A HOSPITAL-BASED CASE-CONTROL STUDY OF FACTORS ASSOCIATED WITH COLORECTAL CANCER

by

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Thesis Submitted in Fulfillment of the Requirements
for the Degree of
Master of Science

August 2016

A HOSPITAL-BASED CASE-CONTROL STUDY OF FACTORS ASSOCIATED WITH COLORECTAL CANCER

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Introduction: Colorectal cancer (CRC) was the second most common cancer in Malaysia after breast cancer. The incidence rates of CRC for both male and female had been reported increasing.

Objective: This study was conducted to determine the associated factors of CRC in selected hospitals in Malaysia.

Methods: A hospital-based case-control study of 128 cases and 128 controls was carried out by using a validated questionnaire. Participants who fulfilled the inclusion and exclusion criteria were included as the case and control groups accordingly. Multiple logistic regression was used for data analysis.

Results: The mean age of CRC was 59.84 years old (standard deviation 11.20). Majority of CRC was males (60.9%) and Malay race (57.8%). The significant factors associated with CRC were age equal and more than 55 years old [Adjusted Odds Ratio (AOR): 4.54; 95% confidence interval (CI): 2.45-8.40; p value <0.001], Chinese ethnicity [AOR: 6.67; 95% CI: 2.01-22.13; p value = 0.002], family history of CRC [AOR: 11.26; 95% CI: 3.02-41.94; p value <0.001], history of polyps [AOR: 5.45; 95% CI: 1.94-15.28; p value <0.001], and ever smoker [AOR: 3.40; 95% CI: 1.63-7.10; p value <0.001].

Conclusion: As a conclusion, factors significantly associated with CRC are older age, chinese ethnicity, family history of CRC, history of polyps and ever smoked. These factors could be used as a reference to guide the people and Ministry

of Health on risk factors to get CRC, adopting a healthy lifestyle in order to decrease the incidence of CRC in Malaysia.

Keywords: colorectal cancer, associated factors, case control

Assoc. Prof. Dr Norsa'adah Binti Bachok : Supervisor
Dr Zaidi Bin Zakaria : Co-Supervisor

ACKNOWLEDGEMENTS

Alhamdulillah, all praises to ALLAH for His blessing and the strengths in finishing this thesis. Foremost, I would like to express my sincere gratitude and billion thanks to the following individuals who contributed in their different ways and have made this thesis possible:

1. Assoc Prof Dr Norsa'adah Bachok, as my supervisor, for making this research possible. Her support, guidance throughout the research project, valuable advices, precious time, contribution, suggestions and patient during the research and preparation of this thesis are greatly appreciated.

2. Dr Zaidi Zakaria, as my co-supervisor from Department of Surgery, Universiti Sains Malaysia, for his support, suggestions and the valuable information he has shared.

3. All lecturers in Unit of Biostatistics and Research Methodology, Universiti Sains Malaysia for the supports and opinions.

4. All staffs and respondents from Hospital Universiti Sains Malaysia, Pusat Perubatan Universiti Kebangsaan Malaysia and Hospital Kuala Lumpur for their supports and cooperation.

5. Human Ethic Committee of Universiti Sains Malaysia for approving this study.

6. Universiti Sains Malaysia for approving the short term research grant which fully fund this research (304/PPSP/61312083).

7. My parents and siblings for their unconditional support, both physically and emotionally throughout my study, and their never-ending love for which I am constantly in debt.

8. My coursemates for their moral support, sharing knowledge, opinion and suggestions during this research.

9. Last but not least, others who were directly or indirectly assist to the success of this research.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AIDS	Acquired Immunodeficiency Syndrome
AJCC	American Joint Committee on Cancer
ASR	Aged Standardized Rates
BMI	Body Mass Index
CAP	College of American Pathologist
CI	Confidence Interval
cm	Centimeter
COC	Commission on Cancer
CR	Crude Rate
CRC	Colorectal Cancer
DCBE	Double-contrast Barium Edema
DRE	Digital Rectal Examination
FOBT	Fecal Occult Blood Test
HIV	Human Immunodeficiency virus
HKL	Hospital Kuala Lumpur
HR	Hazard Ratios
HUSM	Hospital Universiti Sains Malaysia
IWHS	Iowa Women's Health Study
kg	Kilogram
LR	Likelihood Ratio
m	Meter
MLogR	Multiple Logistic Regression
MOH	Ministry of Health
MSI	Microsatellite Instability

NSAIDs	Non-steroidal anti-inflammatory drug
OR	Odds Ratios
ROC	Receiver Operating Characteristic
RR	Relative Ratios
SD	Standard Deviation
SE	Standard Error
SEER	Surveillance Epidemiology End Result
SLogR	Simple Logistic Regression
SPSS	Statistical Packages for Social Sciences
TNM	Tumor, Node and Metastasis
UICC	Union for International Cancer Control
UKM	Universiti Kebangsaan Malaysia
UKMMC	Universiti Kebangsaan Malaysia Medical Centre
USM	Universiti Sains Malaysia
WHO	World Health Organization

