DIETARY PATTERN AND RISK FACTORS ASSOCIATED WITH NEWLY DIAGNOSED COLORECTAL CANCER AND PREDICTIVE FACTORS FOR QUALITY OF LIFE AMONG SURVIVORS

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by

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LIST OF ABBREVIATIONS

BMR	Basal metabolic rate
CI	Confidence interval
CL	Confidence limit
CRC	Colorectal cancer
CTC	Computed tomographic colonography
EI	Energy intake
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30
EORTC QLQ-CR29	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire CR29
FFQ	Food frequency questionnaire
GHS/QOL	Global Health Status/ Quality of Life
GLOBOCAN	Global Cancer Observatory
HC	Hip circimference
HCA	Heterocyclic amines
HCTM UKM	Hospital Canselor Tuanku Muhriz Universiti Kebangsaan Malaysia
HDL cholesterol	High density lipoprotein cholesterol
HRQOL	Health related quality of life
HUSM	Hospital Universiti Sains Malaysia
IBD	Inflammatory bowel disease
IBS	Irritable bowel syndrome

IGF-1	insulin-like growth factor 1
LDL cholesterol	Low density lipoprotein cholesterol
NHANES	National Health and Nutrition Examination Survey
NHMS	National Health and Morbidity Survey
NOC	N-nitroso-compound
OR	Odds ratio
PAH	Polycyclic aromatic hydrocarbons
PAL	Physical activity level
RNI	Recommended nutrient intake
SD	Standard deviation
SPSS	Statistical Package for the Social Sciences
WC	Waist circumference
WHO	World Health Organisation
WHR	Waist-hip ratio

LIST OF APPENDICES

CORAK PEMAKANAN DAN FAKTOR RISIKO YANG BERKAITAN DENGAN PESAKIT YANG BARU DIDIAGNOSIS KANSER KOLON DAN FAKTOR PERAMAL BAGI KUALITI HIDUP DALAM KALANGAN PESAKIT PEMANDIRI

ABSTRAK

Kanser kolon (CRC) adalah kanser kedua tertinggi di Malaysia, dan ketiga di seluruh dunia dan Asia. Kajian ini mempunyai 3 fasa: Fasa kesahan soal selidik kekerapan makanan (FFQ), dasar dan susulan. FFQ mempunyai 142 item dibina secara spesifik berkait dengan risiko CRC. Pada fasa dasar, 341 pesakit (107 kes dan 234 kontrol) melengkapkan pengukuran antropometri dan soal selidik bertujuan untuk meramalkan faktor risiko dan corak pemakanan yang dikaitkan dengan kanser kolon. Penilaian susulan telah dilakukan 6 bulan selepas diagnosis bagi pengukuran antropometrik dan kualiti hidup menggunakan soal selidik EORTC QLQ C30 dan CR29. Dapatan kajian menunjukkan kesahan dan penghasilan semula FFQ adalah bersesuaian. Umur lebih 51 tahun (Nisbah Odds (OR) 7.72; 95% CI = 1.10–54.4), kewujudan darah dalam najis (OR 6.30; 95% CI = 1.89–20.99), penurunan berat badan yang tidak diingini (OR 21.95; 95% CI = 6.04–79.76) dan penurunan jisim lemak (OR 0.92; 95% CI = 0.85–1.00) mempunyai risiko yang lebih tinggi untuk mendapat kanser kolorektal. Sementara itu corak pemakanan makanan terproses (OR = 3.45; 95% CI = 1.25 – 9.52) didapati dikaitkan dengan risiko kanser kolorektal. Kajian susulan mendapati pesakit yang lebih tua dan peringkat penyakit yang kronik mempunyai kualiti hidup yang rendah. Kesimpulannya, FFQ baru sesuai untuk menilai pengambilan makanan pesakit CRC di Malaysia. Faktor risiko CRC adalah berusia 51

tahun ke atas, darah dalam najis, turun berat badan yang tidak diingini, turun jisim lemak badan dan kecenderungan terhadap makan terproses. Faktor yang mempengaruhi kualiti hidup yang rendah adalah pesakit lebih tua dan mempunyai kanser kolorektal tahap kronik. Faktor risiko CRC, pola pemakanan yang berkaitan dengan CRC dan faktor ramalan QOL rendah yang terdapat dalam kajian ini perlu diberi lebih penekanan oleh penggubal dasar dan pengamal kesihatan demi pencegahan dan pengurusan pesakit CRC pada masa hadapan.

DIETARY PATTERN AND RISK FACTORS ASSOCIATED WITH NEWLY DIAGNOSED COLORECTAL CANCER AND PREDICTIVE FACTORS FOR QUALITY OF LIFE AMONG SURVIVORS

ABSTRACT

Colorectal cancer (CRC) is the second most common diagnosed cancer in Malaysia while the third in worldwide and Asia. This study had 3 phases: food frequency questionnaire (FFQ) validation, baseline and follow-up. The FFQ was developed specifically related to CRC risk consisted of 142 food items. At baseline phase, 341 patients (107 cases and 234 controls) enrolled to complete anthropometric assessments and questionnaire to predict risk factors and dietary pattern associated with CRC. Follow up assessment on anthropometric measurements and quality of life (QOL) using EORTC QLQ C30 and CR29 were performed after 6 months post diagnosis. As a result, this FFQ had good reproducibility and validity. Aged >51 years old (Odds ratio (OR) 7.72; 95% CI = 1.10–54.4), blood presence in stool (OR 6.30; 95% CI = 1.89–20.99), unintended weight loss (OR 21.95; 95% CI = 6.04–79.76) and reduced fat mass (OR 0.92; 95% CI = 0.85–1.00) had higher risk of getting CRC. Meanwhile the Processed diet pattern (OR = 3.45; 95% CI = 1.25–9.52) was found to be associated with CRC risk. The follow up study showed older patients and chronic stage predicts low QOL. In conclusion, the newly developed FFQ was good to assess dietary intake related to CRC in Malaysia. Predictor of CRC consisted of aged >51 years old, blood presence in stool, unintended weight loss, reduced fat mass and adherence to the Processed diet pattern. Predictive of low GHS/QOL was related to older patients and those with chronic stage of CRC. The risk factors of CRC, dietary

pattern related to CRC and predictive factors of low QOL found in this study should be given more emphasis by policy makers and healthcare practitioners for the prevention and management of CRC patients in the future.

