

**A PROSPECTIVE CASE-CONTROL STUDY ON
NUTRITIONAL STATUS AND LIFESTYLE RISK
FACTORS TOWARDS QUALITY OF LIFE
AMONG COLORECTAL CANCER AND POLYP
PATIENTS IN MALAYSIA**

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UNIVERSITI SAINS MALAYSIA

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by

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LIST OF ACRONYMS, ABBREVIATIONS AND SYMBOLS

AAPCs	Average annual percentage changes
ADR	Adenoma detection rates
ALB	Albumin
AOR	Adjusted odd ratio
AP	Adenomatous polyp
ANOVA	Analysis of variance
AADs	Advanced adenomas
AAs	Advanced adenomas
AHR	Adjusted hazard ratio
AI	Adequate Nutrition
AJCC/UICC	American Joint Committee on Cancer/Union Internationale Contre le Cancer
APC	Age-period-cohort
APR	Abdominoperineal resection
AR	Anterior resection
ASMR	Age standardized mortality rate
AUC	Area under the curve
BCG	Bromocresol green
BIA	Bioelectrical impedance analysis
B-PROOF	Prevention of Osteoporotic Fractures
BMI	Body mass index
BTC	Biliary tract cancer
B40	Bottom 40 percent

CC	Colon cancer
CCL2	Chemokine (C-C motif) ligand 2
CF	Cystic fibrosis
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
CRA	Colorectal adenoma
CRC	Colorectal cancer
CRCs	Colorectal cancers
CRP	C-reactive protein
CVD	Cardiovascular disease
CVDs	Cardiovascular diseases
DCA	Dichloroacetate
DCA	Deoxycholic acid
DHEA	Dehydroepiandrosterone
DHT	Dihydrotestosterone
DXA	Dual-energy X-ray absorptiometry
DFS	Disease-free survival
EMT	Epithelial–mesenchymal transition
EGF	Epidermal growth factor
ECOG PS	Eastern Collaborative Oncology Group performance status
EOCRC	Early-onset colorectal cancer
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EORTC QLQ-CR29	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Colorectal 29

ESCC	Esophageal squamous cell carcinoma
FAP	Familial adenomatous polyposis
FITs	Faecal immunochemical tests
FPG	Fasting plasma glucose
FXR	Farnesoid X receptor
g	Grams
gFOBTs	Traditional guaiac-based faecal occult blood tests
GI	Gastrointestinal
GI	Glycemic index (GI)
GIS	Geriatric gastrointestinal system
GL	Glycemic load (GL)
GLIM	Global Leadership Initiative Malnutrition
GLOBOCAN	Global Cancer Observatory
GOSAFE	Geriatric Oncology Surgical Assessment and Functional rEcovery after Surgery
GH	Growth hormone
g/day	Grams per day
g/L	Grams per litre
g/dL	Grams per decilitre
Hb	Hemoglobin
HbA1c	Glycated hemoglobin
HC	Hip circumference
HDI	Human Development Index
HDL	High-density lipoprotein
HDL-C	High-density lipoprotein cholesterol

HFCS	High-fructose corn syrup
HP	Hyperplastic polyp
HPFS	Health Professionals Follow-up Study
HPP	Hyperplastic polyp
IARC	International Agency for Research on Cancer
IBD	Inflammatory bowel disease
IGF	Insulin growth factor
IGFs	Insulin-like growth factors
IL	Insulin load
IL-6	Interleukin 6
IP-10	Interferon- γ -inducible protein-10
IQR	Interquartile range
kcal	Kilocalories
kcal/day	Kilocalories per day
kg/m ²	Kilograms per square metre
LAR	Lower anterior resection
LARS	Low anterior resection syndrome
LCA	Lithocholic acid
LCDS	Low-carbohydrate diet score
LCSFA	Long-chain saturated fatty acids
LDL-C	Low-density lipoprotein cholesterol
mCRC	Metastatic CRC
MDG	Malaysia Dietary Guideline
MetS	Metabolic syndrome
mg	Milligrams

mg/day	Milligrams per day
MNA	Mini Nutritional Assessment
MNT	Medical Nutrition Therapy
MRI	Magnetic resonance imaging
MUAMC	Mid upper arm muscle circumference
MUFA	Monounsaturated fatty acids
MyFCD	Malaysian Food Composition Database
M40	Middle 40 percent
NAFLD	Nonalcoholic fatty liver disease
NSAIDS	Non-steroidal anti-inflammatory drugs
NSCLC	Non-small-cell lung cancer
NIH-AARP	National Institutes of Health-American Association of Retired Persons Diet and Health Study cohort
NHMS	National Health and Morbidity Survey
NHS	Nurses' Health Study
NNS	Number needed to screen
NRI	Nutrition risk index
NRS 2002	Nutritional risk screening 2002
OC	Ovarian cancer
ONS	Oral nutritional supplements
OR	Odd ratio
OS	Open surgery
PAI-1	Plasminogen activator inhibitor-1
PDH	Pyruvate dehydrogenase
PG-SGA	Patient Generated Subjective Global Assessment

PLCRC	Prospective Dutch Cohort CRC
PUFA	Polyunsaturated fatty acids
QOL	Quality of life
RC	Rectal cancer
RCC	Red cell count
RCT	Randomized clinical trial
RCTs	Randomized controlled trials
RDA	Recommended Dietary Amount
RNI	Recommended Nutrient Intake
ROC	Receiver operating characteristic
SAT	Subcutaneous adipose tissue
SAD	Sagittal abdominal diameter
SBQ	Sedentary behaviour questionnaire
SD	Standard deviation
SFA	Saturated fatty acids
SGA	Subjective Global Assessment
SPDR	Serrated polyp detection rates
SPS	Sphincter-preserving surgery
SQFFQ	Semi-quantitative food frequency questionnaire
SSLs	Sessile serrated lesions
SMM	Skeletal muscle mass
SSPs	Sessile serrated polyps
TA	Tubular adenoma
TC	Total cholesterol
TGF- β	Transforming growth factor- β