LIST OF SYMBOLS

%	Percentage
<	Less than
=	Equal
>	More than
≤	Equal and less than
≥	Equal and more than
b	Regression coefficient
n	Required sample size

KAJIAN KES-KAWALAN BERASASKAN HOSPITAL MENGENAI FAKTOR-FAKTOR YANG BERKAITAN DENGAN KANSER KOLOREKTAL

ABSTRAK

Kanser kolorektal adalah kanser kedua yang paling kerap di Malaysia selepas kanser payudara. Kadar kejadian kanser kolorektal untuk kedua-dua lelaki dan wanita dilaporkan meningkat. Kajian ini dijalankan untuk menentukan faktor-faktor yang berkaitan dengan kanser kolorektal dalam kalangan penduduk Malaysia di hospital-hospital terpilih. Satu kajian kes-kawalan yang terdiri daripada 128 kes and 128 kawalan berasaskan hospital telah dijalankan dengan menggunakan soal selidik yang telah disahkan. Pesakit yang memenuhi kriteria kemasukan dan penolakan dikelaskan dalam kumpulan kes dan kawalan. Regresi logistik berganda digunakan untuk menganalisis data. Min umur pesakit kanser kolorektal ialah 59.84 (sisihan piawai 11.20) tahun. Majoriti pesakit kanser kolorektal adalah lelaki (60.9%) dan bangsa Melayu (57.8%). Faktor-faktor bererti yang berkaitan dengan kanser kolorektal adalah umur yang sama dan lebih daripada 55 tahun [Nisbah Kemungkinan Terselaras (NKT): 4.54; 95% Julat Keyakinan (JK): 2.45- 8.40; nilai p <0.001], bangsa Cina [NKT: 6.67; 95% JK: 2.01- 22.13; nilai p 0.002], sejarah Kanser Kolorektal [NKT: 11.26; 95% JK: 3.02- 41.94, nilai p <0.001], sejarah polip [NKT: 5.45; 95% JK: 1.94- 15.28; nilai p 0.001], dan sedang atau pernah merokok [NKT: 3.40; 95% JK: 1.63- 7.10; nilai p 0.001]. Kesimpulannya, faktor-faktor positif yang mempengaruhi kanser kolorektal adalah umur yang meningkat, bangsa cina, sejarah keluarga kanser kolorektal, sejarah polip, dan sedang atau pernah merokok. Faktor-faktor ini boleh digunakan sebagai rujukan untuk memberi panduan kepada orang ramai dan Kementerian Kesihatan risiko tentang faktor kanser kolorektal,

supaya membina gaya hidup yang sihat untuk mengurangkan insidens berlakunya kanser kolorektal di Malaysia.

Kata kunci: Kanser Kolorektal, Faktor-faktor yang berkaitan, kes kawalan

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ABSTRACT

Colorectal cancer (CRC) was the second most common cancer in Malaysia after breast cancer. The incidence rates of CRC for both male and female had been reported increasing. This study was conducted to determine the associated factors of CRC in selected hospitals in Malaysia. A hospital-based case-control study of 128 cases and 128 controls was carried out by using a validated questionnaire. Participants who fulfilled the inclusion and exclusion criteria were included as the case and control groups accordingly. Multiple logistic regression was used for data analysis. The mean age of CRC was 59.84 years old (standard deviation 11.20). Majority of CRC was males (60.9%) and Malay race (57.8%). The significant factors associated with CRC were age equal and more than 55 years old [Adjusted Odds Ratio (AOR): 4.54; 95% confidence interval (CI): 2.45-8.40; p value <0.001], Chinese ethnicity [AOR: 6.67; 95% CI: 2.01-22.13; p value = 0.002], family history of CRC [AOR: 11.26; 95% CI: 3.02-41.94; p value <0.001], history of polyps [AOR: 5.45; 95% CI: 1.94-15.28; p value <0.001], and ever smoker [AOR: 3.40; 95% CI: 1.63-7.10; p value <0.001]. As a conclusion, factors significantly associated with CRC are older age, chinese ethnicity, family history of CRC, history of polyps and ever smoked. These factors could be used as a reference to guide the people and Ministry of Health on risk factors to get CRC, adopting a healthy lifestyle in order to decrease the incidence of CRC in Malaysia.