CHAPTER 1
INTRODUCTION

1.1 Background of the study

Global Cancer Observatory (GLOBOCAN) 2018 estimated colorectal cancer (CRC) become the third in incidence and the second top cancer mortality worldwide (American Institute for Cancer Research, 2018). New cases of CRC around 1.36 million were diagnosed from GLOBOCAN 2015 increased to 1.8 million in GLOBOCAN 2018 shows an epidemic concern worldwide (Lee, Keum & Giovannucci, 2016; World Cancer Research Fund/American Institute for Cancer Research, 2018). In Malaysia, an increasing trend of 15,515 cases of CRC (2012-2016 report) from 13,693 cases (2007-2011 report) (National Cancer Institute, 2019) evident by poor awareness among public on CRC screening (Norwati *et al.*, 2014).

The underlying factors of CRC can be rooting from non-modifiable and modifiable risk factors (CS Wong *et al.*, 2019). Non-modifiable risk factors encompass genetic factors, age, sex, ethnicity, and familial history of CRC (CS Wong *et al.*, 2019). CRC burden is also attributable to metabolic and behavioural risk (Aleksandrova, Nimptsch & Pischon, 2013; Perdamaian, 2019). Behavioral or lifestyle factor is a type of risk factor that can be modified to prevent CRC occurrence. Present factors comprise of smoking, overweight and obesity, physical inactivity, alcohol intake, and dietary patterns (Sawicki et al., 2021a).

Dietary patterns enable the investigation of how food and nutrient interactions impact disease outcomes (Castelló *et al.*, 2019). Traditionally, studies examining CRCs have categorized dietary patterns into two main groups: the western/unhealthy pattern and the prudent/healthy pattern (Randall E. *et al.*, 1992; Slattery *et al.*, 1998; Fung *et al.*, 2003; Flood *et al.*, 2008; Satia *et al.*, 2009; Williams *et al.*, 2009; Miller *et al.*, 2010; Mehta *et al.*, 2017). A diet characterized by a western dietary pattern, which includes a high intake of meats (red and processed), refined grains and sugar-rich food (Garcia-Larsen *et al.*, 2019). Meanwhile, prudent dietary pattern had a protective effect of a diet rich in fruits, vegetables, legumes and/or fish (Castelló *et al.*, 2019). Majority of these studies were conducted in Western setting among Caucasians and little in Asia. Difference in body composition and dietary consumption between Asian and Caucasian may produce different outcome measures.

Once CRC patients were diagnosed and received treatment, individuals who have been successfully treated and are considered long-term survivors may experience persistent issues well beyond the completion of their treatment. The assessment of patients' self-reported quality of life (QOL) is crucial in alleviating symptoms, providing optimal care, and facilitating the rehabilitation of patients (Haraldstad *et al.*, 2019). Even though treatments are not curative for most patients, QOL is often considered the predictor of treatment success. As a result, the goals of treatment are oriented towards improving survival, slowing tumor progression, effectively managing symptoms, and enhancing overall QOL (Andre *et al.*, 2021; Flyum *et al.*, 2021).

Taken together, these findings provide the impetus to understand the risk factors which contribute to the development of CRC. Coupled with genetic, lifestyle factors, and dietary patterns may accelerate the onset of CRC (Francescangeli, De Angelis & Zeuner, 2019) and lead to poor QOL during post-treatment. It is also potentially to explore new dietary patterns associated with Malaysian CRC because each population has different food supply and dietary habits. Therefore, this study was designed to explore all these aspects.

1.2 Problem statement

Colorectal cancer is the first and second most common cancer in Malaysian males and females, respectively (National Cancer Institute, 2019). It is the third most commonly diagnosed cancer and the second most common cause of cancer mortality worldwide (Xi & Xu, 2021). The incidence of CRC is more prevalent in highly developed nations, while middle- and low-income countries are experiencing an increasing CRC burden because of westernization (Xi & Xu, 2021). The global new CRC cases is predicted to reach 3.2 million in 2040 after considers factors such as the aging population, population growth, and advancements in human development (Keum & Giovannucci, 2019).

Evidence suggests that diet may be important for primary prevention (Tabung, Brown & Fung, 2017). Having difficulty in study of single dietary factors, therefore the evaluation of dietary patterns in relation to CRC outcomes is an important complementary approach (Cespedes & Hu, 2015). From this perspective, highlighting the dietary pattern is therefore important to aid in predicting, decreasing, and preventing future CRC development. The dietary factors related to CRC are unclear through Malaysian food items and dishes at this point. In order to fill in this knowledge gap, it is a need to establish a CRC-focused Food Frequency Questionnaire (FFQ) which is currently unavailable in Malaysia. Nutrition and lifestyle factors has been suggested as the biological plausible mechanism of CRC development (Guffey, 2013). Since nutrition and lifestyle factors are modifiable, understanding the causal and contributing roles of nutrition and lifestyle may suggest a novel approach for healthy lifestyle changes.

Survival rate of CRC patients is greatly dependent on the cancer stage, for example the 5-year relative survival rate exceeds 90% for the localized stage while less than 10% for the distant stage (Siegel *et al.*, 2020). A significant number of individuals who have survived CRC often endure a substantial load of symptoms, including fatigue, bowel dysfunction, depression, and insomnia (Tantoy *et al.*, 2016). This burden of symptoms has a considerable impact on their QOL following the completion of treatment. It also has a profound influence on the overall CRC survivorship. In view of that, this study was embarked to study which factors affecting the QOL among survivors to provide a better understanding on how to optimize the health related QOL during the post treatment.

1.3 Significance of the study

This study provides a comparison database between CRC cases and controls. Comprehensive parameters related to nutrition and lifestyle factors were examined throughout the study, including nutritional status, dietary pattern, vitamin/ mineral supplementation and smoking. A study examining the validity and reproducibility of a FFQ in relation to CRC has not been conducted among the Malaysian population. It is important to conduct such a study because each population may have unique food supply and dietary habits, necessitating research specific to the Malaysian context. All these data add considerable information to the body of literature pertinent to the gut health in Malaysia. These data may also indicate the future research directions as it can stimulate multiple research ideas especially in the aspect of interventional studies towards CRC patients.

This study too would be a pioneer study in determining dietary pattern associated with CRC among Malaysian. There is a limited application of the dietary pattern associated with CRC to non-western populations, as indicated by the scarcity of studies examining the link between dietary patterns and CRC risk specifically in Asian populations. The investigations of various causative factors of occurrence of CRC will expand the knowledge relating to the mechanistic pathway of pathogenesis. It is hoped that identification of the underlying causes of CRC can provide novel approach to reduce the health burdens and cancer mortality in future. The present findings will therefore provide conclusive evident related to preventive medicine.