TEI	Total energy intake
TG	Triglyceride
TNF- α	Tumor necrosis factor-alpha
TNM	Tumor-node-metastasis
TP	Total protein
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
T20	Top 20 percent
UK	United Kingdom
US	United State
USA	United States of America
USPSTF	US Preventive Services Task Force
USDA	United States Department of Agriculture
VAT	Visceral adipose tissue
VDR	Vitamin D receptor
VIF	Variance inflation factor
WBC	White blood cell
WC	Waist circumference
WCC	White cell count
WHR	Waist-hip ratio
25(OH)D	25-hydroxyvitamin D
25(OH)D3	25-hydroxyvitamin D3
1,25(OH)2D3	1 α ,25-dihydroxyvitamin D3

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**KAJIAN KAWALAN KES PROSPEKTIF MENGENAI STATUS
PEMAKANAN DAN FAKTOR RISIKO GAYA HIDUP TERHADAP
KUALITI HIDUP DALAM KALANGAN PESAKIT KANSER
KOLOREKTAL DAN POLIP DI MALAYSIA**

ABSTRAK

Terdapat peningkatan kadar insiden dan prevalens kanser kolorektal malnutrisi yang berkaitan dengan penyakit dan pendahulunya polip kolorektal di negara-negara Asia Tenggara. Walau bagaimanapun, hanya terdapat sedikit sahaja laporan berkaitan penyakit ini. Rawatan dan penyakit itu sendiri memberi kesan dan menjejaskan kualiti hidup kepada bekas pesakit kanser kolorektal. Tujuan kajian ini adalah untuk menentukan status pemakanan dan faktor risiko gaya hidup terhadap kualiti hidup dalam kalangan pesakit kanser kolorektal dan polip di Malaysia. Kajian ini dijalankan di dua buah hospital universiti di Semenanjung Malaysia bermula Jun 2020 sehingga Disember 2022. Pesakit telah direkrut melalui kaedah persampelan bertujuan dan sejumlah 313 orang pesakit yang terdiri daripada 99 dan 74 masing-masing kanser kolorektal dan polip yang telah disahkan secara patologi dan 140 kawalan telah dimasukkan ke dalam analisis. Maklumat berikut telah dikumpulkan sebelum pesakit menerima rawatan: Sosio-demografi, sejarah perubatan keluarga dan peribadi, pengambilan makanan, tingkah laku sedentari, risiko pemakanan, merokok, patologi klinikal, parameter biokimia, dan profil antropometrik. Data tingkah laku sedentari, risiko pemakanan, parameter biokimia, dan profil antropometrik telah dikumpulkan sekali lagi bersama-sama rawatan dan kualiti hidup enam bulan selepas pesakit menerima rawatan. Model regresi logistik berganda mendedahkan Wilayah

Persekutuan Kuala Lumpur (OR=8.89, 95% CI=3.19-24.83, $p<0.001$), kencing manis jenis dua (OR=4.91, 95% CI=1.81-13.29, $p=0.002$), vitamin/mineral tambahan (OR=5.15, CI=2.33-11.39, $p<0.001$), dan asid lemak tepu (OR=1.19, 95% CI=1.08-1.31, $p<0.001$) mempunyai perkaitan meningkatkan risiko kanser kolorektal sementara bukan Melayu (OR=0.36, 95% CI=0.15-0.87, $p=0.024$), berat badan berlebihan (OR=0.14, 95% CI=0.04-0.48, $p=0.002$), dan peningkatan pengambilan vitamin D (OR=0.71, 95% CI=0.55-0.92, $p=0.008$) dan serat diet (OR=0.81, 95% CI=0.74-0.89, $p<0.001$) mempunyai perkaitan mengurangkan risiko kanser kolorektal selepas disesuaikan dengan umur dan jantina. Bagi polip kolorektal, Wilayah Persekutuan Kuala Lumpur (OR=4.36, 95% CI=2.02-9.41, $p<0.001$) dan peningkatan pengambilan kolesterol (OR=1.003, 95% CI=1.001-1.005, $p=0.006$) dilihat mempunyai perkaitan meningkatkan risiko sementara peningkatan pengambilan tiamin (OR=0.02, 95% CI=0.00-0.11), $p<0.001$) dan buah-buahan (OR=0.997, 95% CI=0.995-1.000, $p=0.035$) dilihat mempunyai perkaitan mengurangkan risiko. Model regresi linear berganda menunjukkan kekurangan zat makanan ($\beta=-18.40$, $p<0.001$) dan obesiti abdominal ($\beta=-10.07$, $p=0.020$) mempunyai kolerasi secara negatif dengan kualiti hidup selepas enam bulan menerima rawatan. Kajian ini meningkatkan pemahaman semasa mengenai laluan pemakanan dan metabolik yang mendasari perkembangan kanser kolorektal dan polip, sekaligus menyediakan asas bagi kajian mekanistik dan intervensi pada masa hadapan.

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ABSTRACT

In Southeast Asian countries, there is a growing incidence and prevalence rate of disease-related malnutrition colorectal cancer (CRC) and its precursor, colorectal polyp, however there are only few reports of this condition. Treatments and the disease itself may affect and impair the overall quality of life (QOL) of CRC survivors. The study aimed to determine the nutritional status and lifestyle risk factors among CRC and polyp patients and their impact on QOL through a prospective case-control study in Malaysia. This study was conducted in two university hospitals in Peninsular Malaysia from June 2020 until December 2022. Patients were recruited through purposive sampling method and a total of 313 patients consisting of 99 and 74 pathologically confirmed CRC and colorectal polyp cases respectively, and 140 controls were included in the analysis. The following information was gathered pre-treatment: Socio-demographic, family and personal medical history, dietary intake, sedentary behaviour, nutritional risk, smoking, clinicopathological, biochemical parameters, and anthropometric profiles. Six months post-treatment, sedentary behaviour, nutritional risk, biochemical parameters, and anthropometric profiles were gathered again, together with treatment and QOL. Multiple logistic regression model revealed that the Kuala Lumpur state (OR=8.89, 95% CI=3.19-24.83; $p<0.001$), type 2 diabetes mellitus (T2DM) (OR=4.91, 95% CI=1.81-13.29, $p=0.002$), vitamin/mineral supplements (OR=5.15, CI=2.33-11.39, $p<0.001$), and

