Age-Period-Cohort web tool (NCI)
141	Zhou 2015 *(156)*	China/Guangzhou	Incidence, age and anatomical site distribution	2000–2011	Visual summary + Join point regression	NR	Joinpoint
142	Zhu 2013 *(157)*	USA	Incidence	1973–2008	Visual summary+ Poisson regression[(P1)] (Age-period-cohort modelling [(APC9)])	NR	SAS
143	Zorzi 2019 *(158)*	Italy	Incidence, mortality	2003–2014	Visual summary + Join point regression	Yes (method only)[M1]	Joinpoint
144	Zorzi 2015 *(159)*	Italy	Incidence	2000–2008	Visual summary + Annual percentage of change analysis (method not specified)	NR	Not reported
145	Ohri 2020 *(160)*	USA	Incidence	2000–2014	Visual summary + Relative change	NA	SEER Stat

Abbreviations: NR: Not reported, NA: Not applicable, CRC: Colorectal cancer, USA: United States of America.

Presentation of incidence trends:

1-Linear regression: L1: percentage of change; L2: difference per decade; L3: Reporting only model formulae.

2-*Poisson regression:* P1: Study reported trends as a percentage of change or as incidence rate ratio (IRR); P2: Study reported trends as merely the slope of the regression line; P3: Study reported trends by only stating the significance of incidence rate trends.

3-APC modelling: APC1: Net drift (age-adjusted annual percentage change); APC2: Local drift (age-specific net annual percentage change); APC3: Longitudinal age curve (Fitted longitudinal age-specific rates in reference cohort adjusted for period deviations); APC4: Cross-sectional age curve (Fitted cross-sectional age-specific rates in reference period p0 adjusted for cohort deviations); APC5.Age, period, and cohort deviations (measure curvature, which describes local changes in trends, independently of the magnitude or direction of the overall trend); APC6.Fitted temporal trends (Fitted rates in reference age group adjusted for cohort deviations); APC7.Period/Cohort rate ration (Ratio of rates in a certain period/cohort relative to reference period/cohort); APC8.Graphical presentation of rates according to age group; APC9.Graphical presentation of trends in age-specific rates by year of birth; APC10.Graphical presentation of trends in age-specific rates by calendar period; APC11.Annual Absolute risk difference in CRC by cohort and age; APC12.Cumulative risk-over the age range (0-74)- of developing CRC according to birth cohorts.

Model validity assessment: M1:Permutation test; M2:likelihood ratio tests; M3:Deviance statistics; M4:The squared correlation coefficient (R^2); M5:Residual analysis; M6:Standard posterior distribution predictive checks (for age-period-cohort modelling).

Appendix B.6: Description of characteristics of included studies

Study characteristics	
Country	***N (% out of 145)***
The United States of America	58 (40.0)
Canada	3(2.0)
Europe	34 (23.4)
Asia	33 (22.8)
Oceania	6 (4.1)
Africa	3 (2.0)
Multiple countries	8 (5.5)
Main outcomes (presented here are the three most common outcomes reported in the included studies)	***N (% out of 145)***
Incidence	144 (99.3)
Mortality	35 (24.1)
Survival	30 (20.7)
Observation period	***N (% out of 145)***
Less than 10 years	21 (14.5)
10-19 years	57 (39.3)
20 years or more	69 (47.6)
Methods used to measure incidence trends	
1. Explanatory methods	***N (% out of 145)***
Visual summaries.	135 (93.1)
Study reported trends using only visual summaries.	23 (15.9)
Study reported trends as a percentage of change (relative change) • Trend presented as relative and absolute change • Study reported the formulae to calculate the relative change • Study reported confidence interval estimates	14 (9.7) 2 (14.3% out of 14) 2 (14.3% out of 14) 0

• Study reported the significance of trends	2 (14.3% out of 14)
Study reported the incidence trend as the mean annual percentage change calculated via a mathematical equation.	1 (0.7)
Study calculated the incidence trend using the incidence rate ratio.	1 (0.7)
2. Statistical modelling methods	
A. Joinpoint regression	***N (% out of 145)***
Study analyzed trends using joinpoint regression.	65 (44.8)
Presentation of trends:	
• Study did not report the percentage of change in trends	1 (1.5% out of 65)
• Study reported only annual percentage of change (APC) ○ Study presented one APC over the whole observation period ○ Study presented several APCs over different time segments	37(56.9% out of 65) 15 (40.5% out of 37) 22 (59.4% out of 37)
• Study reported only average annual percentage change (AAPC) ○ Study stated a clear explanation of AAPC calculation	11 (16.9% out of 65) 1 (9.1% out of 11)
• Study reported APC and AAPC ○ Study explicitly stated the difference in calculation between APC and AAPC ○ Study stated the difference between APC and AAPC by reporting the number of years covered for each measure ○ Study did not state the difference between APC and AAPC	16 (24.6% out of 65) 4 (25.0% out of 16) 6 (37.5% out of 16) 6 (37.5% out of 16)
Software employed for conducting joinpoint regression: • Joinpoint trend analysis software, National Cancer Institute.	58 (89.2% out of 65)
Study reported information on parameter setting in the joinpoint program:	***N (% out of 58)***

• Study specified the used modelling method (Grid search or Hudson's). • Study reported the chosen minimum APC difference worth detecting. • Study reported the minimum number of joinpoints selected. • Study reported the maximum number of joinpoints selected. • Study reported the AAPC segment ranges that were selected. • Study reported the chosen model selection method. • Study reported the method used for estimating confidence intervals. • Study reported the chosen autocorrelated errors option. • Study reported selecting a linear or log-linear model.	0 0 8 (13.8% out of 58) 17(29.3% out of 58) 1(1.7% out of 58) 30(51.7% out of 58) 1(1.7% out of 58) 0 17(29.3% out of 58)
B. Linear regression models	***N (% out of 145)***
Study analyzed trends using linear regression models.	18 (12.4)
Study reported the use of the least-squares method to fit the model.	1 (5.6% out of 18)
Study reported the use of the weighted least-squares method to fit the model.	8 (44.4 out of 18)
Study reported log transformation of the model.	5 (27.8% out of 18)
Presentation of trends: • Percentage of change • Difference per unit of time • Reporting only model formulae with no estimates for trends	 16 (88.9% out of 18) 1 (5.6% out of 18) 1 (5.6% out of 18)
Software employed for conducting linear regression: • SPSS • SAS • SEER Stat • Stata • R • Microsoft Excel • MINITAB	 4 (22.2% out of 18) 3 (16.7% out of 18) 3 (16.7% out of 18) 2 (11.1% out of 18) 2 (11.1% out of 18) 1 (5.6% out of 18) 1 (5.6% out of 18)

C. Generalized linear models	
C1. Poisson regression	***N (% out of 145)***
Study analyzed trends using Poisson regression.	19 (13.1)
Study reported the use of Poisson regression to conduct age-period-cohort analysis.	5 (26.3% out of 19)
Presentation of trends: • Study reported trends as incidence rate ratio (IRR) or percentage of change • Study reported trends as merely the slope of the regression line. • Study reported trends by only stating the significance of incidence rate trends.	 16 (84.2% out of 19) 2 (10.5% out of 19) 1 (5.2% out of 19)
Consideration for dispersion was reported: • Overdispersion corrected using negative binomial distribution • No indication of the method used to correct overdispersion	2 (10.5% out of 19) 1 (5.2% out of 19) 1 (5.2% out of 19)
Software employed for conducting Poisson regression: • Stata • SAS • R • Winbugs • SPSS • Microsoft Excel	 6 (31.5% out of 19) 5 (26.3% out of 19) 2 (10.5% out of 19) 1 (5.2% out of 19) 1 (5.2% out of 19) 1 (5.2% out of 19)
C2. Age-Period-Cohort modelling (APCM)	***N (% out of 145)***
Study analyzed trends using APCM.	18 (12.4)
Study performed only APCM to assess trends.	1 (0.7)
Study performed APCM and joinpoint regression analysis.	9 (6.2)
Presentation of trends:	

• Period/Cohort rate ratio (Ratio of rates in a certain period/cohort relative to reference period/cohort).*
• *Reference category for Period/Cohort rate ratio estimation:*
  ○ Middle calendar period and birth cohort groups
  ○ Earliest period and cohort groups
  ○ The cohort with the lowest incidence rates
	14 (77.8% out of 18)
	
	9 (64.3% out of 14)
	2 (14.3% out of 14)
	1 (7.1% out of 14)

• Local drift (age-specific net annual percentage change).*	7 (38.9% out of 18)
• Net drift (age-adjusted annual percentage change).*	6 (33.3% out of 18)
• Longitudinal age curve (Fitted longitudinal age-specific rates in reference cohort adjusted for period deviations).*	3 (16.7% out of 18)
• Graphical presentation of trends in age-specific rates by year of birth.	5 (27.8% out of 18)
• Graphical presentation of trends in age-specific rates by calendar period.	3 (16.7% out of 18)
• Cross-sectional age curve (Fitted cross-sectional age-specific rates in reference period adjusted for cohort deviations).*	1 (5.5% out of 18)
• Age, period, and cohort deviations (measure curvature, which describes local changes in trends, independently of the magnitude or direction of the overall trend).*	1 (5.5% out of 18)
• Fitted temporal trends (Fitted rates in reference age group adjusted for cohort deviations).*	1 (5.5% out of 18)
• Graphical presentation of rates according to age group.	1 (5.5% out of 18)
• Annual Absolute risk difference in CRC by cohort and age.	1(5.5% out of 18)
• Cumulative risk-over the age range (0-74)- of developing CRC according to birth cohorts.	1(5.5% out of 18)
Software used to apply APCM: • Age-Period-Cohort web tool, National Cancer Institute (NCI) • R (nordpred, brms, macro)	 8 (44.4% out of 18) 4 (22.2% out of 18) 3 (16.7% out of 18)

• STATA • SAS • Winbugs	2 (11.1% out of 18) 1(5.5% out of 18)
D. Other methods	***N (% out of 145)***
• Study reported Time series analysis.	1 (0.7)
• Study reported Interrupted time series analysis.	1 (0.7)
• Study reported Bayesian analysis of spatio-temporal conditional autoregressive models.	1 (0.7)
• Study reported the LOESS method to generate nonparametric local regression smoothing.	1 (0.7)
• Study reported the calculation of APC with no further explanation of the used statistical method.	6 (4.1)
Model validity measures	***N (% out of 104 studies that used modelling)***
Study reported an assessment of model fitness. Study reported the results of the model fit assessment.	39 (37.5) 10 (9.6)
Methods to evaluate the model fit (as reported in studies): • Permutation test (for Joinpoint modelling) • likelihood ratio tests (for Poisson modelling) • Deviance statistics (for age-period-cohort modelling) • The squared correlation coefficient (R2) (for Joinpoint modelling) • Residual analysis (for age-period-cohort modelling) • Standard posterior distribution predictive checks (for age-period-cohort modelling)	 34 (32.7) 2 (1.9) 2 (1.9) 1 (0.9) 1 (0.9) 1 (0.9)
Software reported for estimating incidence trends	***N (% out of 145)***
Study reported software information for incidence trend analysis	111 (76.6)
Software reported for estimating incidence trends:	***N (% out of 111)***
Joinpoint	58 (52.3)
SPSS	14 (12.6)
STATA	13 (11.7)

SAS	12 (10.8)
R	9 (8.1)
Age Period Cohort web tool, NCI	8 (7.2)
SEER Stat	6 (5.4)
Microsoft Excel	6 (5.4)
MINITAB	1 (0.9)
WinBUGS	1 (0.9)
Statistica	1 (0.9)

*Definition of parameter obtained from: Rosenberg PS, Check DP, Anderson WF. A web tool for age-period-cohort analysis of cancer incidence and mortality rates. Cancer Epidemiol Biomarkers Prev. 2014;23(11):2296-2302.