1.4 Objectives

1.4.1 General objectives

The general objective of the study is to predict risk factors and dietary patterns associated with CRC occurrence among Malaysian patients and factors associated with QOL among survivors.

1.4.2 Specific objectives

a. Phase 1:

i. To evaluate the reproducibility and validity of a FFQ for dietary intake related to risk of CRC in Malaysia.

b. Phase 2:

i. To compare socio demographic, socio economic status, health behaviour and CRC symptoms between CRC cases and controls.

ii. To compare nutritional status (anthropometric, biochemical and dietary assessment) between CRC cases and controls.

iii. To predict the associated risk factors of CRC.

iv. To predict dietary patterns related to CRC risk.

c. Phase 3:

i. To assess changes in nutritional status (anthropometric assessment) after 6 months follow-ups in CRC cases.

ii. To predict the associated factors (age, sex, CRC stage and anthropometry) of QOL after 6 months follow-up in CRC cases.

1.5 Research questions

a. Phase I:

i. What are the reproducibility and validity of FFQ for dietary intake related to CRC in Malaysia?

b. Phase II:

i. Is there any difference of socio demographic, socio economic status, health behaviour and CRC symptom between CRC cases and controls?

ii. Is there any difference of nutritional status (anthropometric, biochemical and dietary assessment) between CRC cases and controls?

iii. What are the associated factors of CRC risk?

iv. Which dietary patterns related to CRC risk?

c. Phase III:

i. Is there any changes in nutritional status (anthropometric assessment) after 6 months follow-ups in CRC cases?

ii. What are the associated factors (age, sex, CRC stage and anthropometry) of QOL after 6 months follow-up in CRC cases?

1.6 Alternative hypotheses

a. Phase I:

i. The reproducibility and validity of the FFQ was suitable to assess dietary intake related to CRC in Malaysia.

b. Phase II:

i. Socio demographic, socio economic status, health behaviour and CRC symptom are significantly different between CRC cases and controls.

ii. Nutritional status (anthropometric, biochemical and dietary assessment) is significantly different between between CRC cases and controls.

iii. Associated factors significantly related to CRC risk.

iv. Dietary pattern significantly related to CRC risk.

c. Phase III:

i. Anthropometric changes after 6 months follow-up is significant in CRC cases.

ii. Associated factors significantly related to QOL in CRC cases.

1.7 Conceptual framework

The overall concept of the study is presented in Figure 1.1. This framework is grounded on risk factors of CRC including modifiable and non-modifiable variables (Padmanabhan *et al.*, 2018; Wang *et al.*, 2019). Non-modifiable risk factors are risk factors that cannot be controlled by individuals such as age, sex, ethnic and family history. Meanwhile modifiable risk factors consist of nutrition and lifestyle factors such as nutritional status, dietary patterns, dietary supplementation, and tobacco use. Adiposity, abnormal biochemical reading, unhealthy dietary pattern, no consumption of supplementation and active/ passive smoker may contribute to higher risk of CRC occurrence. The predictive factors for quality of life include age, sex, disease stage and changes in anthropometry after 6 months diagnosed and received treatment.

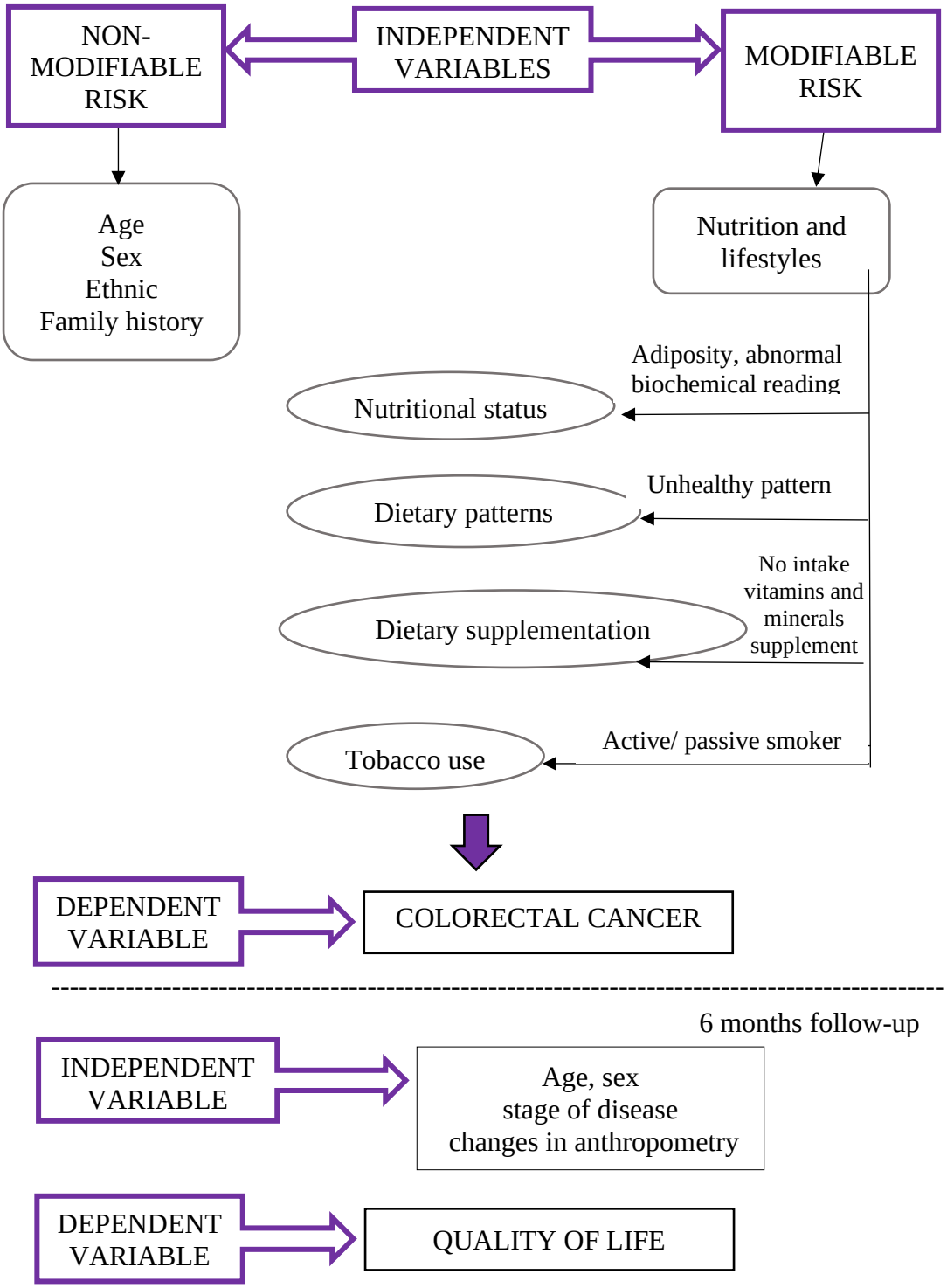

Figure 1.1 Conceptual framework of the study

1.8 Operational definitions

Cancer survivor - Those with cancer history from the time of diagnosis through the balance of life including those living with cancer and those free of cancer (National Cancer Institute, 2024).