saturated fatty acids (SFA) (OR=1.19, 95% CI=1.08-1.31, $p<0.001$) intake were associated with greater risks of CRC while non-Malay (OR=0.36, 95% CI=0.15-0.87, $p=0.024$), overweight (OR=0.14, 95% CI=0.04-0.48, $p=0.002$), increased intake of vitamin D (OR=0.71, 95% CI=0.55-0.92, $p=0.008$) and dietary fibre (OR=0.81, 95% CI=0.74-0.89, $p<0.001$) were associated with reduced risk of CRC after the data were adjusted for age and gender. For colorectal polyp, the Kuala Lumpur state (OR=4.36, 95% CI=2.02-9.41, $p<0.001$) and high cholesterol (OR=1.003, 95% CI=1.001-1.005, $p=0.006$) intake were associated with increased risk while high thiamin (OR=0.02, 95% CI= 0.00-0.11, $p<0.001$) and fruits (OR=0.997, 95% CI=0.995-1.000, $p=0.035$) intake were found associated with decreased of risk. Multiple linear regression model showed that malnourish ($\beta=-18.40$, $p<0.001$) and abdominal obesity ($\beta=-10.07$, $p=0.020$) were negatively associated with QOL after six months of post-treatment. This study advances current understanding of the nutritional and metabolic pathways underlying colorectal cancer and polyp development, providing a foundation for future mechanistic and intervention studies.

CHAPTER 1

INTRODUCTION

1.1 Background of the study

Malnutrition is defined as deficiency (undernutrition) or excessiveness (overnutrition) or imbalance of energy and nutrients intake in an individual's diet (Lee & Nieman, 2010; WHO, 2024). Undernutrition could be divided into 4 broad forms namely underweight, stunting, wasting, and micronutrient deficiency (WHO, 2024) while overnutrition is characterized by two body mass index (BMI) category which is overweight and obesity (Moini *et al.*, 2020).

Both overweight and obesity are associated with increased mortality and morbidity due to their links with a higher risk of hypertension, type 2 diabetes (T2DM), dyslipidemia, and other chronic diseases (Moini *et al.*, 2020). Cancer which is one of the chronic diseases could also be linked to overweight and obesity. Obesity was associated with the increased risk of numerous cancer site or malignancies such as the breast (Dehesh *et al.*, 2023), liver (Sohn *et al.*, 2021), pancreas (Pothuraju *et al.*, 2018), and colorectal (Liu *et al.*, 2019).

Colorectal cancer (CRC) affects various ethnicities and populations across the globe. The age-standardised incidence rate of colon cancer (CC) in both sexes was found highest in Australia/ New Zealand, followed by Southern Europe, Northern Europe, Eastern Europe, Western Europe and Northern America (IARC, 2022). While for rectal cancer the rate was found highest in Eastern Europe, Australia/ New Zealand,

Northern Europe, Western Europe, Southern Europe, and Eastern Asia (IARC, 2022). Although the majority of CRC cases occur in Western countries, Asian countries are also seeing an increase in this trend. This has been proven with a cohort study by Chung et al. (2019) as there was an increment of CRC new cases when population reach their old ages in both Western and Asian countries. According to Global Cancer Observatory (GLOBOCAN) 2018 database, China, Japan, Korea, Malaysia, Singapore, and Turkey exhibited higher 5-year prevalence rates of CRC as compared to other Asian countries, with rates equal to or exceeding 46.5 per 100,000 population (IARC, 2018).

Colorectal polyps are an abnormal growth (Sninsky *et al.*, 2022) and non-cancerous (benign). It normally emerges from the mucosal layer and protrude into the lumen of the large intestine which is divided into neoplastic and nonneoplastic lesions (Sninsky *et al.*, 2022). Neoplastic polyps are adenomatous and serrated polyps (Sninsky *et al.*, 2022). Adenomatous polyps are composed of two-thirds of all colon polyps and are the most common precursor lesions to CRC (Sninsky *et al.*, 2022). Some of the CRC tumour could be originated from small adenomatous polyps which turns out into a larger size and develop into abnormal cell growth known as severe dysplasia (Zhu & Li, 2023) (Figure 1.1). The abnormal cells were then developed into adenocarcinoma and finally become cancerous (Zhu & Li, 2023) (Figure 1.1).

The prevalence of colorectal polyps varies among the countries and population. A colonoscopy screening conducted among US population observed that the prevalence rate of conventional adenomas and sessile serrated polyps (SSPs) for individual ≥ 50 years were 48.5% and 15.3% respectively (Rex *et al.*, 2020). In

Southern Taiwan, the prevalence rate of colorectal polyps among middle-aged and elderly populations were around 46.9% (Loke & Chuah, 2022).

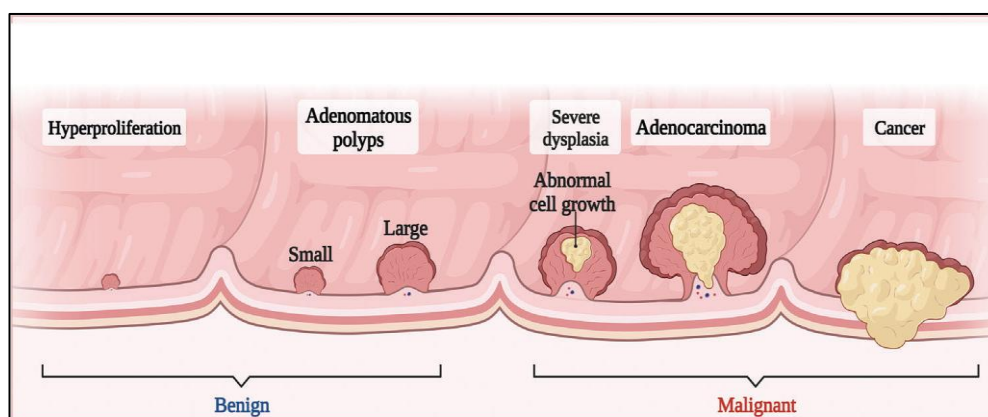


Figure 1.1 Development of CRC

(adopted from Zhu & Li, 2023)

In addition to being linked to a higher risk of CRC and colorectal polyps, poor nutritional status is also linked to a decreased or impaired quality of life (QOL) for CRC survivors following treatment completion. A study among CC patients in Sweeden revealed that smoking, higher BMI, poor physical health, and surgical procedure with stoma were among factors that reduced QOL level at baseline and 6 months follow-up (Tiselius *et al.*, 2021).