Appendix B.7: Quality assessment. Studies are sorted in order from the lowest to highest quality

First author and year	Clear aim and objectives	Appropriate study design	Adequate sample size	Description of study subjects and setting	Valid methods to identify the condition*	Outcome variables were measured correctly using instruments/measurements that had been published previously	Appropriate statistical analysis*	Determine statistical significance and/or precision estimates	Methods sufficiently described enabling reproduction	The limitations of the study discussed	Total
Al Dahhan 2018 *(19)*	√	√	√	√	X	√	X	X	X	X	5
Klugarova 2019 *(55)*	√	√	√	√	X	√	X	X	X	X	5
Klimczak 2011 *(73)*	√	√	√	√	X	√	X	X	X	X	5
Mosli 2012 *(102)*	√	√	√	√	X	√	X	X	X	X	5
Mosli 2012 *(103)*	√	√	√	√	X	√	X	X	X	X	5
Pescatore 2013 *(115)*	√	√	√	√	X	√	X	X	X	X	5
Palmieri 2013 *(123)*	√	√	√	√	X	√	X	X	X	X	5
Baniasadi 2015 *(26)*	√	√	√	√	X	√	X	X	X	X	5
Zhabagin 2015 *(154)*	√	√	√	√	X	√	X	X	X	X	5
Bailey 2015 *(25)*	√	√	√	√	X	√	X	√	X	X	6
Crocetti 2010 *(44)*	√	√	√	√	X	√	X	√	X	X	6
Hasanpour-Heidari 2019 *(52)*	√	√	√	√	X	√	X	√	X	X	6
Lemmens 2010 *(53)*	√	√	√	√	X	√	X	√	X	X	6
Nooyi 2011 *(87)*	√	√	√	√	X	√	X	√	X	X	6
Koblinski 2019 *(93)*	√	√	√	√	X	√	X	√	X	X	6
Rahman 2015 *(98)*	√	√	√	√	X	√	X	√	X	X	6
Araghi 2018 *(20)*	√	√	√	√	X	√	X	X	X	√	6
Bhurgri 2011 *(27)*	√	√	√	√	√	√	X	X	X	X	6
Winther 2016 *(29)*	√	√	√	√	√	√	X	X	X	X	6
Chatterjee 2015 *(35)*	√	√	√	√	X	√	X	X	X	√	6
Alsanea 2015 *(36)*	√	√	√	√	X	√	X	X	X	√	6
Chen 2012 *(38)*	√	√	√	√	X	√	X	X	X	√	6

Koblinski 2018 *(56)*	√	√	√	√	X	√	X	X	X	√	6
Chong 2015 *(42)*	√	√	√	√	X	√	X	X	X	√	6
Kelly 2012 *(60)*	√	√	√	√	√	√	X	X	X	X	6
Fowler 2018 *(66)*	√	√	√	√	X	√	X	X	X	√	6
Merrill 2011 *(72)*	√	√	√	√	√	√	X	X	X	X	6
Davis 2011 *(91)*	√	√	√	√	X	√	X	X	X	√	6
Murphy 2017 *(108)*	√	√	√	√	X	√	X	X	X	√	6
Murphy 2018 *(116)*	√	√	√	√	X	√	X	X	X	√	6
Zhu 2017 *(122)*	√	√	√	√	X	√	X	X	X	√	6
Nowicki 2018 *(125)*	√	√	√	√	√	√	X	X	X	X	6
Oppelt 2019 *(127)*	√	√	√	√	X	√	X	X	X	√	6
Murphy 2019 *(128)*	√	√	√	√	X	√	X	X	X	√	6
Keum 2014 *(134)*	√	√	√	√	X	√	X	X	X	√	6
Ugarte 2012 *(142)*	√	√	√	√	√	√	X	X	X	X	6
Yee 2010 *(151)*	√	√	√	√	√	√	X	X	X	X	6
Ohri 2020 *(160)*	√	√	√	√	X	√	X	X	X	√	6
Garcia 2018 *(82)*	√	√	√	√	X	√	X	X	X	√	6
Domati 2014 *(92)*	√	√	√	√	X	√	X	√	X	X	6
Reggiani-Bonetti 2013 *(124)*	√	√	√	√	X	√	X	√	X	X	6
Abdifard 2013 *(17)*	√	√	√	√	√	√	X	√	X	X	7
Chauvenet 2011 *(37)*	√	√	√	√	√	√	X	√	X	X	7
Abreu 2010 *(18)*	√	√	√	√	√	√	X	√	X	X	7
Ashktorab 2016 *(22)*	√	√	√	√	X	√	X	√	X	√	7
Clarke 2014 *(43)*	√	√	√	√	√	√	X	√	X	X	7
Ellis 2018 *(48)*	√	√	√	√	X	√	X	√	X	√	7
Eser 2018 *(49)*	√	√	√	√	√	√	X	√	X	X	7
May 2017 *(54)*	√	√	√	√	X	√	X	√	X	√	7
Missaoui 2011 *(59)*	√	√	√	√	√	√	X	√	X	X	7
Meester 2019 *(67)*	√	√	√	√	X	√	X	√	X	√	7

Li 2017 *(68)*	√	√	√	√	X	√	X	√	X	√	7
McDevitt 2017 *(79)*	√	√	√	√	√	√	X	√	X	X	7
Khachfe 2019 *(80)*	√	√	√	√	X	√	X	√	X	√	7
Brenner 2017 *(83)*	√	√	√	√	√	√	X	√	X	X	7
Augustus 2018 *(90)*	√	√	√	√	X	√	X	√	X	√	7
Siegel 2017 *(96)*	√	√	√	√	√	√	X	√	X	X	7
Savijarvi 2019 *(97)*	√	√	√	√	X	√	X	√	X	√	7
Van Beck 2018 *(100)*	√	√	√	√	X	√	X	√	X	√	7
Russo 2019 *(104)*	√	√	√	√	√	√	X	√	X	X	7
Perdue 2014 *(107)*	√	√	√	√	X	√	X	√	X	√	7
Siegel 2020 *(110)*	√	√	√	√	√	√	X	√	X	X	7
Shin 2012 *(111)*	√	√	√	√	√	√	X	√	X	X	7
Sung 2019 *(119)*	√	√	√	√	X	√	X	√	X	√	7
Rafiemanesh 2016 *(120)*	√	√	√	√	√	√	X	√	X	X	7
Siegel 2014 *(130)*	√	√	√	√	√	√	X	√	X	X	7
Rejali 2018 *(132)*	√	√	√	√	√	√	X	√	X	X	7
Sarakarn 2017 *(133)*	√	√	√	√	√	√	X	√	X	X	7
Singh 2014 *(135)*	√	√	√	√	X	√	X	√	X	√	7
Thuraisingam 2017 *(140)*	√	√	√	√	X	√	X	√	X	√	7
Ullah 2018 *(143)*	√	√	√	√	X	√	X	√	X	√	7
Wan Ibrahim 2020 *(144)*	√	√	√	√	X	√	X	√	X	√	7
Wen 2018 *(148)*	√	√	√	√	√	√	X	√	X	X	7
Yeo 2017 *(152)*	√	√	√	√	X	√	X	√	X	√	7
Zhang 2018 *(155)*	√	√	√	√	X	√	X	√	X	√	7
Oliphant 2011 *(106)*	√	√	√	√	√	√	X	X	X	√	7
Abdifard 2016 *(16)*	√	√	√	√	√	√	X	√	X	X	7
Brenner 2016 *(30)*	√	√	√	√	√	√	X	X	X	√	7
Carroll 2019 *(33)*	√	√	√	√	√	√	X	X	X	√	7
Chernyavskiy 2019 *(40)*	√	√	√	√	X	√	X	√	X	√	7

Chittleborough 2020 *(41)*	√	√	√	√	X	√	X	√	X	√	7
Dehghani 2019 *(46)*	√	√	√	√	√	√	X	√	X	X	7
Feletto 2019 *(51)*	√	√	√	√	X	√	X	√	X	√	7
Gandhi 2017 *(62)*	√	√	√	√	X	√	X	√	X	√	7
McClements 2012 *(64)*	√	√	√	√	√	√	X	X	X	√	7
Khiari 2017 *(74)*	√	√	√	√	√	√	X	√	X	X	7
Meza 2010 *(77)*	√	√	√	√	√	√	X	X	X	√	7
Jafri 2013 *(78)*	√	√	√	√	√	√	X	X	X	√	7
Meyer 2010 *(81)*	√	√	√	√	X	√	X	√	X	√	7
Fedewa 2019 *(85)*	√	√	√	√	X	√	X	√	X	√	7
Nfonsam 2015 *(99)*	√	√	√	√	√	√	X	X	X	√	7
Stock 2012 *(136)*	√	√	√	√	√	√	X	X	X	√	7
Thirunavukarasu 2010 *(139)*	√	√	√	√	√	√	X	X	X	√	7
Wang 2019 *(147)*	√	√	√	√	√	√	X	X	X	√	7
Yoon 2015 *(153)*	√	√	√	√	√	√	X	X	X	√	7
Zhu 2013 *(157)*	√	√	√	√	√	√	X	X	X	√	7
Melnitchouk 2018 *(86)*	√	√	√	√	X	√	X	√	X	√	7
Al-Zalabani 2020 *(89)*	√	√	√	√	X	√	X	√	X	√	7
Araghi 2019 *(21)*	√	√	√	√	√	√	X	√	X	√	8
Austin 2014 *(23)*	√	√	√	√	√	√	X	√	X	√	8
Aziz 2015 *(24)*	√	√	√	√	√	√	X	√	X	√	8
Boyce 2016 *(28)*	√	√	√	√	√	√	X	√	X	√	8
Brouwer 2018 *(31)*	√	√	√	√	√	√	X	√	X	√	8
Caldarella 2013 *(32)*	√	√	√	√	√	√	X	√	X	√	8
Chambers 2020 *(34)*	√	√	√	√	√	√	X	√	X	√	8
Cheng 2011 *(39)*	√	√	√	√	√	√	X	√	X	√	8
Edwards 2010 *(47)*	√	√	√	√	√	√	X	√	X	√	8
Exarchakou 2019 *(50)*	√	√	√	√	√	√	X	√	X	√	8
Martinsen 2016 *(57)*	√	√	√	√	√	√	X	√	X	√	8

Giddings 2012 *(58)*	√	√	√	√	√	√	X	√	X	√	8
Loomans-Kropp 2019 *(61)*	√	√	√	√	√	√	X	√	X	√	8
Lopez-Abente 2010 *(63)*	√	√	√	√	√	√	X	√	X	√	8
Ladabaum 2014 *(65)*	√	√	√	√	√	√	X	√	X	√	8
Lee 2019 *(71)*	√	√	√	√	√	√	X	√	X	√	8
Jandova 2016 *(75)*	√	√	√	√	√	√	X	√	X	√	8
Li; Lin 2017 *(76)*	√	√	√	√	√	√	X	√	X	√	8
Brenner 2019 *(84)*	√	√	√	√	√	√	X	√	X	√	8
Vuik 2019 *(94)*	√	√	√	√	√	√	X	√	X	√	8
Sheneman 2017 *(105)*	√	√	√	√	√	√	X	√	X	√	8
Vardanjani 2018 *(113)*	√	√	√	√	√	√	X	√	X	√	8
Siegel; Fedewa 2017 *(114)*	√	√	√	√	√	√	X	√	X	√	8
Siegel 2012 *(117)*	√	√	√	√	√	√	X	√	X	√	8
Sierra 2016 *(121)*	√	√	√	√	√	√	X	√	X	√	8
Phipps 2012 *(126)*	√	√	√	√	√	√	X	√	X	√	8
Innos 2018 *(129)*	√	√	√	√	√	√	X	√	X	√	8
Sia 2014 *(131)*	√	√	√	√	√	√	X	√	X	√	8
Sun 2020 *(137)*	√	√	√	√	√	√	X	√	X	√	8
Tawadros 2015 *(138)*	√	√	√	√	√	√	X	√	X	√	8
Troeung 2017 *(141)*	√	√	√	√	√	√	X	√	X	√	8
Wang 2017 *(145)*	√	√	√	√	√	√	X	√	X	√	8
Wang; de Grubb 2017 *(146)*	√	√	√	√	√	√	X	√	X	√	8
Wessler 2010 *(149)*	√	√	√	√	√	√	X	√	X	√	8
Zhou 2015 *(156)*	√	√	√	√	√	√	X	√	X	√	8
Zorzi 2019 *(158)*	√	√	√	√	√	√	X	√	X	√	8
Zorzi 2015 *(159)*	√	√	√	√	√	√	X	√	X	√	8
Crosbie 2018 *(45)*	√	√	√	√	√	√	X	√	X	√	8
Jayarajah 2020 *(69)*	√	√	√	√	√	√	X	√	X	√	8
Katsidzira 2016 *(70)*	√	√	√	√	√	√	X	√	X	√	8