Colorectal cancer - Cancer that develops in the colon including the longest part of the large intestine and/or the rectum (the last several inches of the large intestine before the anus) (National Cancer Institute, 2023a).

Dietary patterns - defined as the quantity, variety, or combination of different foods and beverage in a diet and the frequency which they are habitually consumed (United States Department of Agriculture, 2014).

Nutritional status – the assessment of anthropometric, biochemical and dietary to represent states of personal's health.

Obesity – having body mass index exceeding 25 kg/m^2 as outline by WHO (World Health Organization (WHO), 2000).

Objective measurement – measurement does not rely on written or verbal responses from the respondent under study but instead record phenomena to increase accuracy (Medical Research Council, 2023).

Processed dietary pattern – Adherence to the intake of confectionaries and fast foods

Quality of Life - measure aspects of an individual's sense of well-being and ability to carry out activities of daily living (National Cancer Institute, 2023b).

Reproducibility - is obtaining consistent results using the same input data; computational steps, methods, and code; and conditions of analysis (National Library of Medicine, 2019).

Risk factor - Variable that increases the chance of developing a disease (National Cancer Institute, 2023c).

Validity - the extent to which an instrument is accurately measured in a quantitative study (Heale & Twycross, 2015).

CHAPTER 2
LITERATURE REVIEW

2.1 Colorectal cancer (CRC)

Human cells divide normally as required and die when getting old throughout lifetime. However, cancer cells initiated when normal physiology become interrupted which led to aggressive growth of cancer cells making normal cells crowd out (American Cancer Society, 2022). Cancer can emerge anywhere in the body and is named according to where it originated. Two main categories of cancer which are hematologic cancers (cancers of the blood cells: leukemia, lymphoma, and multiple myeloma) and solid tumor cancers (cancers from organs or tissues) (American Cancer Society, 2022). CRC is a disease in which cells in the colon or rectum grow abnormally and actively (Centers for Disease Control and Prevention, 2023). Colon cancer and rectal cancer are usually grouped together because both have almost common features (American Cancer Society, 2020).

Water and salt absorbed by the colon from the excess food matter after passing through small intestine. Section of colon consists of ascending colon, followed by transverse, descending and sigmoid colon. The waste leftover then goes into the rectum to be stored until it passes the anus. Both ascending and transverse sections are labelled as proximal colon, while descending and sigmoid colon as distal colon (Figure 2.1) (American Cancer Society, 2020).

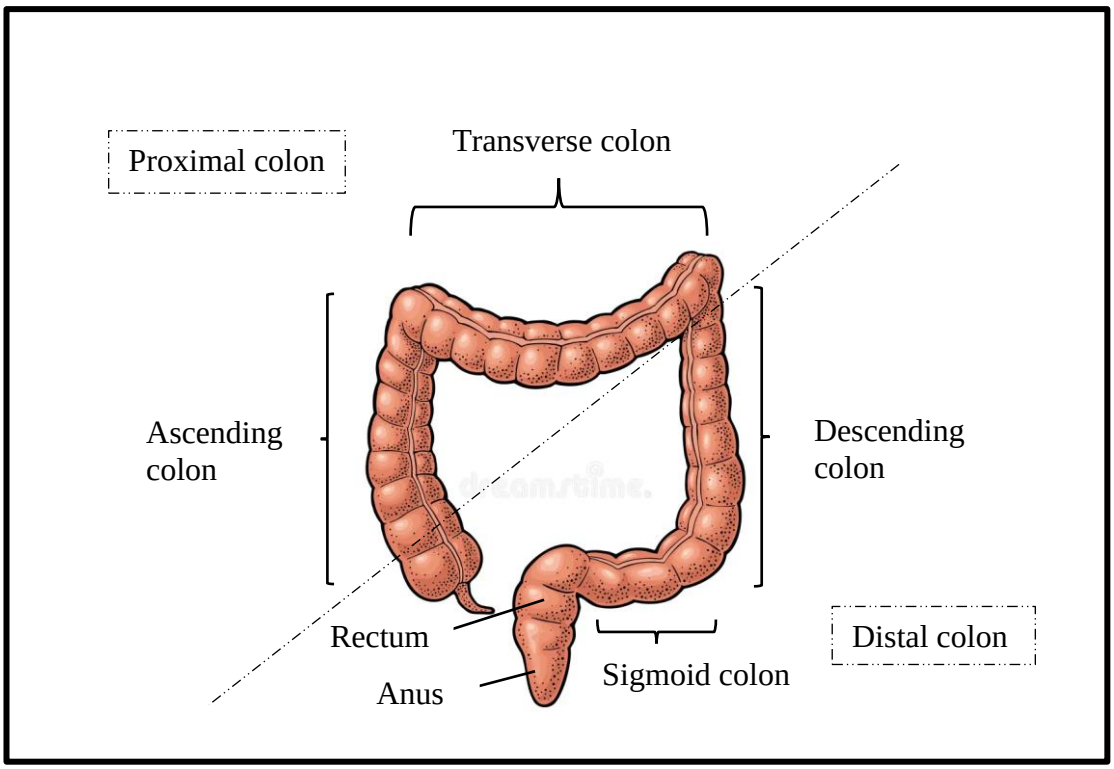

Figure 2.1 Anatomy of large intestine (colon)

(Source: Adopted and modified from American Society of Colon & Rectal Surgeons)

At an early phase, physicians carry out physical examination and subject examination before consult patients' family history, risk factors, and appropriate diagnosis method (Sawicki *et al.*, 2021). Colonoscopy, sigmoidoscopy and fecal occult blood test are the most frequently utilised screening test after computed tomographic colonography (CTC) and DNA stool test (Lauby-Secretan *et al.*, 2018). In the United States, colonoscopy become the predominant screening test and to be performed every 10 years as a recommendation (Davidson *et al.*, 2021). However, colonoscopy is more invasive and burdensome compared to fecal occult blood test and sigmoidoscopy for patients, and it requires more clinical resources (Bretthauer *et al.*, 2022). Typical symptoms of CRC patients include rectal bleeding, microcytic anaemia, changed bowel habits, and persistent stomach pain (SEER, 2021). Additional diagnostics such

as imaging studies may be required to determine local stage, enlarged lymph nodes and distant metastases and the obstruction risk (Sawicki *et al.*, 2021).