Furthermore, a study among GI cancer survivor in US observed that non-Hispanic Whites, married/having partner, higher education levels, employed, higher income, and healthcare access within the past year with a primary care provider were positively associated with health-related QOL (Han *et al.*, 2023). However, variables that were negatively associated with health-related QOL were status of current smoking, lack of physical activity, and alcohol consumption (Han *et al.*, 2023).

A prospective cohort study conducted in Sweeden and Denmark shows that there was impairment of QOL level in rectal cancer patients as compared to reference population before treatments (Walming *et al.*, 2020). Walming *et al.* (2020) which also reported that the QOL level was similar with reference population, after 12 and 24 months of follow-up and problems with stoma, urinary, and bowel function were found associated with reducing QOL after 24 months.

1.2 Problem statement

Abundance of observational epidemiological study was carried out in Western (Murphy *et al.*, 2019; Kim *et al.*, 2021; Li *et al.*, 2022; Mandic *et al.*, 2023) and Asia (Huang *et al.*, 2018, 2020; Seo *et al.*, 2023) countries purposely to determine risk factors of CRC. Nevertheless, data in South-Eastern Asia particularly Malaysia is limited whilst most of the studies focused on incidence and mortality trends (Ismail *et al.*, 2022), predictor of CRC survival (Muhamad *et al.*, 2023), CRC public awareness (Schliemann *et al.*, 2020), and willingness for CRC screening test (Naing *et al.*, 2014).

Additionally, Malaysia National Cancer Registry (MNCR) database shows that the incidence rate of CRC increased from 2007 until 2021 among both male and female Malaysian population (IKN, 2019). Therefore, the current study was carried out to investigate the causes of CRC pathogenesis comprehensively by taken into consideration multiple factors including non-modifiable and modifiable risk factors.

Similarly, there are very few reports of observation epidemiological studies in Malaysia to identify the risk factors for colorectal polyps. To the best of my

knowledge, there was only one study conducted by Sharif et al. (2022) in Malaysia, however some of the factors were not included in the analysis. Since the formation of cancerous cells takes about 10 years (Øines et al., 2017) and about 10% (Hossain et al., 2022) of CRC tumours may be gradually caused by or originate from adenomatous polyps, it is essential to identify the predictors that may influence the development of adenomatous polyps so that preventative measures can be implemented earlier.

In addition, more than 50% of pre-treatment CRC patients are at risk of malnutrition based on Mini Nutritional Assessment (MNA) (Daniele *et al.*, 2017). One of the malnourished symptoms which is weight loss was experienced by early-onset colorectal cancer (EOCRC) patients where the proportion of weight loss (>5kg) was found higher in cases than control before colonoscopy procedures (Low *et al.*, 2020).

According to Negrichi & Taleb (2020) weight loss is evident in CRC patients as indicated by an increase in the proportion of underweight individuals from 1% before diagnosis to 14% after diagnosis. Screening and evaluating the nutritional status of patients is essential because pre-treatment malnutrition can lead to negative outcomes like complications during (Cordeiro De Souza *et al.*, 2013) and after surgery, disruption and poor response to treatments (Reber *et al.*, 2021), an increase in side effects like fatigue, nausea, and vomiting (Arends *et al.*, 2017), adverse reactions like sepsis and cardiac toxicity (O Regan, 2007), and increased readmission rates to the hospital (Reber *et al.*, 2021).

Latest advancement of medical, pharmaceutical, and biotechnology field to come out with therapeutic modalities such as surgical, chemo, radio, and targeted

therapy for CRC treatment has successfully decreased the mortality and increase survival rate. However, such treatment also had some disadvantages as it may negatively affect their nutritional status, overall QOL, function, and symptoms.

According to Winkels *et al.* (2016), stage II and III CRC patients experience body weight increment during and after chemotherapy treatments. The level of symptomatology among metastatic CRC was found high for pain, diarrhea, nausea and vomiting after 6 months of bevacizumab and chemotherapy treatments (Moisuc *et al.*, 2023). While treatment could affect long-term health (van Zutphen *et al.*, 2019) and sarcopenic obesity (Winkels *et al.*, 2016) due to weight gain and changes, respectively, and worsen QOL (Moisuc *et al.*, 2023), it is important to evaluate nutritional status and QOL and identify its predictors prospectively or at post-treatment so that healthcare professionals could administer nutritional and treatment interventions to the affected patients.

A review of the existing literature reveals a critical gap in data regarding the risk factors associated with CRC and colorectal polyps, particularly within the Malaysian context. Additionally, there is a notable lack of research on the nutritional status and QOL of CRC patients both pre- and post-treatment as well as limited understanding of the factors influencing these outcomes. This current study seeks to address these deficiencies by generating comprehensive, evidence-based data specific to the Malaysian population.

The results of this research are intended to support policymakers in formulating effective prevention and management strategies aimed at reducing the incidence of

CRC and colorectal polyps. Furthermore, the findings will contribute to improved post-treatment monitoring and long-term surveillance of CRC survivors.

1.3 Rationale and significance of the study

The data collected from this study are latest and comprehensive which could be used to establish fundamental database for CRC and colorectal polyps. The database consisting of data on socio-demographic, family and personal medical history, nutritional risk, anthropometric profiles, biochemical parameters, dietary intake, QOL, and other variables could guide researchers to plan and strategize future studies on gastrointestinal related diseases in various designs, not only observational but also experimental or randomised clinical trials.

The findings will be useful for technical working group members in updating and revising several Malaysian nutritional guidelines including Recommended Nutrient Intake (RNI), Malaysia Dietary Guideline (MDG), and Medical Nutrition Therapy (MNT) Guideline for CRC. Furthermore, RNI and MDG would guide the healthy population in Malaysia to acquire standard macro- and micronutrient intakes and promoting healthy eating practice respectively which may consequently mitigate and prevent risks for the individual or population with CRC and colorectal polyp. Whereas MNT Guidelines would be useful for dietitians to aid them in monitoring nutritional status of the patients with the illness which is before, during and after treatments.