Keywords: colorectal cancer, associated factors, case control

CHAPTER I

INTRODUCTION

1.1 Overview of Colorectal Cancer

Cancer is one of the leading cause of high mortality rates around the world which stated by World Health Organization (WHO) reported that 84 million people will die of cancer between 2005 and 2015 and estimated that this will doubled between the year 2000 and 2020 and nearly triple by the year of 2030. The report also stated that in the last 30 years of 20th century, the global cancer burden will be doubled (World Health Organization, 2010).

Among the 10 principal causes of death in year 2007 in the Ministry of Health Malaysia (MOH) Hospitals, cancer was at the third ranking with 11.28% after heart diseases and diseases of pulmonary circulation with 16.49%, and septicemia with 13.38% (Zainal Ariffin and Nor Saleha, 2011). According to the report, other causes of death in Malaysia included cerebrovascular diseases (8.50%), pneumonia (7.43%), accidents (5.20%), diseases of the digestive system (4.86%), certain conditions originating in the perinatal period (4.11%), nephritis, nephrotic syndrome and nephrosis (4.09%), and III-defined conditions (2.55%).

Colorectal cancer (CRC) was one of the cancers that cause death in the world. CRC was coded as C18-C21 from the Tenth Revision of the International Statistical Classification of Diseases and Related Health Problems (Tower *et al.*, 2011). In 2000, CRC was the third most common cancer worldwide after breast and lung

cancers, with 945,000 new cases diagnosed each year worldwide (9.4% cases); and responsible for 492,000 cancer death yearly (7.9% deaths) (Parkin, 2001). The incidence rates of CRC for both male and female were significantly increased from 1983-1987 to 1998-2000 for 27 of 51 cancer registries in the world (Center *et al.*, 2009b).

Table 1.1: Ten Principle Causes of Death in Ministry of Health Malaysia Hospitals, 2007

	Diseases	Percentage (%)
1.	Heart Diseases & Diseases of Pulmonary Circulation	16.49
2.	Septicaemia	13.38
3.	Malignant Neoplasm	11.28
4.	Cerebrovascular Diseases	8.50
5.	Pneumonia	7.43
6.	Accidents	5.20
7.	Diseases of the Digestive System	4.86
8.	Certain Conditions Originating in The Perinatal Period	4.11
9.	Nephritis, Nephrotic Syndrome & Nephrosis	4.09
10.	III-define conditions	2.55
	All causes	100.0

Source: Health Informatic Centre, Planning and Development Division, Ministry of Health, Malaysia

According to the World Gastroenterology Organization/International Digestive Cancer Alliance, 2007, CRC was the second most common cause of cancer mortality among men and women worldwide, with an incidence of approximately 1 million cases per year and more than 500,000 death (Winawer *et al.*, 2007). More than 1 million new cases diagnosed in 2008 accounted for 664,000 new cases in male and 571,000 new cases in female which CRC was the second most common cause of death from cancer after lung cancer in Europe (Ferlay *et al.*, 2010).

CRC was relatively uncommon in Africa and many of Asian countries and it was more common in male than in female (Perera *et al.*, 2012). Incidence of CRC

was highest in high-income and developed countries such as North America and Western Europe, also several Asian countries such as Japan, Singapore and North Korea which experience transition of nutrition (Ferlay *et al.*, 2010).

In 2006, Malaysian Cancer Statistics reported that CRC was at the second most frequent overall cancers incidence in Malaysia with 13.2% after the breast cancer (16.5%), followed by lung (9.4%), cervix uteri (4.9%), nasopharynx (4.5%), thyroid gland (4.1%), liver (3.6%), stomach (3.6%), prostate gland (3.4%), and lymphoma (3.2%) (Zainal Ariffin *et al.*, 2006).

A total of 18,219 cancer incidence were diagnosed and registered in 2007 by the National Cancer Registry; which included 8,123 males (44.6%) and 10,096 females (55.4%) (Zainal Ariffin and Nor Saleha, 2011). The report indicated that Penang had the highest proportion of cancer (18.8%) followed by Johor (18.4%), Selangor (11.3%), Perak and Sarawak (8.7%), Sabah (8.2%), Federal Territory of Kuala Lumpur (7.1%), Kedah (5.5%), Pahang (4.9%), Kelantan (4.7%), Malacca (3.9%), Terengganu (3.5%), Negeri Sembilan (3.4%), Perlis (0.6%), and Federal Territory of Labuan (0.01%).

In the report also stated that CRC was the second most common cancer in Malaysia with 12.3% represent 2,246 cases diagnosed after breast cancer (18.1%); with the incidence of CRC was high in males (ASR 13.4 per 100,000 population) compared to females (ASR 10.2 per 100,000 population). CRC is also the second most common cancer in males (14.6%) after lung cancer (16.3%) and females (10.0%) after breast cancer (32.1%) (Zainal Ariffin and Nor Saleha, 2011).