Basically colonoscopy-guided biopsy confirms the primary cancer while biopsy of the liver, lung, or lymph node confirms metastases (Biller & Schrag, 2021). Localised CRC consist of nonmetastatic or stage I to III, meanwhile metastatic CRC (stage IV) defined as cancer that has spread at a distant site outside the original colorectal mass. The most common metastasis sites are lymph nodes, liver, lung, and peritoneum (Riihimäki *et al.*, 2016).

2.2 CRC prevalence

Worldwide, CRC is the third most common diagnosed cancer after breast and lung cancer according to GLOBOCAN 2020 (Figure 2.2) (International Agency for Research on Cancer, 2023a). However, CRC become the second leading cause of cancer death after lung cancer (Sung *et al.*, 2021). GLOBOCAN 2020 granting online database of global cancer estimates and statistics of incidence and mortality for 36 cancer types in 185 countries (International Agency for Research on Cancer, 2023b). By 2040, the global cancer burden is predicted to be 28.4 million cases, a 47% rise from 2020, with a larger increase in transitioning countries (64% to 95%) compared to transitioned countries (32% to 56%) due to demographic changes, although this may be further worsened by increasing risk factors associated with globalization and a growing economy (Sung *et al.*, 2021).

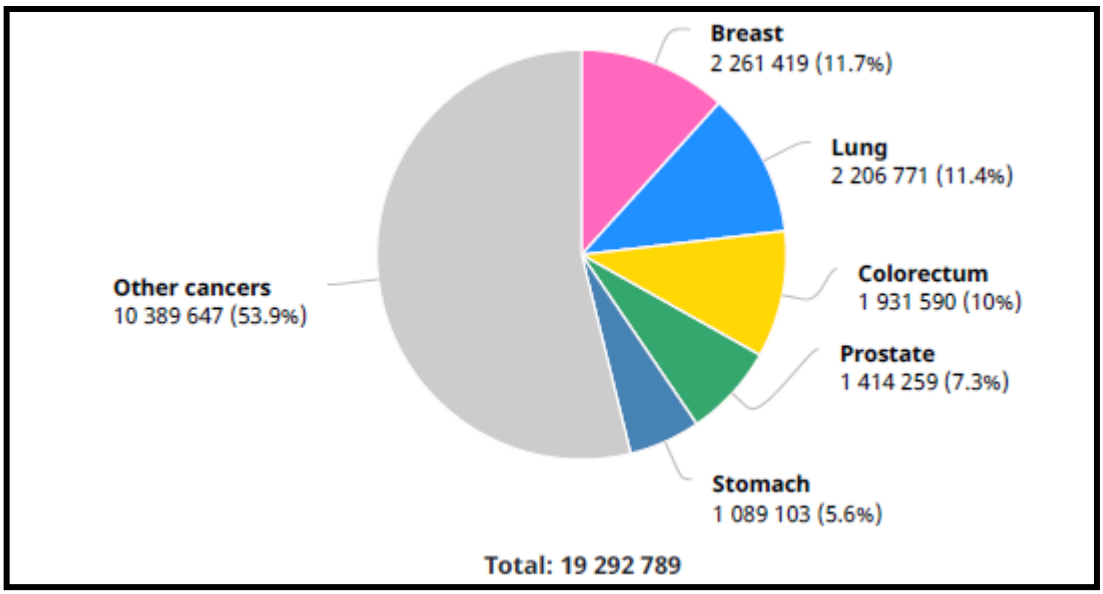

Figure 2.2 Number of new cases in 2020 for both male and female at all ages, worldwide.
(Source: Adopted from GLOBOCAN 2020)

In Asia, CRC is also the third most diagnosed new cases after lung and breast cancer in 2020 (International Agency for Research on Cancer, 2023a). Furthermore, it become the second most common diagnosed cancer for male and female following lung cancer (male) and breast cancer (female) (Figure 2.3).