Early diagnosed or pre-treatment and post-treatment patients may experience poor nutritional status and impairment of QOL. Identifying their nutritional status and QOL at this period may provide information for healthcare professionals to manage patients timely, correctly, and comprehensively in their clinical practice by forming a multidisciplinary team from various background including surgeons, oncologist, anesthetists, dietitians, and nurses.

1.4 Objectives

1.4.1 General objective

To determine the nutritional status and lifestyle risk factors in CRC and polyp patients and their impact on QOL through a prospective case-control study in Malaysia.

1.4.2 Specific objectives

a. Phase I (Case-control study):

- i. To compare nutritional status, biochemical parameters, and sedentary behaviour of CRC patients, colorectal polyp patients, and controls.
- ii. To identify predictors of CRC.
- iii. To identify predictors of colorectal polyp.

b. Phase II (Follow-up):

- i. To compare changes of nutritional status, biochemical parameters, and sedentary behaviour of CRC patients between baseline and six months follow-up.
- ii. To assess the QOL of CRC patients, six months post-treatment.
- iii. To identify the predictors of QOL for CRC patients six months post-treatment.

1.5 Research questions

a. Phase I (Case-control study):

- i. Is there any difference of nutritional status, biochemical parameters, and sedentary behaviour between CRC patients, colorectal polyp patients and controls?
- ii. What are the predictors of CRC?
- iii. What are the predictors of colorectal polyp?

b. Phase II (Follow-up):

- i. Are there any changes of nutritional status, biochemical parameters, and sedentary behaviour of CRC patients between baseline and six months follow-up?
- ii. What is the level of QOL of CRC patients at six months post-treatment?
- iii. What are predictors of QOL for CRC patients at six months post-treatment?

1.6 Null hypotheses

a. Phase I (Case-control study):

- i. There is no difference of nutritional status, biochemical parameters, and sedentary behaviour of CRC patients, colorectal polyp patients, and controls.
- ii. Kuala Lumpur, T2DM, vitamin/mineral supplements, saturated fatty acids (SFA), non-Malay, overweight, vitamin D, and dietary fibre are not predictors of CRC
- iii. Kuala Lumpur, cholesterol, thiamin, and fruits are not predictors of colorectal polyp

b. Phase II (Follow-up):

- i. There are no changes of nutritional status, biochemical parameters, and sedentary behaviour of CRC patients between baseline and six months follow-up.
- ii. The QOL of CRC patients is poor at six months post-treatment.
- iii. Malnourish and abdominal obesity are not predictors of QOL of CRC patients at six months post-treatment.

1.7 Alternative hypotheses

a. Phase I (Case-control study):

- i. There is a difference in nutritional status, biochemical parameters, and sedentary behaviour of CRC patients, colorectal polyp patients, and controls.

- ii. The Kuala Lumpur state, T2DM, vitamin/mineral supplements, saturated fatty acids (SFA), non-Malay, overweight, vitamin D, and dietary fibre are predictors of CRC
- iii. The Kuala Lumpur state, cholesterol, thiamin, and fruits are predictors of colorectal polyp

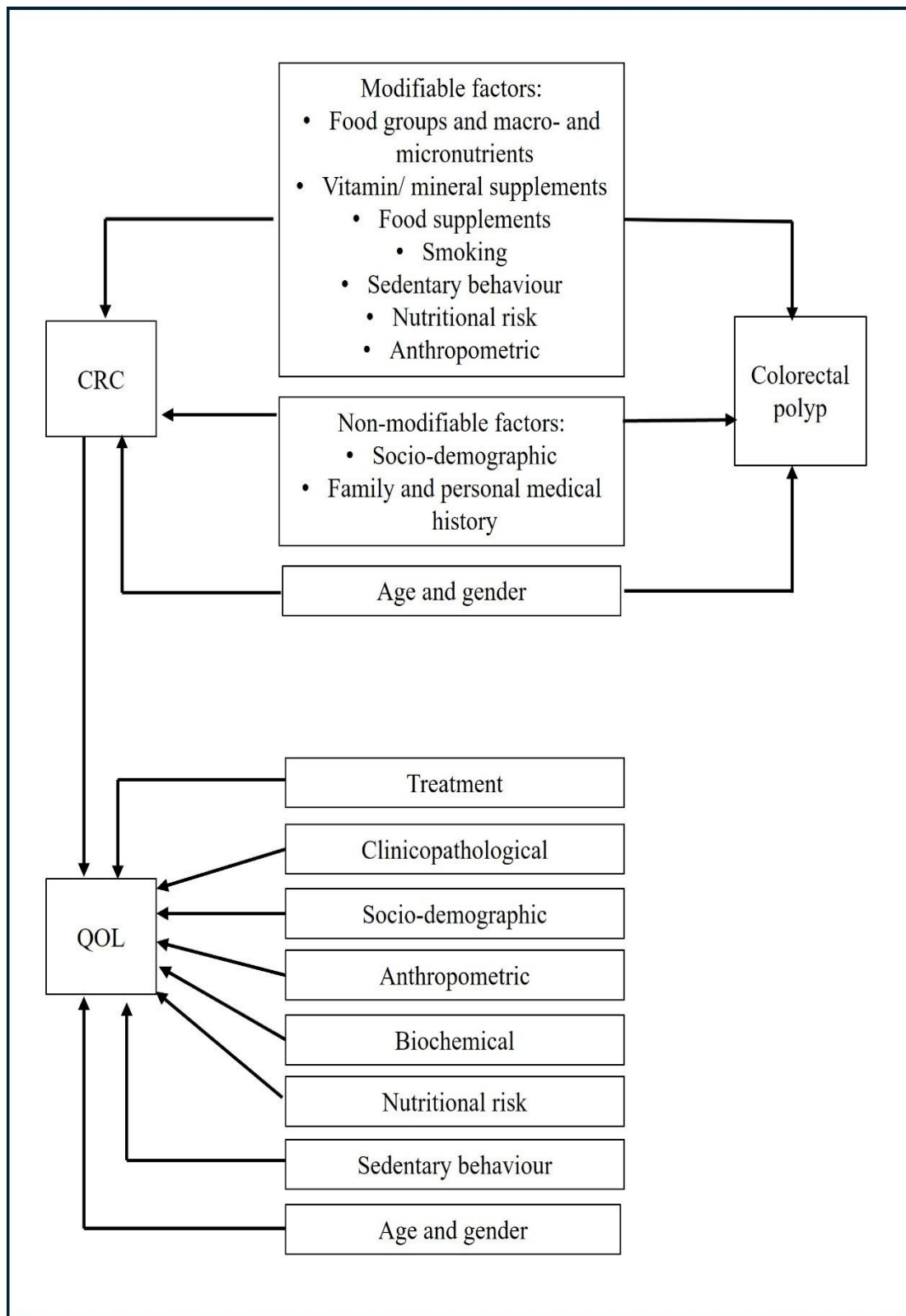
b. Phase II (Follow-up):