Shafqat 2015 *(95)*	√	√	√	√	√	√	X	√	X	√	8
Shah 2012 *(109)*	√	√	√	√	√	√	X	√	X	√	8
Patel 2016 *(112)*	√	√	√	√	√	√	X	√	X	√	8
Siegel; Medhanie 2019 *(118)*	√	√	√	√	√	√	X	√	X	√	8
Wu 2018 *(150)*	√	√	√	√	√	√	X	√	X	√	8
Siegel 2019 *(88)*	√	√	√	√	√	√	X	√	X	√	8
Wong 2020 *(101)*	√	√	√	√	√	√	X	√	X	√	8

***Explanation of indicators:**

- **Valid methods to identify the condition**: This indicator assessed if the study clearly reported the classification system used to assess colorectal cancer and the site codes included in the analysis.
- **Appropriate statistical analysis**: This indicator assessed if the study clearly reported the numerator and denominator data in incidence calculation and described the analytical methods employed in detail.

Appendix B.8: Results of joinpoint regression analysis

First author and year	**Study period** (Number of years)	**Estimated measure***	**Joinpoint analysis** (Number of time segments/number of joinpoints)	**Providing information on setting parameters in the joinpoint program***
Araghi 2019 *(20)*	10	AAPC	One time segment	Not applicable
Chambers 2020 *(34)*	41	APC (for various periods)	(2-3 / 1-2)	Yes [3,4,6,9]
Clarke 2014 *(43)*	17	APC (for the whole period)	(1/0)	Yes [6]
Crocetti 2010 *(44)*	21	APC (for various periods)	(2/1)	No
Crosbie 2018 *(45)*	36	APC (for various periods)	(1-3/ 0-2)	Yes [6]
Edwards 2010 *(47)*	32	APC (for various periods) and AAPC[2]	(5/ 4)	Yes [6]
Ellis 2018 *(48)*	25	Triannual percentage change (for the whole period)	(1/0)	Yes [3,4,6]
Eser 2018 *(49)*	6	APC (for the whole period)	(1/0)	No
Exarchakou 2019 *(50)*	44	APC (for various periods)	(2-3/ 1-2)	Yes [4,6,9]
Feletto 2019 *(51)*	33	APC (for various periods) and AAPC[3]	(1-4/ 0-3)	Yes [6]
Hasanpour-Heidari 2019 *(52)*	10	AAPC	One time segment	Yes [6]
May 2017 *(54)*	38	APC (for various periods) and AAPC[2]	(3-5/2-4)	Yes [6]
Martinsen 2016 *(57)*	23	APC (for various periods)	(1-2/0-1)	No
Giddings 2012 *(58)*	20	APC (for the whole period)	(1/0)	Yes [3,4,9]
Loomans-Kropp 2019 *(61)*	37	APC (for various periods)	(2-5/1-4)	Yes [4,6]
Ladabaum 2014 *(65)*	15	APC (for various periods)	(1-3/0-2)	Not applicable
Meester 2019 *(67)*	49	AAPC	One time segment	Yes [9]
Li 2017 *(68)*	15	APC (for various periods)	(1-2/0-1)	No
Jayarajah 2020 *(69)*	10	APC (for the whole period)	(1/0)	Yes [9]
Katsidzira 2016 *(70)*	10	AAPC	One time segment	No
Khiari 2017 *(74)*	16	APC (for the whole period)	(1/0)	No
Li; Lin 2017 *(76)*	5	AAPC	One time segment	No
McDevitt 2017 *(79)*	18	APC (for the whole period)	(1/0)	Not applicable
Khachfe 2019 *(80)*	11	APC (for the whole period)	(1/0)	No
Meyer 2010 *(81)*	33	APC (for various periods)	(2/1)	No
Brenner 2017 *(83)*	42	APC (for various periods)	(1-4/0-3)	Yes [3,4,6,9]
Brenner 2019 *(84)*	45	APC (for various periods)	(4-5/3-4)	Yes [3,4,6,9]

Fedewa 2019 *(85)*	16	APC (for the whole period)	(1/0)	No
Melnitchouk 2018 *(86)*	16	APC (for various periods) and AAPC[3]	(1-2/0-1)	Yes [6]
Siegel 2019 *(88)*	10	AAPC[1]	One time segment	Not applicable
Al-Zalabani 2020 *(89)*	21	APC (for various periods)	(3/2)	Yes [6]
Augustus 2018 *(90)*	15	APC (for various periods)	(1-3/0-2)	No
Domati 2014 *(92)*	23	APC (for the whole period)	(1/0)	Yes [6,9]
Vuik 2019 *(94)*	27	APC (for various periods)	(1-2/0-1)	Yes [9]
Shafqat 2015 *(95)*	12	APC (for the whole period)	(1/0)	No
Siegel 2017 *(96)*	14	APC (for various periods) and AAPC[4]	(1-3/0-2)	Yes [4]
Rahman 2015 *(98)*	18	AAPC	One time segment	Not applicable
Van Beck 2018 *(100)*	40	APC (for various periods)	(1-2/0-1)	Yes [9]
Wong 2020 *(101)*	10	APC (for various periods) and AAPC[2]	(1-2/0-1)	Not applicable
Russo 2019 *(104)*	17	APC (for various periods)	(1-2/0-1)	Yes [4,9]
Perdue 2014 *(107)*	20	APC (for various periods)	(1-2/0-1)	Yes [4,6]
Siegel 2020 *(110)*	22	APC (for various periods) and AAPC[3]	(2-5/1-4)	No
Patel 2016 *(112)*	42	APC (for various periods) and AAPC[3]	(2-4/1-3)	Yes [3,6]
Vardanjani 2018 *(113)*	10	APC (for the whole period)	(1/0)	No
Siegel; Fedewa 2017 *(114)*	40	APC (for various periods)	(2-5/1-4)	Yes [6,9]
Siegel 2012 *(117)*	17	APC (for various periods)	(2-3/1-2)	Yes [4,6]
Siegel; Medhanie 2019 *(118)*	10	AAPC	One time segment	Yes [6]
Sung 2019 (*119)*	16/20	APC (for various periods) and AAPC[2]	(1-3/0-2)	Yes [6,9]
Rafiemanesh 2016 *(120)*	6	APC (for the whole period)	(1/0)	Yes [9]
Reggiani-Bonetti 2013 *(124)*	23	APC (for various periods)	(2/1)	Yes [6]
Phipps 2012 *(126)*	10	AAPC	One time segment	Yes [5,6]
Innos 2018 *(129)*	10	APC (for various periods) and AAPC[4]	(1-3/0-2)	No
Siegel 2014 *(130)*	10	APC (for various periods) and AAPC[3]	(1-2/0-1)	Yes [4]
Sia 2014 *(131)*	11	AAPC	One time segment	No
Rejali 2018 *(132)*	12	APC (for various periods) and AAPC[4]	(3/2)	Yes [6]
Sarakarn 2017 *(133)*	24	APC (for various periods) and AAPC[3]	(2/1)	Yes [3,6]
Keum 2014 *(134)*	35	Not reported	Not reported	No
Singh 2014 *(135)*	22	Biannual percentage change (for the whole period)	(1/0)	Not applicable
Sun 2020 *(137)*	55	APC (for various periods) and AAPC[4]	(1-5/0-4)	Yes [4,6,7,9]
Troeung 2017 *(141)*	26	APC (for the whole period)	(1/0)	Yes [6]

Wen 2018 *(148)*	16	Average Biannual percentage change (for the whole period)	(1/0)	Yes [3,4]
Wu 2018 *(150)*	39	APC (for various periods) and AAPC[4]	(1-3/0-2)	Yes [4,6]
Zhang 2018 *(155)*	30	APC (for various periods) and AAPC[4]	(1-2/0-1)	Yes [6,9]
Zhou 2015 *(156)*	5/7	APC (during two predefined periods)	(1/0)	No
Zorzi 2019 *(158)*	12	APC (for various periods)	(1-3/0-2)	Yes [6,9]

Abbreviations: APC: Annual percentage change, AAPC: Average annual percentage change.

Estimated measure/ Definition of APC and AAPC:

1. Study stated a clear explanation of AAPC calculation.
2. Study explicitly stated the difference in calculation between APC and AAPC.
3. Study stated the difference between APC and AAPC by reporting the number of years covered for each measure.
4. Study did not state the difference between APC and AAPC.

Parameters setting:

1. Study specified the used modelling method (Grid search or Hudson's).
2. Study reported the chosen minimum APC difference worth detecting.
3. Study reported the minimum number of joinpoints selected.
4. Study reported the maximum number of joinpoints selected.
5. Study reported the AAPC segment ranges that were selected.
6. Study reported the chosen model selection method.
7. Study reported the method used for estimating confidence intervals.
8. Study reported the chosen autocorrelated errors option.
9. Study reported selecting a linear or log-linear model.

Appendix C: Study Three supplementary materials

Appendix C.1: Clinical characteristics of Saudi CRC cases at diagnosis in the Saudi cancer registry during 1997-2017, overall and by sex

Characteristic	Number (percentage)		
	Total	**Male**	**Female**
	19463	**10688**	**8775**
	(100.0)	**(54.9)**	**(45.1)**
Anatomical site			
Colon	11629 (59.7)	6200 (58.0)	5429 (61.9)
Rectosigmoid	2948 (15.1)	1645 (15.4)	1303 (14.8)
Rectal	4886 (25.1)	2843 (26.6)	2043 (23.3)
Anatomical subsite			
C18.0 Cecum	1233 (6.3)	673 (6.3)	560 (6.4)
C18.1 Appendix	295 (1.5)	131 (1.2)	164 (1.9)
C18.2 Ascending colon	1121 (5.8)	640 (6.0)	481 (5.5)
C18.3 Hepatic flexure of colon	331 (1.7)	179 (1.7)	152 (1.7)
C18.4 Transverse colon	573 (2.9)	329 (3.1)	244 (2.8)
C18.5 Splenic flexure of colon	371 (1.9)	223 (2.1)	148 (1.7)
C18.6 Descending colon	1034 (5.3)	544 (5.1)	490 (5.6)
C18.7 Sigmoid colon	4157 (21.4)	2116 (19.8)	2041 (23.3)
C18.8 Overlapping lesion of colon	602 (3.1)	360 (3.4)	242 (2.8)
C18.9 Colon, NOS	1912 (9.8)	1005 (9.4)	907 (10.3)
C19.9 Rectosigmoid junction	2948 (15.1)	1645 (15.4)	1303 (14.8)
C20.9 Rectum, NOS	4886 (25.1)	2843 (26.6)	2043 (23.3)
Morphology			
Adenocarcinoma, NOS	14997 (77.1)	8165 (76.4)	6832 (77.9)
Mucinous adenocarcinoma	1800 (9.2)	1039 (9.7)	761 (8.7)
Neoplasm, malignant	396 (2.0)	210 (2.0)	186 (2.1)
Adenocarcinoma in tubulovillous	387 (2.0)	204 (1.9)	183 (2.1)
adenoma	354 (1.8)	211 (2.0)	143 (1.6)
Signet ring cell carcinoma	326 (1.7)	172 (1.6)	154 (1.8)
Adenocarcinoma in villous adenoma	307 (1.6)	172 (1.6)	135 (1.5)