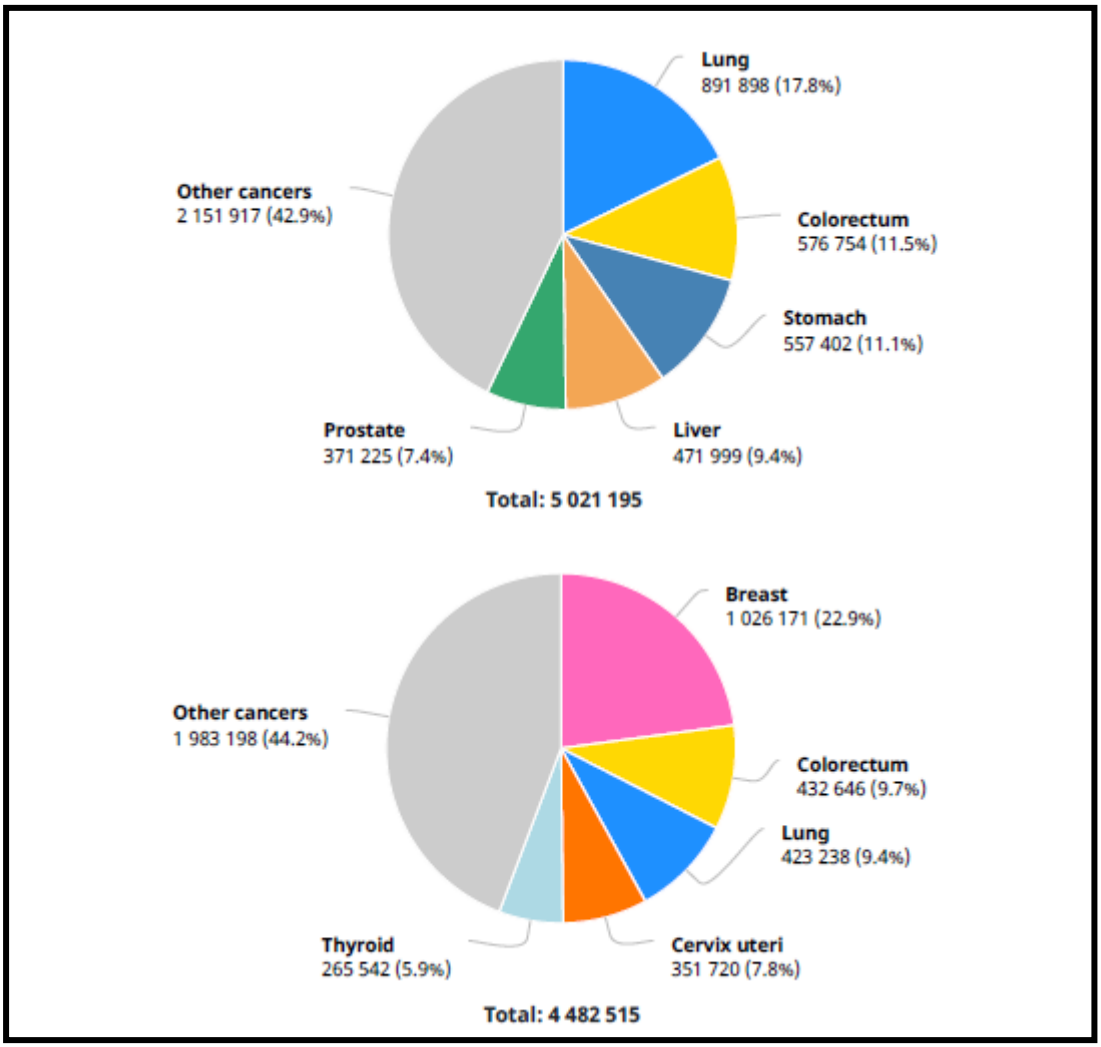

Figure 2.3 Number of new cases in 2020 for male (top) and female (bottom) in Asia.
(Source: Adopted from GLOBOCAN 2020)

The latest Malaysia National Cancer Registry Report 2012- 2016 reported ten most common cancers in Malaysia: breast, colorectal, lung trachea bronchus, lymphoma, nasopharynx, leukemia, prostate, liver, cervix uteri, and ovary cancer (Figure 2.4). CRC remained the second incidence cancer since Malaysia National Cancer Registry Report 2007- 2011 until the latest report (National Cancer Institute, 2019).

Figure 2.4 Ten most common cancers in Malaysia

(Source: Adopted from Malaysia National Cancer Registry 2012-2016)

CRC is the commonest cancer among males and the second commonest cancer amongst females. A total of 15,515 CRC cases were registered for the span of 2012-2016 compared with 13,693 cases in 2007-2011 report. Males made up 56.1% of the total registered, while females made up 43.9% (National Cancer Institute, 2019). The trend of incidence in 2012-2016 is similar to 2007- 2011 with increased rates seen between age 55 and 64 years old for males. However, higher rates are seen after the age of 50 years old in females (Figure 2.5).

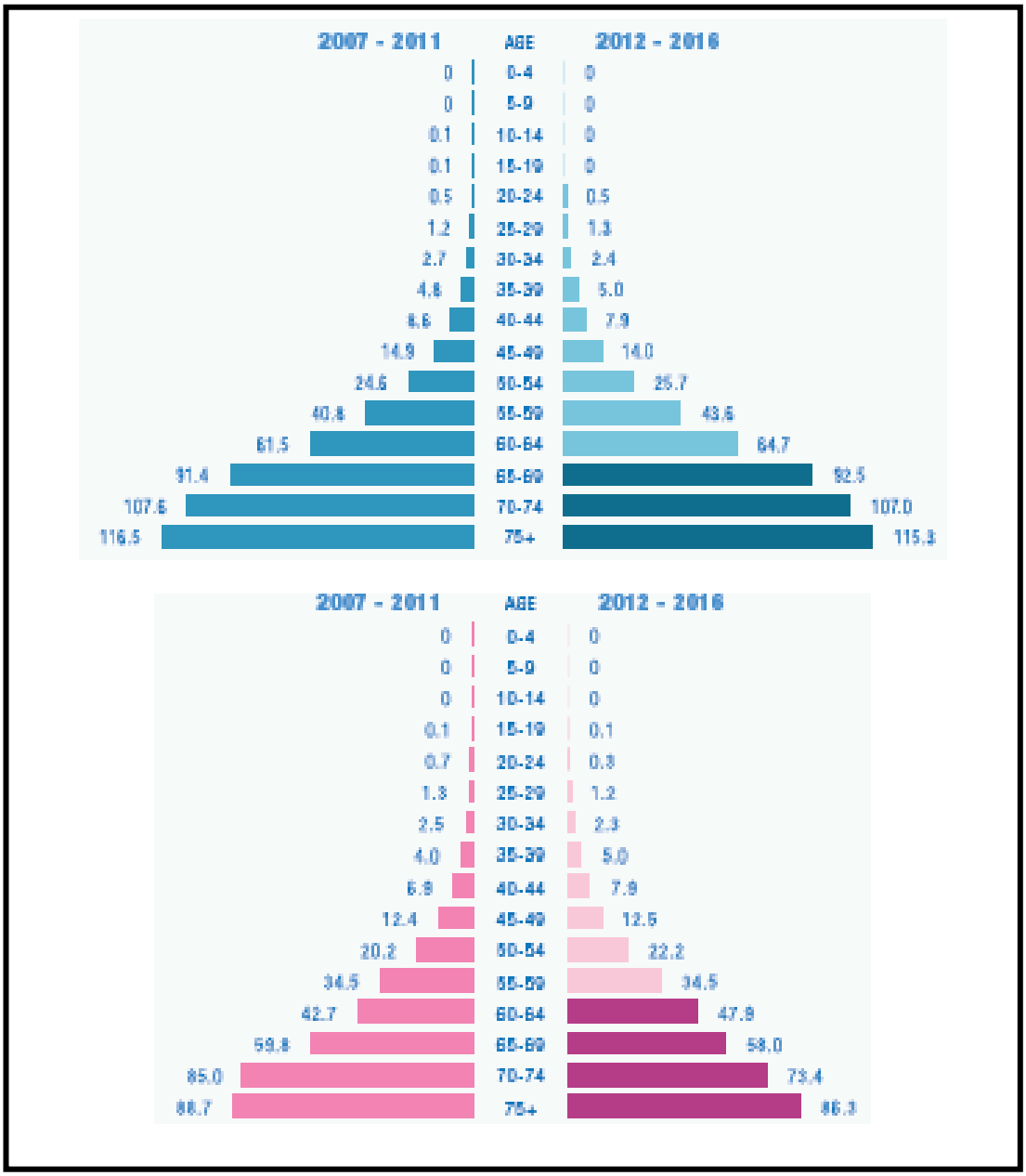

Figure 2.5 Age specific incidence rate for male (top) and female (bottom)