- i. There are changes in nutritional status, biochemical parameters, and sedentary behaviour of CRC patients between baseline and six months follow-up.
- ii. The QOL of CRC patients is good at 6 months post-treatment.
- iii. Malnourish and abdominal obesity are predictors of QOL for CRC patients at six months post-treatment.

1.8 Conceptual framework

The conceptual framework of the study is presented in Figure 1.2. The framework explains the complex interplay of factors associated with both CRC and polyps risks as well as the QOL of CRC survivors. The first part of the framework addresses the risk factors for CRC and polyps which are categorised into modifiable and non-modifiable risk factors.

Amongst modifiable or lifestyle risk factors are nutritional status consisting of diet (e.g. food groups and macro and micronutrients, vitamin/mineral supplements, and food supplements), nutritional risk (e.g. malnourished), and anthropometric (e.g. body mass index [BMI] and abdominal obesity), smoking, and sedentary behaviour



CRC: Colorectal cancer; QOL: Quality of life

Figure 1.2 Conceptual framework of the study

(Ionescu *et al.*, 2023). While amongst non-modifiable risk factors are socio-demographic (e.g. race and location) and family and personal medical history (e.g. family history of CRC and inflammatory bowel disease [IBD]) (Sawicki *et al.*, 2021).

CRC itself has a direct impact on the QOL. Therefore, the second part of the framework address several factors that may influence the QOL of survivors including socio-demographic (e.g. race, marital status, and educational level) (Magaji *et al.*, 2019), nutritional status consisting of nutritional risk (malnourished) and anthropometric (e.g. body weight, BMI, and abdominal obesity) (Vissers *et al.*, 2017), biochemical parameters (e.g. albumin and total cholesterol), clinicopathological (e.g. tumor location and tumor-node-metastasis (TNM) staging), and treatments (e.g. surgery, chemotherapy, and radiotherapy) (Law *et al.*, 2023). Age and gender are statistically controlled for in the analysis to better isolate the impacts of other variables because they are known to affect biological processes, disease susceptibility, lifestyle behaviours, and access to healthcare (Jayasekara *et al.*, 2017).

This conceptual framework provides a thorough foundation for analysing the predicting indicators at the pre-treatment and post-treatment stages of CRC. It is intended to support empirical investigation and contribute to the development of targeted strategies for prevention and early detection of CRC and polyp and as supportive care for survivors.

1.9 Operational definitions

An operational definition refers to the specific procedures used to quantify or measure a variable and these procedures must be clear, precise, and comprehensive (Winne, 2023).

Food groups, micro and macronutrients- Food and beverages consumed by individuals were assessed using a semi-quantitative food frequency questionnaire (SQFFQ) where daily intake is estimated by multiplying the frequency of intake per day by the total number of servings and the weight of food in one serving.

Vitamin/mineral supplements- These are dietary supplements that contain vitamins or minerals. The National Health and Morbidity Survey (NHMS) 2014's Module E1 on vitamin and mineral supplement intake was used for measurement. Yes, no, don't know, and refuse to answer were the recorded responses. Multivitamins and minerals, vitamin A and carotenoids, vitamin B complex, vitamin B12, and vitamin C are examples of supplements.

Food supplements- Supplements containing vitamin, mineral, fatty acids, amino acids, and others used to improve an individual's diet. Data were collected using the Module E2 of food supplement intake by National Health and Morbidity Survey (NHMS) 2014 with responses categorised as yes, no, don't know, and refuse to answer. Example of supplements are fish oil, essence of chicken, *haruan* fish stock, garlic pil, birds's nest stock, evening primrose oil, and collagen.

Smoking- Self-reported smoking history indicating either a yes or no responses.

Sedentary behaviour- Sedentary behaviour was operationally defined using the Sedentary Behaviour Questionnaire (SBQ) which assesses time spent in nine sedentary activities (e.g. watching television, playing computer or video games, sitting, and listening to music) separately for weekdays and weekends. Then, total sedentary time was calculated in hours per day for weekdays and weekends individually allowing for distinct analysis of sedentary patterns across the week.

Nutritional risk- Nutritional risk was operationally defined using the nutritional risk screening 2002 (NRS 2002) tool which assesses a patient's nutritional status and disease severity based on BMI, recent weight loss, recent dietary intake, and the impact of illness with an additional point added for patients aged 70 years and above. A total score of three or higher which was used to identify patients at nutritional risk.

BMI- Calculated by dividing weight in kilograms by the square of height in meters.

Race- Defined based on self-reported socio-demographic categories such as Malay, Chinese, and Indian races.

Family history of CRC- Self-reported under family and personal medical history by responding to yes or no responses.

Albumin- Measured in grams per litre (g/L) of blood serum using methods such as bromocresol green (BCG) or enzyme-linked immunosorbent assay (ELISA) as recorded in the hospital information system.

Tumour location- Measured based on biopsy procedure and imaging test such as computed tomography (CT) scan. The tumor location is obtained from the patient's medical folder.

Surgery- Surgical removal of a tumor from the bowel through procedures such as anterior resection and colectomy as documented in the patient's medical folder.