Carcinoma, NOS	213 (1.1)	132 (1.2)	81 (0.9)
Adenocarcinoma in adenomatous polyp	158 (0.8)	88 (0.8)	70 (0.8)
Adenocarcinoma, intestinal type	102 (0.5)	59 (0.6)	43 (0.5)
Neuroendocrine carcinoma, NOS	423 (2.2)	236 (2.2)	187 (2.1)
Other			
Grade			
Well-differentiated	2185 (13.2)	1173 (11.0)	1012 (11.5)
Moderately-differentiated	12722 (76.6)	6935 (64.9)	5787 (65.9)
Poorly-differentiated	1551 (9.3)	912 (8.5)	639 (7.3)
Undifferentiated	156 (0.9)	85 (0.8)	71 (0.8)
Missing	2849 (14.6)	1583 (14.8)	1266 (14.4)
Stage of cancer			
Localized	4869 (27.8)	2737 (25.6)	2132 (24.3)
Regional	7533 (42.9)	4193 (39.2)	3340 (38.1)
Distant metastasis	5139 (29.3)	2713 (25.4)	2426 (27.6)
Missing	1922 (9.9)	1045 (9.8)	877 (10.0)
Basis of Diagnosis			
Death certificate only (DCO)	291 (1.5)	160 (1.5)	131 (1.5)
Clinical	18 (0.1)	10 (0.1)	8 (0.1)
Medical Imaging (Radiology)	70 (0.4)	40 (0.4)	30 (0.3)
Surgery (Visualization without Biopsy)	3 (0.0)	3 (0.0)	0 (0.0)
Cytology/Hematological	77 (0.4)	47 (0.4)	30 (0.3)
Histology of metastases	303 (1.6)	139 (1.3)	164 (1.9)
Histology of primary	18628 (96.1)	10255 (95.9)	8373 (95.4)
Missing	73 (0.4)	34 (0.3)	39 (0.4)

Note: NOS: Not otherwise specified. Percentage of cases are shown in brackets.

Appendix C.2: Supplementary methods file

Population statistics

The General Authority of Statistics (GASTAT) provided population data for 17 (5-year) age groups for 1997-2017, excluding 1997, 1998, 2001, 2002, and 2003. We used the available data to calculate the annual growth rate (AGR) and then used it to estimate the population statistics for the missing years. For a more rigorous AGR calculation, the AGR was calculated for each sex and all 17 age groups. For the period 2000-2004, we derived the AGR by dividing the 2004 population by that of 2000 for each sex and age group, computing the log of the result, dividing the log output by 4, and then exponentiating the final output. We then applied this rate to estimate populations for 2001-2003 sequentially. Similarly, we derived a new AGR for the years before 1999 using the 1999 and 2000 data. We divided 1999 population figures by the new AGR to obtain 1998 values, then repeated the process for 1998 figures to obtain 1997 population data.

Joinpoint regression

Joinpoint regression employs a grid search technique to fit a series of joined straight lines to the natural logarithm of observed rates, while permutation tests determine the best-fitting model. Initially, the model assumes zero joinpoints and iteratively adds more if found significant, thereby estimating the annual percentage change (APC) for each segment and the overall average annual percentage change (AAPC) along with 95% confidence intervals. The APC is calculated from the slope of the log-linear model and represents the constant percentage change in rates from one year to the next. The AAPC summarizes the trend across the entire study period (1997-2017) as a weighted average of all APCs, with weights corresponding to the length of each APC interval [1]. The APC and AAPC were considered significantly different from zero at p-values < 0.05, using a two-sided test. In this study, the joinpoint software was set to consider between zero and three joinpoints based on the 21-year analysis period [2]. We assumed homoscedasticity for random errors and applied the ordinary least squares method for regression estimates, with confidence intervals determined via the software's default parametric method.

References

1. Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute. Joinpoint Regression Program [computer software]. Version 4.9.1.0. NCI, 2022. Available from: https://surveillance.cancer.gov/joinpoint/
2. National Cancer Institute. Joinpoint Trend Analysis Software: Joinpoint Help system, Number of Joinpojnts. [Online]. 2024 [Accessed 20th February 2024]. Available from: https://surveillance.cancer.gov/help/joinpoint/setting-parameters/method-and-parameters-tab/number-of-joinpoints

Appendix C.3: Characteristics of patients with known and unknown disease stage at CRC diagnosis

Characteristic	Known stage N (%)	Missing stage N (%)
	17541 (90.1)	1922 (9.9)
Age in years		
0-39	1981 (11.3)	208 (10.8)
40-49	3039 (17.3)	270 (14.0)
50-59	4335 (24.7)	417 (21.7)
60-69	4111 (23.4)	457 (23.8)
70-79	2872 (16.4)	314 (16.3)
80+	1196 (6.8)	252 (13.1)
Mean age (SD)	57.9 (14.8)	60.4 (16.5)
Sex		
Female	7898 (45.0)	877 (45.6)
Male	9643 (54.9)	1045 (54.4)
Marital status		
Married	15847 (90.3)	1781 (92.7)
Unmarried	1694 (9.7)	141 (7.3)
Region		
Riyadh	5370 (30.6)	516 (26.8)
Eastern	2992 (17.1)	308 (16.0)
Makkah	4350 (24.8)	408 (21.2)
Madina	940 (5.4)	185 (9.6)
Asir	1257 (7.2)	137 (7.1)
Jazan	316 (1.8)	37 (1.9)
Najran	168 (1.0)	22 (1.1)
Hail	332 (1.9)	69 (3.6)
Qassim	814 (4.6)	100 (5.2)
Baha	255 (1.5)	26 (1.4)
Jouf	145 (0.8)	24 (1.2)
Northern	112 (0.6)	23 (1.2)
Tabuk	355 (2.0)	41 (2.1)

Anatomical site		
Colon	10540 (60.1)	1089 (56.7)
Rectosigmoid	2720 (15.5)	228 (11.9)
Rectal	4281 (24.4)	605 (31.5)

Note: N: Number; SD: Standard deviation. Percentage of cases are shown in brackets.

Appendix C.4: Annual number of CRC cases diagnosed per age group, overall and by sex

Sex	Year																					
All	**1997**	**1998**	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**Total**
0-39	63	42	59	54	80	81	80	94	97	80	112	114	120	125	139	118	155	137	140	150	149	2189
40-49	36	46	44	63	80	96	105	123	143	146	159	171	215	217	228	219	239	215	239	272	253	3309
50-59	55	53	86	100	87	85	125	127	175	165	187	224	266	278	317	320	393	376	429	449	455	4752
60-69	66	80	94	83	102	106	144	167	182	200	200	205	243	258	295	294	332	326	381	367	443	4568
70-79	43	47	62	49	63	85	75	107	131	114	140	148	191	188	189	226	266	230	255	285	292	3186
80+	18	23	28	22	40	45	37	47	57	61	69	70	94	92	99	103	87	96	100	133	127	1448
Total	281	291	373	371	452	498	566	665	785	766	867	932	1129	1158	1267	1280	1472	1380	1544	1656	1719	19452
Males	**1997**	**1998**	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**Total**
0-39	34	25	20	21	34	41	46	50	42	40	55	65	63	53	72	63	71	64	68	83	72	1082
40-49	15	26	22	37	36	55	57	66	74	73	72	74	105	104	112	110	113	103	126	147	133	1660
50-59	31	29	50	53	45	41	67	73	96	82	97	114	144	132	169	184	197	218	246	247	236	2551
60-69	33	42	52	47	54	64	86	93	124	108	129	113	147	142	180	169	176	186	203	205	227	2580
70-79	23	30	31	27	34	42	49	69	84	76	86	80	106	117	111	130	163	147	168	193	178	1944
80+	16	15	15	12	26	30	18	24	35	37	36	43	61	57	60	58	51	58	62	76	73	863
Total	152	167	190	197	229	273	323	375	455	416	475	489	626	605	704	714	771	776	873	951	919	10680
Females	**1997**	**1998**	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**Total**
0-39	29	17	39	33	46	40	34	44	55	40	57	49	57	72	67	55	84	73	72	67	77	1107
40-49	21	20	22	26	44	41	48	57	69	73	87	97	110	113	116	109	126	112	113	125	120	1649
50-59	24	24	36	47	42	44	58	54	79	83	90	110	122	146	148	136	196	158	183	202	219	2201
60-69	33	38	42	36	48	42	58	74	58	92	71	92	96	116	115	125	156	140	178	162	216	1988
70-79	20	17	31	22	29	43	26	38	47	38	54	68	85	71	78	96	103	83	87	92	114	1242
80+	2	8	13	10	14	15	19	23	22	24	33	27	33	35	39	45	36	38	38	57	54	585
Total	129	124	183	174	223	225	243	290	330	350	392	443	503	553	563	566	701	604	671	705	800	8772

Appendix C.5: Annual number of CRC cases with localized tumors diagnosed per age group, overall and by sex

Sex	Year																					
All	**1997**	**1998**	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**Total**
0-49	29	18	28	33	28	31	41	54	49	55	74	76	68	88	75	58	88	84	82	113	104	1276
50-74	54	33	60	51	49	54	91	89	97	98	106	108	149	185	164	184	237	216	261	247	285	2818
75+	12	8	15	6	12	19	25	24	23	27	35	28	47	49	53	55	47	42	74	85	86	772
Total	95	59	103	90	89	104	157	167	169	180	215	212	264	322	292	297	372	342	417	445	475	4866
Male	**1997**	**1998**	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**Total**
0-49	14	12	14	11	8	18	20	32	24	30	40	46	43	27	39	30	39	38	46	70	55	656
50-74	31	15	37	32	27	32	55	45	68	60	68	52	86	98	86	108	128	126	150	152	168	1624
75+	11	6	6	3	9	10	14	16	12	18	21	16	21	31	32	31	32	23	46	51	45	454
Total	56	33	57	46	44	60	89	93	104	108	129	114	150	156	157	169	199	187	242	273	268	2734
Female	**1997**	**1998**	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**Total**
0-49	15	6	14	22	20	13	21	22	25	25	34	30	25	61	36	28	49	46	36	43	49	620
50-74	23	18	23	19	22	22	36	44	29	38	38	56	63	87	78	76	109	90	111	95	117	1194
75+	1	2	9	3	3	9	11	8	11	9	14	12	26	18	21	24	15	19	28	34	41	318
Total	39	26	46	44	45	44	68	74	65	72	86	98	114	166	135	128	173	155	175	172	207	2132

Appendix C.6: Annual number of CRC cases with regional tumors diagnosed per age group, overall and by sex

Sex	Year																					
All	**1997**	**1998**	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**Total**
0-49	37	39	43	43	75	89	81	71	93	91	109	112	144	134	143	156	141	132	146	163	168	2210
50-74	41	57	86	74	98	101	122	131	170	191	182	208	234	224	288	319	345	320	392	407	429	4419
75+	5	19	22	16	21	39	13	28	31	25	43	41	64	52	53	60	60	87	54	96	72	901
Total	83	115	151	133	194	229	216	230	294	307	334	361	442	410	484	535	546	539	592	666	669	7530
Male	**1997**	**1998**	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**Total**
0-49	19	22	18	24	35	47	51	41	47	45	55	55	66	70	79	83	73	63	72	93	87	1145
50-74	18	36	53	32	48	51	64	70	103	110	107	109	142	120	169	195	181	189	224	251	217	2489
75+	4	13	12	10	14	17	9	17	18	15	21	25	39	37	32	39	39	57	36	59	44	557

Total	41	71	83	66	97	115	124	128	168	170	183	189	247	227	280	317	293	309	332	403	348	4191
Female	**1997**	**1998**	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**Total**
0-49	18	17	25	19	40	42	30	30	46	46	54	57	78	64	64	73	68	69	74	70	81	1065
50-74	23	21	33	42	50	50	58	61	67	81	75	99	92	104	119	124	164	131	168	156	212	1930
75+	1	6	10	6	7	22	4	11	13	10	22	16	25	15	21	21	21	30	18	37	28	344
Total	42	44	68	67	97	114	92	102	126	137	151	172	195	183	204	218	253	230	260	263	321	3339