(Source: Adopted from Malaysia National Cancer Registry 2012-2016)

2.3 CRC risk factors

Multiple determinants have been involved in the development of CRC. Basically, risk factors were differentiated into non-modifiable and modifiable risk factors. Non-modifiable risk factors are determinants that cannot be controlled by individuals, while modifiable risk factors are individual lifestyle or habits that can be altered (Hossain *et al.*, 2022). Family and personal medical history and personal background are examples for non-modifiable risk factors, while lifestyle is a modifiable risk factor as in Figure 2.6 (Sawicki et al., 2021a).

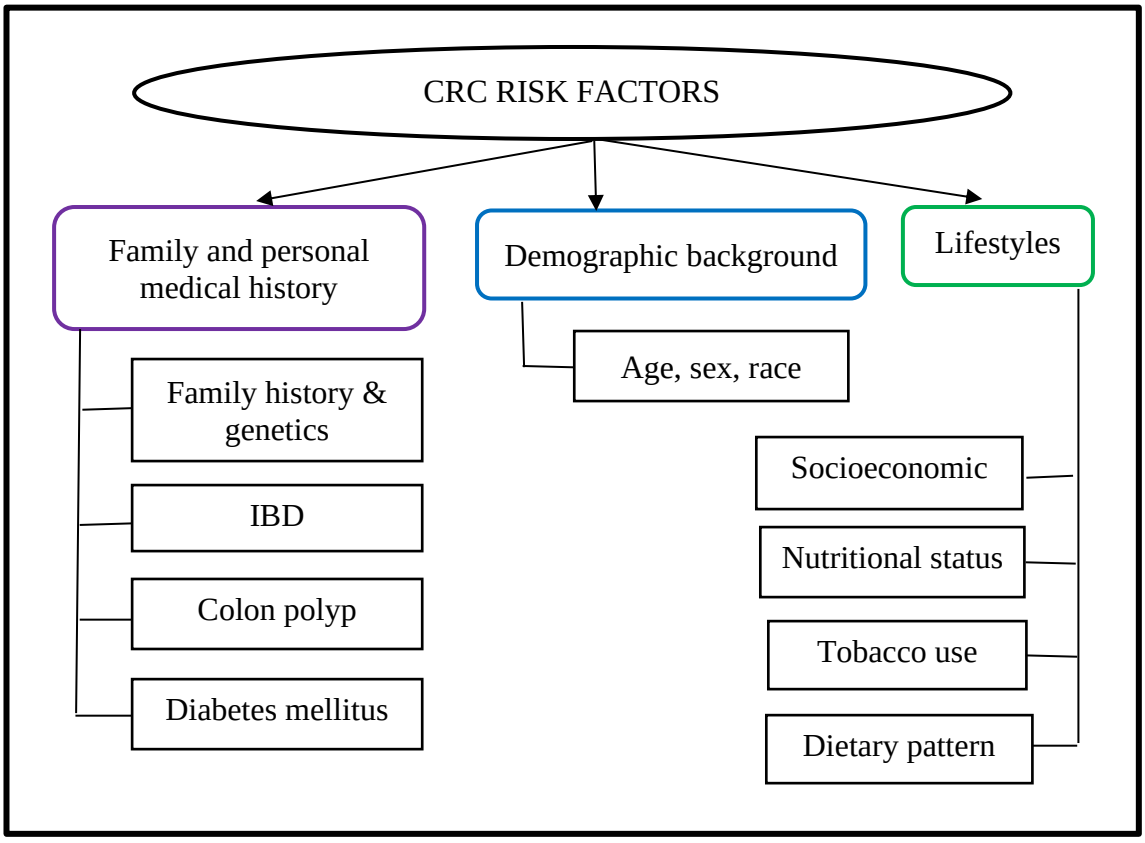

Figure 2.6 Risk factors associated with CRC

(Source: Adapted and modified from Sawicki et al., 2021)

2.3.1 Family and personal medical history

2.3.1(a) Family history and genetics

Family history is commonly divided into first-degree relatives (parent, siblings, and offspring) and second-degree relatives (grandparent, aunty, uncle, nieces, nephew or grandchild). This history has always been asked by the doctor during screening prior to diagnosis. CRC genetics also known as hereditary CRC, which exhibit around one-third familial clustering of CRC cases, but only 5 to 16% of cases are related to germline or likely-pathogenic variant in a CRC-predisposition gene (Rebuzzi, Ulivi & Tedaldi, 2023).

2.3.1(b) Inflammatory bowel disease (IBD)

IBD incorporating ulcerative colitis and Crohn's disease, is depicted by prolong inflammation in the colon (Rawla Prashanth and Sunkara, 2019). This results in raised cell turnover and higher rates of sporadic mutations (Hossain *et al.*, 2022). CRC patients with previous history of IBD may initiate tumorigenesis due to chronic inflammation over long period of time with combination of other carcinogenesis factors (Baker *et al.*, 2018). In a meta-analysis of 13 cohort studies with 44,799 IBD patients had presented the risk of CRC to be 2.93 times greater due to IBD (RR 2.93, 95% CI 1.79–4.81) (Johnson *et al.*, 2013).

2.3.1(c) Colon polyp

Colon polyps are defined as abnormal growths that projecting from the mucosal layer of the colon and extend into the lumen. Colon polyps are histologically

categorised into neoplastic and non-neoplastic lesions (Sninsky *et al.*, 2022). Neoplastic (adenomatous polyp) had possibility to become adenocarcinoma (malignant) within 5 to 15 years, influenced by individual age, polyp size, and degree of dysplasia (Sawicki et al., 2021a).