CHAPTER 2

LITERATURE REVIEW

2.1 Nutritional status

Nutritional status plays a critical role in the development, progression, and clinical outcomes of colorectal diseases, including colorectal cancer (CRC) and colorectal polyps. Multiple studies have highlighted varying patterns of malnutrition, obesity, and dietary risk factors among affected individuals both at the time of diagnosis or after being diagnosed and during the pre-treatment phase.

2.1.1 Colorectal cancer (CRC)

The nutritional status of CRC patients may vary at diagnosis and post-treatments. A cross-sectional study from Nigeria found that the percentage of underweight patients increased before CRC diagnosis and after CRC appearance (1.1% to 14.4%) and normal weight also increased from 35.6% to 54.4% (Negrichi & Taleb, 2020). While for overweight patients the rate decreased from 32.2% to 18.9% and for obesity it decreased from 31.1% to 12.2% (Negrichi & Taleb, 2020).

Nutrition risk index (NRI) has shown a significantly high percentage of male patients having malnutrition (Negrichi & Taleb, 2020). A retrospective study among stage II and III CRC observed that 41% of the patients classified as malnourished based on the nutritional screening tool, Subjective Global Assessment (SGA) (Wimmer, 2024). An observational study conducted among cancer patients in UK showed that

the risk of malnutrition was high (53.3–56.7%), depending on the assessment method used (Plyta *et al.*, 2020).

The cross-sectional study in Malaysia found that the percentage of severely malnourished, mild to moderately malnourished, and well-nourished patients among early diagnosed of CRC was around 48%, 17%, and 34% respectively (Krishnasamy *et al.*, 2017). The nutritional status of the patients assessed by using Mini Nutritional Assessment (MNA) observed that 29.4%, 46.1%, and 24.3% of patients undergoing CRC surgery was well nourished, at risk of malnutrition, and malnourished respectively (Daniele *et al.*, 2017).

Retrospective study design conducted in Italy reported that by using MNA as assessment tool, the percentage of malnourished and well-nourished among CRC patients were around 21.3% and 11.9% during their first visit in oncology clinic (Muscaritoli *et al.*, 2023). On the other hand, by using the Patient Generated Subjective Global Assessment (PG-SGA), an observational study in Portugal found that the prevalence of malnutrition among cancer patients were high with approximately around 89% classified as moderately or severely malnourished (Trabulo *et al.*, 2022).

2.1.2 Colorectal polyp

Poor nutritional status is commonly observed among patients with colorectal polyp. Recent evidence indicated a high proportion of obesity and abdominal obesity in this population along with elevated dietary inflammation scores (DIS) where by, out of 55 respondents with colorectal adenoma (CRA), there were around 11 and 10

respondents classified in the obese and visceral obesity category (de Freitas *et al.*, 2020). The percentage patients with body mass index (BMI) ≥ 30 was higher in polyp (36.3%) than non-polyp group (27.7%) while percentage of patients with BMI < 25 and BMI between $25 \leq$ to < 30 was lower in polyp (28.9% and 34.7% respectively) as compared to non-polyp (35.0% and 37.3% respectively) group (Najafi Mobaraki *et al.*, 2024).

According to Byrd *et al.* (2020), patients with CRA consumed more total energy (2054 kcal/day vs. 1985 kcal/day), a higher percentage of energy from fat (31.3 % kcal vs. 30.2 % kcal), and processed meats (2.7 servings/week vs. 2.1 servings/week) than controls. However, they consumed less total calcium (474 mg/1,000 kcal/day vs. 511 mg/1,000 kcal/day) and fruit (16.0 servings/week vs. 17.8 servings/week) than controls. Furthermore, patients with colorectal adenoma had a higher DIS (-0.5 vs. -0.7) and lifestyle inflammation scores (LIS) (0.4 vs. 0.2) suggesting the patients with colorectal adenoma are adherence to more inflammatory diet and lifestyle as compared to controls (Byrd *et al.*, 2020).

Moreover, pooled data from three case-control studies shows that CRA patients consumed more red and processed meats (1.1 servings/day vs. 0.9 servings/day), total fat (65.8 % vs. 60.6%), saturated fat (22.5% vs. 20.7%), total energy (2071 kcal/day vs. 1991 kcal/day), alcohol (4.8 drinks/week vs. 3.4 drinks/week) and had higher height (170.9 cm vs. 168.1 cm) and BMI (27.5 kg/m^2 vs. 26.8 kg/m^2) as compared to polyp-free controls (Mujtaba & Bostick, 2018). A cross-sectional study in Korea shows that the mean of waist circumference (WC) and BMI were higher in adenoma than non-adenoma particularly in female patients (Kim *et al.*, 2017). Nevertheless, the

differences in mean daily intake of specific fatty acids, calories, macronutrients, and other nutrients between adenoma and non-adenoma patients was not observed in both genders (Kim *et al.*, 2017).

2.2 Epidemiology of colorectal cancer (CRC)

Epidemiology is the study of the distribution of disease and disease determinants in populations (Schwartz, 2024). The epidemiology of colorectal cancer including incidence, mortality, survival, and risk factors which varies significantly across countries, age groups, and socioeconomic levels. Monitoring these trends is essential for early detection, preventive strategies, and effective public health interventions.

2.2.1 Incidence and trend of colorectal cancer (CRC)

According to the International Agency for Research on Cancer (IARC) (2022), the estimated number of CRC incidence or new cases are around 1.9 million cases and this placed CRC as third commonly diagnosed cancer globally. While the first and second commonly diagnosed cancer was dominated by lung and female breast with the incidence rate around 2.5 and 2.3 million cases respectively (IARC, 2022).

The epidemiology of colorectal cancer (CRC) varies markedly by age, gender, ethnicity, and geographic regions around the world (Baidoun *et al.*, 2021). The age standardised incidence rate of colon and rectum is higher in male patients (12.4 and 9.1 respectively) than female patients (9.2 and 5.4 respectively) (IARC, 2022).

According to Wong et al. (2021) continuous increase of colon and rectal incidence rate could be observed in medium to high Human Development Index (HDI) countries and among the younger population.