Appendix C.7: Annual number of CRC cases with distant tumors diagnosed per age group, overall and by sex

Sex	**Year**																					
All	**1997**	**1998**	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**Total**
0-49	18	20	13	20	40	35	41	71	74	62	64	84	93	96	113	96	117	120	120	127	110	1534
50-74	34	38	31	35	48	62	64	94	110	108	124	166	160	185	206	193	218	237	246	256	287	2902
75+	7	9	7	13	15	14	16	19	33	19	35	35	48	42	41	49	54	41	65	66	74	702
Total	59	67	51	68	103	111	121	184	217	189	223	285	301	323	360	338	389	398	431	449	471	5138
Male	**1997**	**1998**	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**Total**
0-49	8	12	8	10	22	14	19	33	35	29	24	33	47	49	48	42	49	56	57	59	52	706
50-74	20	19	13	16	23	37	40	59	67	53	72	91	87	98	115	103	113	136	131	128	149	1570
75+	6	6	5	7	9	9	8	10	22	11	19	24	31	28	22	24	34	25	44	46	47	437
Total	34	37	26	33	54	60	67	102	124	93	115	148	165	175	185	169	196	217	232	233	248	2713
Female	**1997**	**1998**	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**Total**
0-49	10	8	5	10	18	21	22	38	39	33	40	51	46	47	65	54	68	64	63	68	58	828
50-74	14	19	18	19	25	25	24	35	43	55	52	75	73	87	91	90	105	101	115	128	138	1332
75+	1	3	2	6	6	5	8	9	11	8	16	11	17	14	19	25	20	16	21	20	27	265
Total	25	30	25	35	49	51	54	82	93	96	108	137	136	148	175	169	193	181	199	216	223	2425

Appendix C.8: Overall annual frequency and percentage of CRC cases diagnosed between 1997 and 2017

Diagnostic date	Frequency (%)	Diagnostic date	Frequency (%)
1997	281 (1.4)	**2008**	932 (4.8)
1998	292 (1.5)	**2009**	1129 (5.8)
1999	373 (1.9)	**2010**	1158 (5.9)
2000	371 (1.9)	**2011**	1267 (6.5)
2001	452 (2.3)	**2012**	1281 (6.6)
2002	500 (2.6)	**2013**	1472 (7.6)
2003	566 (2.9)	**2014**	1380 (7.1)
2004	665 (3.4)	**2015**	1545 (7.9)
2005	785 (4.0)	**2016**	1661 (8.5)
2006	766 (3.9)	**2017**	1720(8.8)
2007	867 (4.5)		

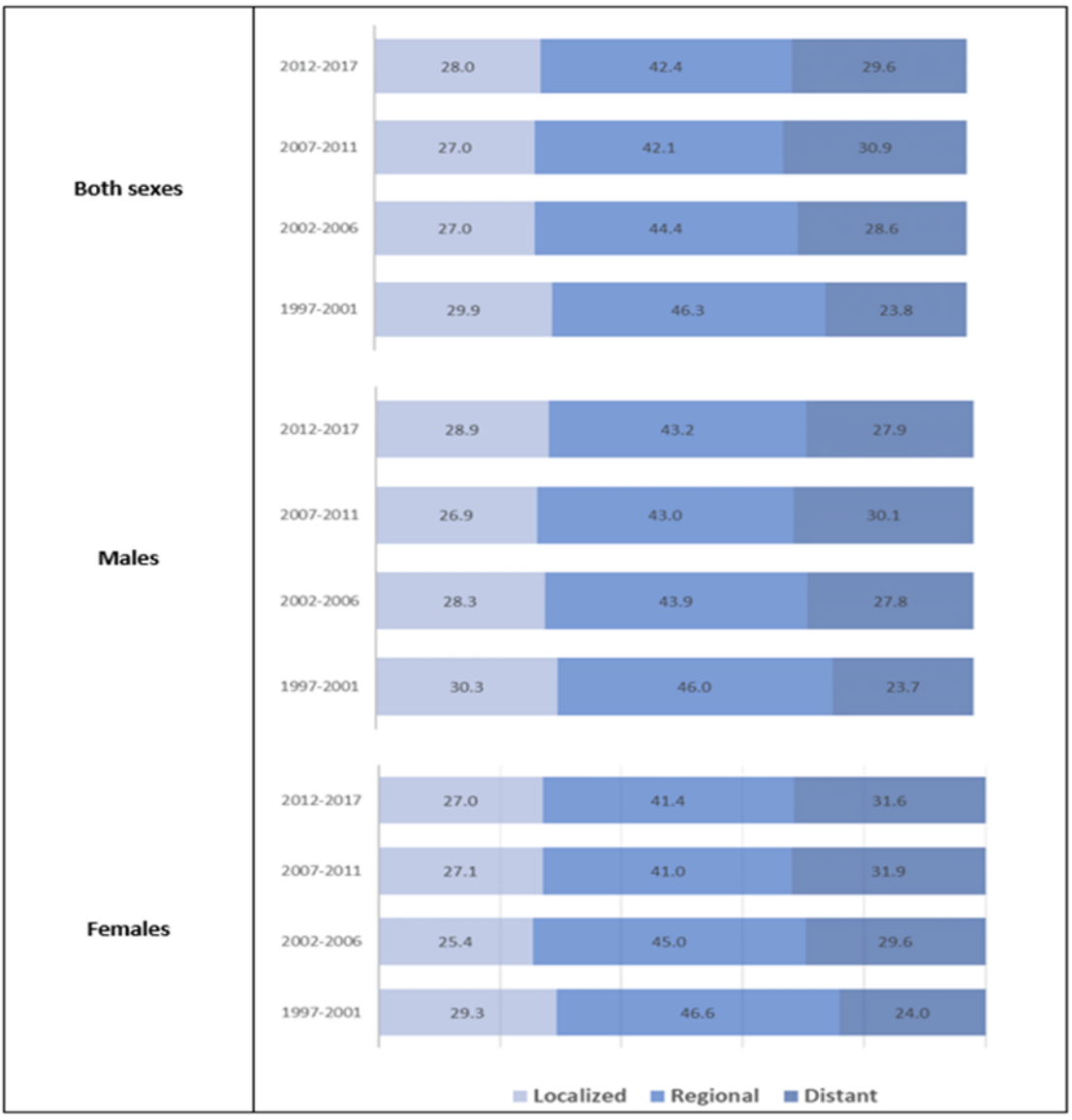
Appendix C.9: Demographic characteristics of Saudi CRC cases at diagnosis in the Saudi Cancer Registry during 1997-2017, overall and by sex

Characteristic	Number (percentage)		
	Total	**Male**	**Female**
	19463 (100.0)	**10688 (54.9)**	**8775 (45.1)**
Age			
Median (IQR)	58 (48-69)	60 (49-70)	57 (47-67)
0-19	82 (0.4)	42 (0.4)	40 (0.5)
20-24	162 (0.8)	84 (0.8)	78 (0.9)
25-29	380 (2.0)	183 (1.7)	197 (2.2)
30-34	597 (3.1)	297 (2.8)	300 (3.4)
35-39	968 (5.0)	476 (4.5)	492 (5.6)
40-44	1359 (7.0)	690 (6.5)	669 (7.6)
45-49	1950 (10.0)	970 (9.1)	980 (11.2)
50-54	2327 (12.0)	1179 (11.0)	1148 (13.1)
55-59	2425 (12.5)	1372 (12.8)	1053 (12.0)
60-64	2377 (12.2)	1286 (12.0)	1091 (12.4)
65-69	2191 (11.3)	1294 (12.1)	897 (10.2)
70-74	1868 (9.6)	1132 (10.6)	736 (8.4)
75-79	1318 (6.8)	812 (7.6)	506 (5.8)

80+	1448 (7.4)	863 (8.1)	585 (6.7)
Missing	11 (0.1)	8 (0.1)	3 (0.0)
Marital status			
Single	867 (4.5)	532 (5.0)	335 (4.3)
Married	15417 (79.2)	8876 (83.0)	6541 (74.5)
Divorced	145 (0.7)	19 (0.2)	126 (1.4)
Widowed	823 (4.2)	46 (0.4)	777 (8.9)
Missing	2211 (11.4)	1215 (11.4)	996 (11.4)
Region			
Riyadh	5886 (30.5)	3162 (29.6)	2724 (31.0)
Eastern	3300 (17.1)	1843 (17.2)	1457 (16.6)
Makkah	4758 (24.7)	2650 (24.8)	2108 (24.0)
Madina	1125 (5.8)	639 (6.0)	486 (5.5)
Asir	1394 (7.2)	765 (7.2)	629 (7.2)
Jazan	353 (1.8)	197 (1.8)	156 (1.8)
Najran	190 (1.0)	99 (0.9)	91 (1.0)
Hail	401 (2.1)	213 (2.0)	188 (2.1)
Qassim	914 (4.7)	493 (4.6)	421 (4.8)
Baha	281 (1.5)	129 (1.2)	152 (1.7)
Jouf	169 (0.9)	95 (0.9)	74 (0.8)
Northern	135 (0.7)	69 (0.6)	66 (0.8)
Tabuk	396 (2.1)	231 (2.2)	165 (1.9)
Missing	161 (0.8)	103 (1.0)	58 (0.7)

Note: IQR: Interquartile range. Percentage of cases are shown in brackets.

Appendix C.10: Percentage stage distribution at diagnosis of CRC per calendar period in Saudi Arabia, overall and by sex



Appendix C.11: Annual age-standardized incidence rates of CRC per 100,000 person-years in men and women in Saudi Arabia (1997-2017), overall and by stage at diagnosis

Characteristic	Year																				
Overall ASR	**1997**	**1998**	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**
Total	4.0	4.3	5.3	5.0	5.3	5.4	5.6	6.0	7.0	6.7	7.4	7.7	9.2	9.3	10.0	10.2	11.5	10.7	11.9	12.5	12.9
Male	4.0	4.5	5.3	5.3	5.4	5.8	6.4	7.0	8.4	7.5	8.4	8.2	10.4	10.1	11.4	11.4	12.2	12.3	13.6	14.5	14.0
Female	4.2	4.1	5.4	4.7	5.3	5.0	4.7	5.1	5.6	5.9	6.4	7.2	8.1	8.6	8.8	9.0	10.7	9.2	10.2	10.5	11.9
ASR by stage Total																					
Localized	1.4	0.9	1.4	1.2	1.1	1.1	1.6	1.5	1.5	1.6	1.8	1.8	2.2	2.6	2.4	2.4	3.0	2.7	3.3	3.4	3.6
Regional	1.1	1.7	2.1	1.8	2.3	2.5	2.1	2.1	2.6	2.7	2.8	2.9	3.6	3.3	3.8	4.2	4.2	4.2	4.5	5.1	4.9
Distant	0.9	1.0	0.8	0.9	1.2	1.2	1.2	1.6	1.9	1.6	1.9	2.3	2.5	2.6	2.8	2.6	3.0	3.0	3.3	3.3	3.6
Male																					
Localized	1.5	0.9	1.6	1.3	1.1	1.3	1.8	1.7	1.9	1.9	2.3	1.9	2.5	2.7	2.6	2.8	3.3	3.0	3.9	4.2	4.1
Regional	1.0	2.0	2.3	1.7	2.2	2.4	2.4	2.4	3.0	3.1	3.1	3.1	4.1	3.7	4.5	5.0	4.5	4.9	5.1	6.1	5.1
Distant	0.9	1.0	0.8	0.9	1.2	1.3	1.4	1.9	2.3	1.6	2.1	2.5	2.8	2.9	2.9	2.7	3.2	3.3	3.6	3.5	3.9
Female																					
Localized	1.2	0.8	1.4	1.1	1.0	1.0	1.3	1.3	1.1	1.2	1.4	1.6	1.9	2.5	2.2	2.1	2.7	2.4	2.7	2.6	3.1
Regional	1.3	1.5	2.0	1.9	2.3	2.5	1.8	1.8	2.1	2.3	2.5	2.8	3.1	2.9	3.2	3.4	3.9	3.5	3.9	4.0	4.8
Distant	0.9	1.0	0.8	1.0	1.2	1.1	1.0	1.4	1.6	1.6	1.7	2.2	2.2	2.3	2.6	2.6	2.9	2.7	3.0	3.2	3.4