2.3.1(d) Diabetes mellitus

Epidemiologic evidence proved the association between diabetes mellitus and many cancers such as CRC, breast cancer, and pancreatic cancer (Satija *et al.*, 2015). Key factors that encourage cancer aggression are hyperglycemia alone or in conjunction with hyperinsulinemia (Supabphol *et al.*, 2021). Hyperglycemia can enforce the carcinogenic shift to glycolysis by hastening glucose metabolism (Rawla Prashanth and Sunkara, 2019). Meanwhile, hyperinsulinemia may contribute to carcinogenesis directly by accelerating colonic cell proliferation and indirectly by expanding insulin-like growth factor 1(IGF-1) level that promotes cell growth and reduces cell death (Ma *et al.*, 2018).

2.3.2 Personal background

2.3.2(a) Age, sex, race

Age, sex and race (ethnicity) play roles in non-modifiable risk factors. The most CRC occurrence diagnosed at the age of over 50 years old (Hossain *et al.*, 2022) even though an alarming increase takes place in the United States and other developed countries in early-onset CRC (Sinicrope, 2022). According to GLOBOCAN 2020 data, the global CRC incidence rate in males (23.4 cases per 100,000 persons) is 44% higher

than that in females (16.2 cases per 100,000 persons) (Xi & Xu, 2021). In the United States, approximately 4.4% males (1 in 23) and 4.1% females (1 in 25) will develop and be diagnosed with CRC during their lifetime (Siegel et al., 2020).

In Malaysia, the CRC incidence rise with age and peak at the age of ≥70 for both male and female. The lifetime risk for males was 1 in 55, while for females was 1 in 76. The incidence of CRC was highest among Chinese for both sexes, followed by Malay and Indian ethnic (National Cancer Institute, 2019). However, the trend is decreasing compared to previous report (Malaysia National Cancer Registry Report 2012-2016) as in Figures 2.7.

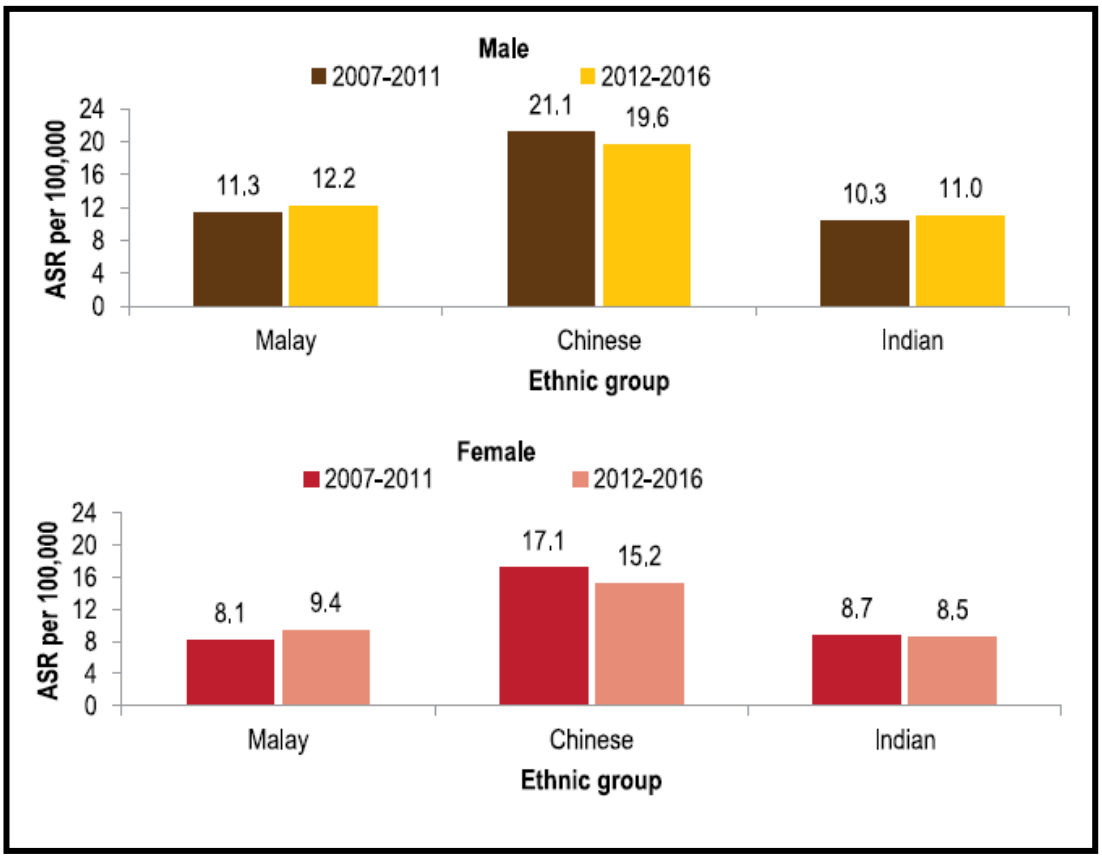

Figure 2.7 Comparison of age-standardised rate by year, major ethnic group, and sex in CRC Malaysia
(Source: Adopted from Malaysia National Cancer Registry Report 2012-2016)

2.3.3 Lifestyles

2.3.3(a) Socioeconomic

Health is influenced not only by genetic and lifestyle but also by social factors such as social relationship and socioeconomic factors. Society from low socioeconomic background is presumed to have a higher risk of developing cancer because of several factors. Limited accessibility to health care services and high-quality treatment resources might be barriers in term of facilities provided. Moreover, self-health concerns such as poor dietary intake, inactive lifestyle and smoking also related to low socioeconomic population (Carethers & Doubeni, 2020). A cohort study in Southern US showed lower endoscopy use and reduced CRC incidence among individuals with low socioeconomic background (Warren Andersen S. *et al.*, 2019). In Malaysia, lower socioeconomic region (Kuching, Sarawak) was a significant factor for late diagnosis and more advanced stage, as well as poor survival rates compared to higher socioeconomic region (Kuala Lumpur) (Kong *et al.*, 2010).

2.3.3(b) Nutritional status

Nutritional status can be part of modifiable risk factors besides physical inactivity, unhealthy dietary pattern, and smoking. Physical inactivity may lead to obesity, which had adverse effect to health as proved by many studies such as premature death (Censin *et al.*, 2019), diabetes mellitus, hypertension, dyslipidemia (Al-Raddadi *et al.*, 2019), cardiovascular disease, obstructive sleep apnea, chronic obstructive pulmonary diseases (Censin *et al.*, 2019), and cancer (Hingorani, Finan & Schmidt, 2020). Emerging epidemiological data identified a strong positive correlation between obesity and CRC carcinogenesis (Garcia & Song, 2019; Ye *et al.*, 2020).