The trend of CRC incidence varies among the countries depending on the different level of screening programmes. The screening programmes that is normally recommended are faecal immunochemical test (FIT), guaiac-based faecal occult blood test (gFOBT), fecal-immunochemical test-deoxyribonucleic acid (FIT-DNA) which is also known as multitargeted stool DNA testing, sigmoidoscopy, colonoscopy, and virtual colonoscopy (NIH, 2021; US Preventive Services Task Force, 2021).

Cardoso et al. (2021) reported that the incidence of CRC in countries with earlier screening programme such as Austria, Czech Republic, and Germany showed decreasing of average annual percentage changes (AAPCs) over time which is from -2.5% to -1.6% in men and from -2.4% to -1.3% in women. For countries with no large-scale screening programme such as Bulgaria, Estonia, Norway, and Ukraine the incidence of CRC showed an increment with the AAPCs value from 0.3% to 1.9% in men and from 0.6% to 1.1% in women (Cardoso *et al.*, 2021).

Nowadays, the trend of colorectal incidence increases among adults younger than 50 years. The average annual percentage change of colon cancer (CC) incidence was found increased among people younger than 50 years old, residing in Denmark (by 3.1%; per year), New Zealand (2.9% per year), Australia (2.9% per year), and the UK (1.8% per year) (Araghi *et al.*, 2019). Meanwhile for the rectal cancer incidence, the average annual percentage change also showed an increment in those age group

particularly for people residing in Canada (by 3.4% per year), Australia (2.6% per year), and the UK (1.4% per year) (Araghi *et al.*, 2019).

The CRC incidence was not only rising among younger age adults in Western and high-income countries but also seen across Asia. Taiwan and Korea were found to have higher rates of colon and rectal cancer among men and women under 50 (Sung *et al.*, 2019). The increasing of the incidence was most obviously observed among male rectal cancer by 3.9% per year in Taiwan and 6.0% per year in Korea (Sung *et al.*, 2019). A study among the China population showed that, the age-standardized incidence rate (ASIR) of CRC in people aged 15-49 years increased from 3.35 per 100,000 in 1990 to 7.32 per 100,000 in 2016 (Zhang *et al.*, 2019). Moreover, the average annual percentage change (AAPC) for those age group was found highest among other groups (Zhang *et al.*, 2019).

The annual percentage change (APC) of CRC incidence in adults aged <50 years was found to increase faster than aged ≥ 50 years, not only in Western countries such as Australia (+1.10% vs. -0.35%), Brazil (+9.20% vs. +5.72%), Canada (+2.60% vs. -0.91%), United Kingdom (UK) (+3.33% vs. +0.77%), and United States (US) (+1.98% vs. -2.88%) but also in the Eastern countries including China-Hong Kong (+1.82% vs. -0.10%), China-Shanghai (+1.13% vs. -2.68%), and Japan (+2.63% vs. +0.90%) (Lui *et al.*, 2019).

In northern Malaysia, the ASIR of CRC was stable and increased from 17.03 per 100,000 in 2012 to 20.01 per 100,000 in 2016 (Ismail *et al.*, 2022). This uptrend could be observed among the population aged between 60 to 69 years particularly

among Malays. Such findings were not surprising as this demographic represent majority of the patients that commonly access care from public health institutions and has a higher chance to be offered a stool-based screening test (Ismail *et al*, 2022).

Another study conducted in Northern Malaysia found that the ASIR of CRC among individual under 50 remained stable from 2007 to 2017 (Wan Ibrahim *et al.*, 2020). During the period of 1997-2002 and 2003-2007, the incidence rate was stable which was 3.00 per 100,000 and 3.85 per 100,000 respectively (Muhammad Nawawi *et al.*, 2021). However, the incidence rate was found elevated to 6.12 per 100,000 in 2008-2012 and declining to 4.54 per 100,000 in the 2013-2017 (Muhammad Nawawi *et al.*, 2021).

2.2.2 Mortality and trend of colorectal cancer (CRC)

The estimated number of death cases of CRC is around 904,000 and this estimation ranked CRC as the second leading cause of cancer mortality worldwide (IARC, 2022). There is a reduction of CRC mortality rate in twenty-four countries such as Oceania, North America, and majority of the European countries. However, there is an elevation of the rate in several countries in Southern Europe, Latin America, and Asia based on 39 countries of World Health Organization (WHO) database (Wong *et al.*, 2021).

According to World Health Organization (WHO) mortality database from 42 countries between 1989–2016, the mortality rates for CC was expected to keep decreasing in most countries from Asia, Europe, North America, and Oceania, with

the exception of countries in Latin America and the Caribbean (Araghi *et al.*, 2018). For rectal cancer, the mortality rates were similar to those of CC (Araghi *et al.*, 2018). However, the rates were predicted to increase significantly in Costa Rica (+73.6%), Australia (+59.2%), the US (+27.8%), Ireland (+24.2%), and Canada (+24.1%) (Araghi *et al.*, 2018).

The Global Cancer Observatory (GLOBOCAN) database which includes 60 countries between 2000-2019 showed that the trend of mortality decreased in several high-HDI countries where the greatest declines could be observed in Austria (AAPC, -2.74) and Germany (AAPC, -2.51) (Lu *et al.*, 2021). According GLOBOCAN 2018 database, the mortality rate for CRC varies by countries and population and HDI (Goodarzi *et al.*, 2019). Cardoso *et al.* (2021) reported a largest reduction of CRC mortality for countries with earlier or long-standing screening programmes such as Germany, Austria, and the Czech Republic while a modest reduction was found for countries without nationwide large-scale screening programmes namely Sweden and Norway.

A study in China shows that the cancer deaths rose from 81,100 in 1990 to 167,100 in 2016, yet the ASMR remained fairly constant (-0.04 , 95% CI -0.13 , 0.05) (Zhang *et al.*, 2019). The ASMR in males were slightly increased (AAPC = 0.42 , 95% CI 0.34 , 0.51) while in females the rate significantly decreased (AAPC = -0.75 , 95% CI -0.90 , -0.60) (Zhang *et al.*, 2019). Zhang *et al.* (2019) also reported that CRC deaths was predicted to increase from 167,100 in 2016 to 221,100 in 2025.