Appendix C.12: Annual age-specific incidence rates of CRC per 100,000 person-years in Saudi Arabia (1997-2017), overall and by sex

Characteristic	Year																				
	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Total																					
0-39	0.5	0.4	0.5	0.4	0.6	0.7	0.7	0.8	0.8	0.6	0.9	0.9	0.9	0.9	1.0	0.8	1.1	0.9	1.0	1.0	1.0
40-49	4.0	5.0	4.3	5.7	6.3	6.6	6.3	6.5	7.3	7.3	7.8	8.2	10.1	10.0	10.4	9.9	10.7	9.5	10.4	11.7	10.7
50-59	9.9	9.4	14.1	15.2	11.3	9.5	12.0	10.5	14.0	12.9	14.3	16.8	19.5	20.0	22.6	22.5	27.4	26.0	29.2	30.2	30.1
60-69	14.4	17.6	21.7	19.9	22.1	20.7	25.3	26.3	27.9	29.9	29.2	29.3	34.0	35.6	40.2	39.6	44.2	42.9	49.6	47.2	56.0
70-79	20.8	22.2	26.8	19.1	23.8	31.0	26.4	36.3	43.2	36.8	44.1	45.6	57.7	56.6	56.1	66.2	76.8	65.6	71.7	79.1	79.5
80+	16.3	20.5	23.1	16.9	30.1	33.2	26.7	33.0	39.0	40.8	45.1	44.7	58.8	57.4	60.9	62.5	52.1	56.7	58.3	76.5	71.7
Male																					
0-39	0.6	0.4	0.3	0.3	0.5	0.7	0.7	0.8	0.7	0.6	0.8	1.0	0.9	0.7	1.0	0.9	1.0	0.9	0.9	1.1	0.9
40-49	3.3	5.6	4.4	6.7	5.7	7.6	6.9	6.9	7.5	7.2	7.0	7.0	9.7	9.4	10.0	9.7	9.8	8.9	10.7	12.4	11.0
50-59	11.7	10.7	17.1	16.6	12.0	9.2	12.8	11.8	15.0	12.5	14.5	16.6	20.5	18.4	23.4	25.0	26.5	29.1	32.4	32.2	30.2
60-69	13.3	17.3	22.8	21.8	22.9	24.8	30.2	29.4	38.0	32.3	37.7	32.2	41.0	38.8	48.5	45.0	46.4	48.5	52.4	52.3	56.9
70-79	16.4	21.3	21.6	18.5	23.4	29.0	34.0	48.2	56.8	50.1	55.4	50.3	65.1	71.6	66.9	77.1	95.5	85.0	95.8	108.5	98.1
80+	24.0	22.2	21.1	16.0	35.6	42.2	26.0	35.5	50.2	51.7	49.1	57.3	79.4	73.9	76.6	72.9	63.3	71.0	74.9	90.6	85.4
Female																					
0-39	0.5	0.3	0.6	0.5	0.7	0.6	0.6	0.7	0.9	0.6	0.9	0.7	0.8	1.0	1.0	0.8	1.2	1.0	1.0	0.9	1.0
40-49	4.7	4.3	4.3	4.6	6.9	5.6	5.8	6.1	7.2	7.4	8.7	9.5	10.5	10.7	10.9	10.1	11.5	10.1	10.1	11.0	10.4
50-59	8.3	8.2	11.4	13.9	10.8	9.8	11.2	9.1	13.0	13.3	14.2	16.9	18.4	21.8	21.9	19.9	28.3	22.5	25.8	28.2	30.0
60-69	15.6	18.1	20.6	17.9	21.2	16.6	20.3	23.1	17.7	27.5	20.8	26.4	27.0	32.4	31.7	34.1	42.0	37.2	46.8	42.1	55.1
70-79	29.9	24.1	35.2	19.9	24.3	33.3	18.6	25.0	30.3	24.0	33.4	41.2	50.5	42.1	45.7	55.5	58.7	46.7	48.3	50.4	61.3
80+	4.6	17.9	26.1	18.0	23.4	23.3	27.4	30.7	28.8	30.7	41.4	33.2	39.8	42.1	46.3	52.8	41.6	43.4	42.8	63.4	58.9

Appendix C.13: Annual age-specific incidence rates of localized CRC per 100,000 person-years in Saudi Arabia (1997-2017), overall and by sex

Characteristic	Year																				
	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Total																					
0-49	0.2	0.1	0.2	0.2	0.2	0.2	0.3	0.4	0.3	0.4	0.5	0.5	0.4	0.5	0.5	0.4	0.5	0.5	0.5	0.7	0.6
50-74	4.8	2.9	5.1	4.1	3.5	3.4	5.1	4.4	4.7	4.6	4.9	4.8	6.6	8.0	7.0	7.8	9.9	8.9	10.6	10.0	11.3
75+	6.1	4.0	7.2	2.7	5.2	8.4	10.1	9.3	8.7	10.0	12.6	9.9	16.2	17.0	18.1	18.5	15.6	13.7	23.8	27.6	26.8
Male																					
0-49	0.2	0.2	0.2	0.2	0.1	0.3	0.3	0.5	0.3	0.4	0.5	0.6	0.5	0.3	0.5	0.4	0.5	0.4	0.5	0.8	0.6
50-74	5.2	2.5	6.1	5.1	3.9	4.0	6.1	4.4	6.4	5.6	6.1	4.6	7.4	8.3	7.2	8.9	10.4	10.2	12.0	12.0	13.0
75+	8.9	4.8	4.7	2.3	7.0	7.9	11.2	12.9	9.4	13.8	15.7	11.7	15.0	22.2	22.5	21.5	21.8	15.5	30.5	33.2	28.7
Female																					
0-49	0.2	0.1	0.2	0.3	0.3	0.2	0.3	0.3	0.4	0.3	0.5	0.4	0.3	0.8	0.5	0.4	0.6	0.6	0.4	0.5	0.6
50-74	4.3	3.3	4.0	3.1	3.2	2.8	4.0	4.4	2.8	3.6	3.5	5.1	5.6	7.7	6.8	6.6	9.3	7.6	9.3	7.8	9.5
75+	1.4	2.7	10.9	3.3	3.0	8.1	9.0	6.0	8.0	6.4	9.8	8.2	17.4	12.1	13.9	15.7	9.7	12.1	17.6	21.1	24.9

Appendix C.14: Annual age-specific incidence rates of regional CRC per 100,000 person-years in Saudi Arabia (1997-2017), overall and by sex

Characteristic	Year																				
	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Total																					
0-49	0.3	0.3	0.3	0.3	0.5	0.6	0.6	0.5	0.6	0.6	0.7	0.7	0.9	0.8	0.9	0.9	0.8	0.8	0.9	0.9	1.0
50-74	3.6	5.0	7.3	6.0	7.0	6.4	6.8	6.5	8.2	9.0	8.3	9.3	10.3	9.7	12.3	13.5	14.4	13.2	16.0	16.4	17.0
75+	2.6	9.6	10.5	7.2	9.2	16.4	5.3	10.9	11.7	9.2	15.5	14.5	22.1	18.0	18.1	20.2	19.9	28.4	17.4	30.5	22.4
Male																					
0-49	0.3	0.3	0.3	0.3	0.5	0.7	0.7	0.6	0.6	0.6	0.7	0.7	0.8	0.9	0.9	1.0	0.9	0.7	0.8	1.1	1.0
50-74	3.0	6.0	8.7	5.1	6.8	6.4	7.1	6.9	9.8	10.2	9.7	9.6	12.2	10.1	14.1	16.0	14.7	15.2	17.9	19.8	16.8
75+	3.2	10.5	9.5	7.7	10.9	13.4	7.2	13.8	14.1	11.5	15.7	18.2	27.8	26.5	22.5	27.0	26.6	38.3	23.8	38.5	28.1
Female																					
0-49	0.3	0.3	0.4	0.3	0.6	0.6	0.4	0.4	0.6	0.6	0.7	0.7	1.0	0.8	0.8	0.9	0.8	0.8	0.9	0.8	0.9
50-74	4.3	3.9	5.7	6.8	7.2	6.4	6.5	6.0	6.5	7.7	7.0	9.0	8.2	9.2	10.4	10.7	14.0	11.1	14.0	12.9	17.2
75+	1.4	8.1	12.1	6.5	6.9	19.8	3.3	8.2	9.5	7.1	15.3	10.9	16.8	10.1	13.9	13.7	13.5	19.1	11.3	22.9	17.0

Appendix C.15: Annual age-specific incidence rates of distant CRC per 100,000 person-years in Saudi Arabia (1997-2017), overall and by sex

Characteristic	Year																				
	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Total																					
0-49	0.1	0.2	0.1	0.1	0.3	0.3	0.3	0.5	0.5	0.4	0.4	0.5	0.6	0.6	0.7	0.6	0.7	0.7	0.7	0.7	0.6
50-74	3.0	3.3	2.6	2.8	3.4	3.9	3.6	4.6	5.3	5.1	5.7	7.4	7.0	8.0	8.8	8.1	9.1	9.8	10.0	10.3	11.4
75+	3.6	4.5	3.3	5.9	6.5	5.9	6.5	7.4	12.4	7.0	12.6	12.3	16.6	14.6	14.0	16.5	17.9	13.4	20.9	21.0	23.0
Male																					
0-49	0.1	0.2	0.1	0.1	0.3	0.2	0.3	0.5	0.5	0.4	0.3	0.4	0.6	0.6	0.6	0.5	0.6	0.6	0.7	0.7	0.6
50-74	3.4	3.2	2.1	2.6	3.3	4.7	4.5	5.8	6.3	4.9	6.5	8.0	7.5	8.3	9.6	8.5	9.2	11.0	10.4	10.1	11.5
75+	4.9	4.8	3.9	5.4	7.0	7.1	6.4	8.1	17.2	8.4	14.2	17.5	22.1	20.1	15.5	16.6	23.2	16.8	29.1	30.0	30.0
Female																					
0-49	0.2	0.1	0.1	0.1	0.3	0.3	0.3	0.5	0.5	0.4	0.5	0.7	0.6	0.6	0.8	0.7	0.8	0.8	0.8	0.8	0.7
50-74	2.6	3.5	3.1	3.1	3.6	3.2	2.7	3.5	4.2	5.2	4.8	6.8	6.5	7.7	8.0	7.8	9.0	8.5	9.6	10.6	11.2
75+	1.4	4.0	2.4	6.5	5.9	4.5	6.5	6.7	8.0	5.7	11.2	7.5	11.4	9.4	12.6	16.4	12.9	10.2	13.2	12.4	16.4

Appendix D: Study Four supplementary materials

Appendix D.1: Supplemental methods

Fast and Frugal Trees (FFT):

Fast and Frugal Trees (FFT) is a specialized decision tree model designed to make quick, efficient decisions with limited resources. FFT analysis follows a heuristic approach, optimizing cues based on metrics such as classification accuracy, sensitivity, or specificity. The tree-building process starts by selecting the cues (predictor) with the highest accuracy. This predictor is then used to create the first decision node, and the process is repeated recursively until no further improvement in classification accuracy is possible. The result is a simple, interpretable tree that makes classifications based on a small number of decision rules (1). To implement FFT analysis, we used the "FFTrees" package in R, maintaining the package's default settings, specifically, goal.chase = NULL, max.levels = NULL, and sens.w = 0.5.

Handling of missing covariate data:

Three covariates had missing data. Marital status had the highest percentage of missing values (n=1658, 9.5%), followed by region (n=135, 0.8%) and age at diagnosis (n=7, 0.04%). While we were unable to empirically verify if the missing values of covariates were missing at random (MAR), we operated under the assumption that they were MAR. Consequently, we handled the missingness using the multiple imputation by chained equations (MICE) technique. Implemented in R, we generated ten imputed datasets. Each of these datasets underwent up to 50 iterations. The imputation method employed was Predictive Mean Matching, a non-parametric technique known for generating plausible imputations, as the replaced values are actual observed responses in the dataset. To ensure the reproducibility of our results, a random seed of 500 was set (2). Rubin's Rules (3) were used to combine statistical estimates (e.g., coefficients, standard errors) from analyses performed on each separate imputed dataset to yield a single combined estimate that incorporates the uncertainty introduced by the imputation process. For the FFT analysis, we conducted separate analyses on ten imputed datasets. Upon comparing the decision splits across these datasets, they demonstrated consistent results. Therefore, we reported the model results based on the first imputed dataset.

Imputation of missing outcome data in sensitivity analysis:

There were 1,922 (9.9%) CRC patients with missing stage information. In primary analysis, we performed a complete stage-data analysis to prevent potential bias introduction associated with outcome imputation.

Examination of the pattern of missingness throughout the study period revealed fluctuations over time, with the highest percentage of missing stage data observed in the earliest calendar period (Appendix D.7). When comparing characteristics of patients with and without missing stage data (Appendix D.2), the eldest patients (80+) had markedly lower stage data completeness. We, therefore, conducted a sensitivity analysis by simultaneously imputing missing stage data and covariates using multiple imputations with chained equations, generating ten datasets.

References

1. Phillips ND, Neth H, Woike JK, Gaissmaier W. FFTrees: A toolbox to create, visualize, and evaluate fast-and-frugal decision trees. Judgment and Decision Making. 2017;12(4):344-68.

2. van Buuren, S. Flexible Imputation of Missing Data. CRC Press; 2018.

3. Rubin DB. Multiple imputation for nonresponse in surveys. New York: John Wiley, 1987.

Appendix D.2: Characteristics of patients with known and unknown disease stage at CRC diagnosis

Characteristic	Known stage N (%)	Missing stage N (%)
	17541 (90.1)	1922 (9.9)
Age in years		
0-39	1981 (11.3)	208 (10.8)
40-49	3039 (17.3)	270 (14.0)
50-59	4335 (24.7)	417 (21.7)
60-69	4111 (23.4)	457 (23.8)
70-79	2872 (16.4)	314 (16.3)
80+	1196 (6.8)	252 (13.1)
Mean age (SD)	57.9 (14.8)	60.4 (16.5)
Sex		
Female	7898 (45.0)	877 (45.6)
Male	9643 (54.9)	1045 (54.4)
Marital status		
Married	15847 (90.3)	1781 (92.7)
Unmarried	1694 (9.7)	141 (7.3)
Region		
Riyadh	5370 (30.6)	516 (26.8)
Eastern	2992 (17.1)	308 (16.0)
Makkah	4350 (24.8)	408 (21.2)
Madina	940 (5.4)	185 (9.6)
Asir	1257 (7.2)	137 (7.1)
Jazan	316 (1.8)	37 (1.9)
Najran	168 (1.0)	22 (1.1)
Hail	332 (1.9)	69 (3.6)
Qassim	814 (4.6)	100 (5.2)
Baha	255 (1.5)	26 (1.4)
Jouf	145 (0.8)	24 (1.2)
Northern	112 (0.6)	23 (1.2)
Tabuk	355 (2.0)	41 (2.1)
Anatomical site		
Colon	10540 (60.1)	1089 (56.7)

Rectosigmoid	2720 (15.5)	228 (11.9)
Rectal	4281 (24.4)	605 (31.5)

Note: N: Number; SD: Standard deviation.

Appendix D.3: Sensitivity analysis using multiple imputation for stage data in logistic regression. Adjusted odds ratios for late versus early-stage CRC presentation (N=19,463)

Variable	OR (95%CI)
Age in years	
0-39	1.09 (0.98, 1.21)
40- 49	1.12 (1.02, 1.22)
50-59	1.00 *P*=0.018
60- 69	1.02 (0.93, 1.12)
70-79	1.09 (0.98, 1.20)
80+	1.08 (0.93, 1.22)
Sex	
Male	1.00 *P*=0.001
Female	1.12 (1.05, 1.18)
Marital status	
Married	1.00 *P*=0.08
Unmarried	1.06 (0.96, 1.17)
Region	
Riyadh	1.00 *P*<0.0001
Eastern	1.11 (1.01, 1.21)
Makkah	0.91 (0.83, 1.00)
Madina	0.82 (0.65, 1.00)
Asir	0.91 (0.76, 1.06)
Jazan	0.79 (0.53, 1.06)
Najran	1.10 (0.76, 1.44)
Hail	1.16 (0.93, 1.38)
Qassim	1.06 (0.90, 1.22)
Baha	0.70 (0.40, 1.00)
Jouf	1.51 (1.18, 1.84)
Northern	1.51 (1.14, 1.89)
Tabuk	1.17 (0.95, 1.39)

Diagnosis date	
1997-2001	1.00 *P*<0.0001
2002-2006	1.23 (1.09, 1.37)
2007-2011	1.34 (1.21, 1.48)
2012-2017	1.27 (1.14, 1.40)
Anatomical site	
Colon	1.00 *P*=0.003
Rectosigmoid	1.16 (1.07, 1.25)
Rectal	1.01 (0.94, 1.09)

Note: CI: Confidence interval; N: Number; OR: odds ratios adjusted for all factors in the table using multiple imputation of covariates and disease stage. The p-values are derived from the overall likelihood ratio tests for association.

Appendix D.4: Sensitivity analysis using multiple imputation for stage data in logistic regression. Adjusted odds ratios for late versus early-stage CRC presentation, by sex (N=19,463)

Variable	Males (N= 10,688)	Females (N= 8,775)
	OR (95%CI)	OR (95%CI)
Age in years		
0-39	0.96 (0.79, 1.13)	1.22 (1.05, 1.38)
40-49	1.04 (0.89, 1.18)	1.19 (1.05, 1.33)
50-59	1.00 *P*=0.01	1.00 *P*=0.006
60-69	0.95 (0.83, 1.08)	1.09 (0.94, 1.23)
70-79	1.09 (0.95, 1.24)	1.06 (0.90, 1.23)
80+	1.18 (0.99, 1.37)	0.92 (0.70, 1.14)
Marital status		
Married	1.00 *P*=0.42	1.00 *P*=0.01
Unmarried	1.12 (0.93, 1.31)	1.21 (1.07, 1.36)
Region		
Riyadh	1.00 *P*<0.0001	1.00 *P*<0.0001
Eastern	1.20 (1.06, 1.34)	1.03 (0.89, 1.18)
Makkah	0.96 (0.84, 1.08)	0.87 (0.74, 1.00)
Madina	0.90 (0.69, 1.11)	0.75 (0.52, 0.99)
Asir	0.90 (0.71, 1.09)	0.97 (0.76, 1.17)
Jazan	0.94 (0.59, 1.28)	0.63 (0.22, 1.04)

Najran	1.33 (0.87, 1.79)	0.90 (0.41, 1.38)
Hail	1.35 (1.04, 1.66)	0.89 (0.54, 1.24)
Qassim	1.15 (0.93, 1.37)	0.94 (0.71, 1.18)
Baha	0.80 (0.36, 1.23)	0.62 (0.21, 1.04)
Jouf	1.86 (1.43, 2.28)	1.20 (0.69, 1.70)
Northern	1.18 (0.63, 1.74)	1.87 (1.32, 2.41)
Tabuk	1.25 (0.96, 1.55)	1.09 (0.75, 1.43)
Diagnosis date		
1997-2001	1.00 *P*=0.001	1.00 *P*<0.001
2002-2006	1.19 (0.99, 1.38)	1.26 (1.05, 1.48)
2007-2011	1.34 (1.16, 1.52)	1.40 (1.20, 1.59)
2012-2017	1.20 (1.03, 1.37)	1.39 (1.21, 1.57)
Anatomical site		
Colon	1.00 *P*=0.02	1.00 *P*=0.06
Rectosigmoid	1.17 (1.04, 1.30)	1.16 (1.02, 1.30)
Rectal	0.99 (0.88, 1.09)	1.04 (0.92, 1.16)

Note: CI: Confidence interval; N: Number; OR: odds ratios adjusted for all factors in the table using multiple imputation of covariates and disease stage. The p-values are derived from the overall likelihood ratio tests for association.

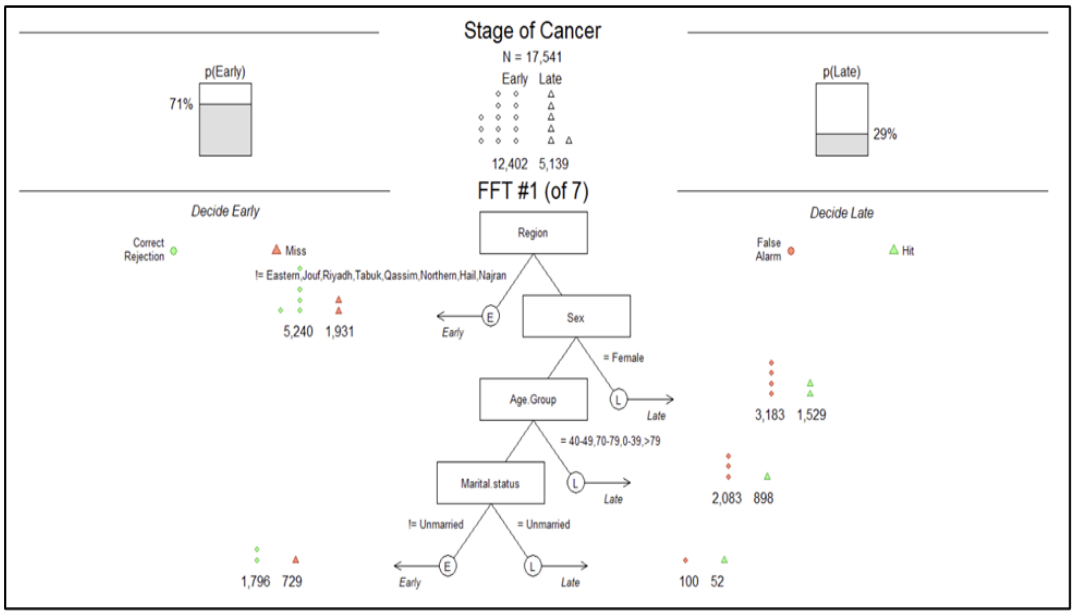
Appendix D.5: Decision tree analysis results

In the Fast and Frugal Tree (FFT) analysis, presented in Appendix D.6, each node is represented as a rectangle and denotes a predictor variable. Two branches extend from each node, where either one or both branches is an exit branch leading to a leaf (circle). Leaves are where decisions are made. Our FFT analysis indicated that if patients reside in the Riyadh, Eastern, Najran, Hail, Qassim, Jouf, Northern, and Tabuk regions, they were classified as having a late-stage disease. If not, they will be classified based on sex, with women having a late-stage CRC and men classified based on age. If men were younger than 50 or older than 70, they were more likely to have late-stage disease. If not, they will be further classified based on marital status, with unmarried men usually presenting with distant disease.

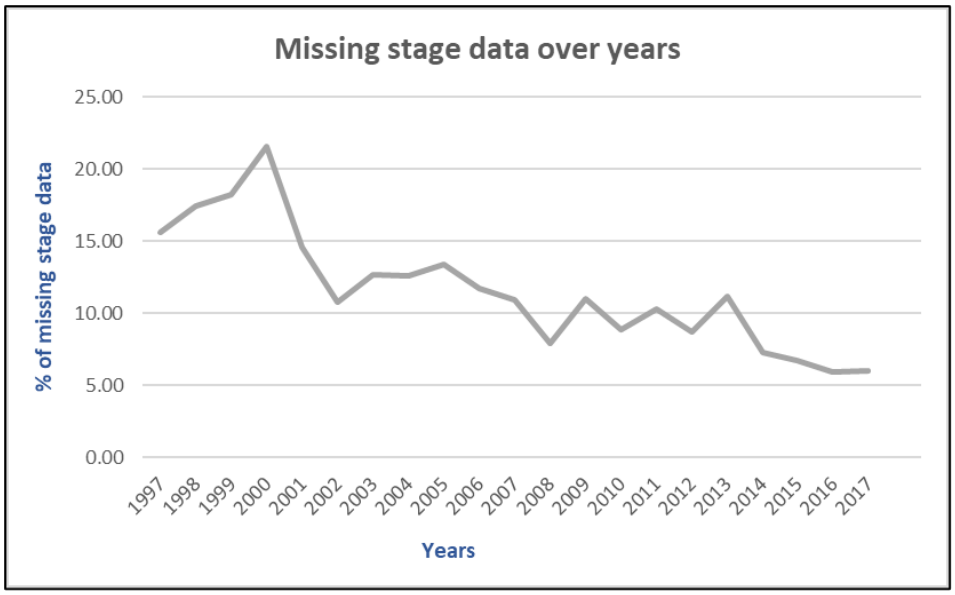
The FFT analysis provided further insights into the structure of our dataset. The primary node that emerged was the geographical region, highlighting its substantial influence on explaining the observed heterogeneity of our data. Regions were categorized into two separate groups based on this geographical division. Group A (high risk for late-stage CRC) included Riyadh, Eastern, Najran, Hail, Qassim, Jouf, Northern, and Tabuk regions, while Group B encompassed Makkah, Madina, Asir, Jazan, and Baha. Sex was the second node identified in the FFT analysis,

highlighting the importance of further stratifying the regression analysis by sex. Our FFT model performance evaluation revealed a Misclassification Cost of 2.1, with sensitivity at 48% and specificity at 57%, resulting in an overall accuracy of 54% and a balanced accuracy of 52%. These metrics suggest moderate performance in differentiating early from late-stage cancer.

Appendix D.6: A fast-and-frugal tree (FFT) for classifying patients as having late or early-stage CRC



Appendix D.7: Percentage of missing stage data for CRC in the Saudi Cancer Registry between 1997 and 2017



Appendix E: Study Five supplementary materials

Appendix E.1: Interview guide

Thank you for agreeing to take part in this study. I am interested in understanding the opinions and perceptions of Saudi women toward colorectal cancer screening (CRCS).

Before we start the interview, I would like to inform you that some topics we touch upon today might be considered personal or sensitive. However, my role here is not to pass judgment but to listen and understand. Additionally, I would like to reiterate some of your rights as a participant in this study. You have full autonomy to stop the interview at any time, take a break, or choose not to respond to any particular question. You also have the right to withdraw from the study at any point without an explanation provided.

Please note that this interview will be recorded, but rest assured that all your responses will be kept confidential. If your words are quoted in any of our reports, your identity will be protected by the use of a pseudonym (a number). Any identifiable details in your quotes, such as names and specific locations, will also be anonymised. If you have any questions or concerns after the interview related to our discussion, please don't hesitate to contact me. This interview should take between 30 to 45 minutes.

Permission to record

Ask participants for their permission to record the interview. Start the recording to capture their name and obtain verbal consent.

For the consent, the participant will be asked, "Do you agree to participate in this interview?". After they agree, the interview will start.

Questions

Topics	Interview questions
A) Health-seeking behaviour	1. What actions do you take when you feel ill or have health concerns? Why? 2. What do you know about screening tests for diseases? 3. Could you describe your experiences with health check-ups? Do you typically schedule these based on a doctor's recommendation, or are they initiated by you? Please explain.
B) Colorectal cancer & its screening	1. What do you know about colorectal cancer (CRC)? 2. What do you know about the screening methods for CRC?

	Probe: Do you know that colorectal cancer screening (CRCS) is available? (Skip if respondents mentioned undergoing CRCS in section (A) and move to question 3). *If yes, can you describe what the screening process entails?* *If no, what do you think the screening involves?* 3. For those who have ever been screened for CRC, can you describe your experience?
C) Colorectal cancer screening program	1. What do you know about the CRCS program developed by the Saudi Ministry of Health (MOH)? *Probe: Where did you hear about the program? (media, family or friends, doctor, other)* *Probe: What type of screening procedure is offered, where is the service provided, and who is eligible?*
D) Benefits and barriers to the colorectal cancer screening program	*The interviewer explains the current Saudi MOH screening program, the targeted at-risk population, and the FIT test (stool test). The interviewer will use the information provided in the guide published by the MOH to explain the FIT test. (https://www.moh.gov.sa/awarenessplateform/VariousTopics/Documents/EarlyDiagnosticColorectalCA.pdf)* 1. If you had never undergone CRCS, how would you react to your doctor recommending a screening using the FIT test? (Skip to question 2 if the respondent had CRCS using FIT in the past) 2. What positive aspects do you see in participating in the screening? 3. Are there any obstacles or concerns that might discourage you from participating in CRCS (again)?
E) Enabling factors to colorectal cancer screening uptake	1. What factors motivate you or others to undergo a CRCS test?

Debrief

Thank you so much for sharing your views and opinions about the factors influencing CRCS participation. I want to remind you that all your answers today will be anonymised and securely saved at the University of Leeds.

Before we end, do you have any questions or concerns you wish to discuss?

Can you please provide some demographic details that will enhance our analysis?

- How old are you?
- What is your educational level?
- Do you have a personal or family history of cancer? Yes/ No
- Do you have a personal or family history of CRC? Yes/ No

Please do not hesitate to contact me for any further inquiries.

Thank you for your time.

Appendix F: Discussion supplementary materials

Appendix F.1: Annual age-specific incidence rates of CRC per 100,000 person-years in Saudi Arabia (1997-2017) in females

Age group	Year																				
	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
0-19	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
20-24	0.5	0.2	0.9	0.7	0.5	0.8	0.8	0.4	0.5	0.4	0.4	0.6	0.5	0.6	0.4	0.1	0.3	0.2	0.4	0.2	0.4
25-29	1.2	0.6	1.6	1.2	1.7	0.9	0.4	0.6	1.1	1.0	1.4	1.3	1.2	1.0	1.7	0.9	2.5	1.3	1.2	0.7	1.3
30-34	2.2	0.5	2.0	1.5	1.1	1.2	2.3	1.3	2.1	2.0	1.9	1.3	2.0	3.8	2.6	2.1	2.7	2.4	2.3	2.2	2.1
35-39	3.2	3.2	2.7	3.1	5.2	4.1	1.8	3.9	4.1	2.2	3.6	3.1	3.7	3.8	3.7	3.8	4.6	4.8	4.9	5.0	5.4
40-44	5.4	3.8	3.4	3.5	7.8	3.7	5.0	4.1	5.1	6.1	5.1	7.7	7.3	7.1	7.2	8.3	7.8	7.1	7.7	7.9	7.3
45-49	3.7	5.1	5.5	6.1	5.7	8.1	6.7	8.5	9.6	9.0	13.0	11.7	14.4	15.1	15.3	12.3	16.0	13.8	13.0	14.9	14.2
50-54	7.6	7.5	8.6	13.8	8.7	9.1	10.9	8.5	12.7	11.9	13.8	14.1	17.0	21.5	22.6	20.3	25.9	19.3	20.1	27.7	25.8
55-59	9.2	9.0	14.8	13.9	13.3	10.6	11.5	9.7	13.3	15.3	14.6	20.7	20.3	22.2	20.9	19.3	31.5	26.8	33.4	28.8	35.6
60-64	17.5	23.0	18.6	16.4	18.4	13.8	19.4	22.7	19.6	24.2	19.8	25.2	19.0	31.0	30.2	31.3	38.1	32.7	43.0	41.7	51.7
65-69	13.7	13.3	22.9	20.1	25.6	20.6	21.7	23.8	15.0	32.3	22.3	28.2	38.7	34.5	34.0	38.3	47.7	43.8	52.3	42.7	60.1
70-74	39.3	26.8	32.7	14.9	24.4	25.5	19.5	30.3	25.4	24.9	29.5	46.8	41.1	43.7	44.2	51.2	62.7	46.2	47.5	45.1	58.4
75-79	17.4	20.3	39.4	29.9	24.1	47.0	17.0	16.8	37.8	22.5	39.4	32.4	65.1	39.6	48.0	62.2	52.5	47.4	49.6	58.7	65.7
80+	4.6	17.9	26.1	18.0	23.4	23.3	27.4	30.7	28.8	30.7	41.4	33.2	39.8	42.1	46.3	52.8	41.6	43.4	42.8	63.4	58.9

Appendix F.2: Annual age-specific incidence rates of CRC per 100,000 person-years in Saudi Arabia (1997-2017) in males

Age group	Year																				
	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
0-19	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.1	0.0	0.0	0.0
20-24	0.6	0.6	0.7	0.2	0.4	0.5	0.9	0.4	0.0	0.1	0.7	0.6	0.4	0.1	0.7	0.5	0.8	0.4	0.4	0.6	0.4
25-29	1.6	1.6	0.6	0.6	0.9	0.6	1.0	0.9	1.0	0.7	1.4	2.1	1.2	0.9	1.4	1.5	1.1	1.0	0.8	1.3	0.8
30-34	1.5	0.2	1.6	1.3	1.6	1.6	1.8	2.3	1.2	1.8	2.0	1.5	2.1	1.5	1.9	2.5	3.7	2.0	2.3	3.0	2.7
35-39	4.0	3.4	1.4	2.9	4.2	3.7	3.1	3.6	3.8	2.9	3.2	4.1	3.9	3.9	4.7	2.9	2.9	4.0	4.3	5.0	4.7
40-44	4.2	5.2	4.8	5.4	6.2	6.0	5.0	4.4	5.4	4.7	5.0	5.6	8.3	6.8	8.2	7.4	7.5	6.0	9.1	8.9	6.3
45-49	2.1	6.2	3.7	8.4	5.1	9.6	9.1	9.9	10.0	10.2	9.3	8.7	11.3	12.4	12.1	12.3	12.6	12.3	12.7	16.6	16.7
50-54	10.7	10.5	11.5	12.3	9.0	8.4	11.2	8.6	12.3	9.5	12.2	14.0	18.7	15.1	22.3	21.0	18.9	23.2	24.4	28.7	24.4
55-59	13.0	11.0	24.2	22.3	15.8	10.3	14.8	15.9	18.6	16.4	17.4	19.9	22.7	22.6	24.8	30.1	36.3	36.8	42.7	36.6	37.7
60-64	11.2	18.2	28.7	22.3	20.6	19.7	28.7	23.4	29.1	25.0	24.9	24.8	31.4	29.0	30.8	38.1	44.1	38.6	44.8	50.5	47.6
65-69	14.7	16.6	18.0	21.3	25.4	31.1	32.3	39.3	52.7	44.3	58.7	44.5	57.4	55.6	77.7	56.3	50.1	64.8	64.8	55.3	72.2
70-74	16.8	14.3	17.1	15.3	22.2	29.1	38.6	49.3	61.1	56.4	46.5	46.5	62.6	69.3	67.4	78.1	86.9	80.3	86.9	96.1	95.4
75-79	15.8	31.8	28.7	23.7	25.4	28.9	26.9	46.4	50.1	40.4	69.1	56.2	70.6	75.4	66.1	77.1	109.1	92.3	109.7	127.9	102.4
80+	24.0	22.2	21.1	16.0	35.6	42.2	26.0	35.5	50.2	51.7	49.1	57.3	79.4	73.9	76.6	72.9	63.3	71.0	74.9	90.6	85.4