There are many identified associated factors of CRC in previous studies done by local and abroad researchers. The factors include socio-demography (age, gender, race, educational level, marital status, occupation, and monthly income), medical history (family history, polyps, long term abdominal pain, post-menopause, additional supplements, other diseases, and screening test), lifestyle (physical activity, smoking and diet), and knowledge, attitude and practice (KAP) of CRC (Andrieu *et al.*, 2003; Bingham *et al.*, 2003; Campbell *et al.*, 2007; Hannan *et al.*, 2009; Huxley *et al.*, 2009; Johnson *et al.*, 2009; Harmy *et al.*, 2011; Doubeni *et al.*, 2012; Kushi *et al.*, 2012).

1.2 Justification of Study

CRC was one of the leading causes of death in Malaysia. The increasing incidence of CRC every year causes the increased mortality rate. Many previous studies had been carried out to recognize the causes of CRC and the associated factors (Chan *et al.*, 2011). The previous study reported that environmental, diet and lifestyle factors were the main determinants of CRC risk which indicated by the increasing CRC incidence parallel with economic development and adoption of Western lifestyle (Center *et al.*, 2009a).

Malaysian population has different lifestyles and diet compared to the western populations. Thus, this study was conducted to identify the associated factors of CRC in the Malaysian population as the factors included were the socio-demography, medical history, knowledge and attitude towards CRC, dietary and screening practicing among those attended the selected hospitals.

By identifying the risk factors of CRC, the occurrence of CRC may be prevented. This study also may help researchers, epidemiologists and physicians to develop a strategy to reduce the incidence of CRC in Malaysia and carried out more study in detail about its risk and protective factors.

1.3 Objectives

1.3.1. Research Questions

i. What are the profiles of CRC patients in HUSM, UKMMC, and HKL?
ii. What are the factors associated with the occurrence of CRC?

1.3.2. General Objective

To determine the association between socio-demography, medical history, attitude, knowledge and practices of lifestyle and diet and the occurrence of CRC.

1.3.3. Specific objectives

i. To determine the profiles of CRC patients in HUSM, UKMMC, and HKL.
ii. To identify the associated factors of CRC including socio-demography, medical history, knowledge, attitude and practices regarding CRC.

1.3.4. Research Hypothesis

The factors significantly associated with CRC are socio-demography characteristics, medical history, knowledge, attitude and practices (lifestyle and diet) regarding CRC.

CHAPTER II

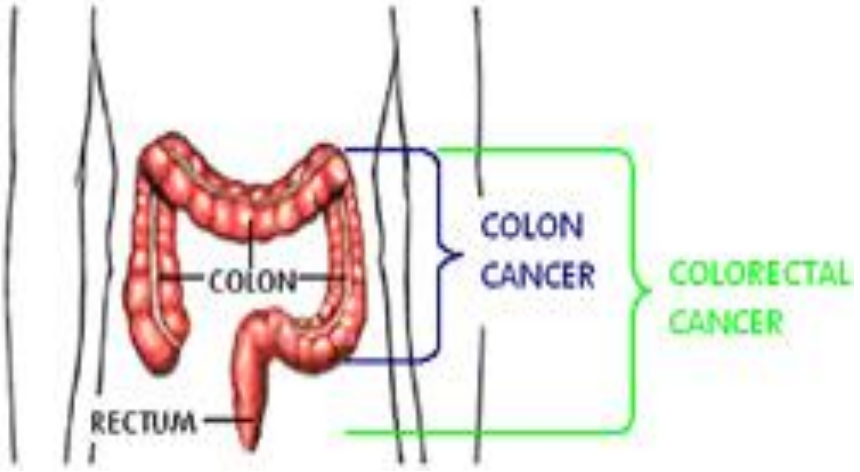
LITERATURE REVIEW

2.1 General Definition of Cancer

Cancer arises from abnormal and uncontrolled division of cells that then invade and destroy the surrounding tissues. The cancer is named based on the location of the tumour started. The cancer cells can spread to the other part of the body and this condition is called metastasis. This can occur via blood stream, lymphatic channel, and across body cavities such as pleural. The stimulation of new blood vessels growth provides blood supply to the cancer cells which make the cell cancer survive (Martin, 2002).

2.2 Colorectal Cancer

The digestive system comprises of colon and rectum which are main segments of the large intestine that functions digestion and remove the waste. The CRC usually occurs at the wall layer of colon and rectum which start as a polyp (a growth tissue lining and growth in the colon and rectum) called as adenoma (American Cancer Society, 2011). It also different from colon cancer or rectal cancer even they involve the same organ. The colon cancer involves only the colons and the rectal cancer involves only the rectum part. The cancer that involving of both organ which are colon and rectum known as the colorectal cancer (Figure 2.1).



Source: Malaysian Oncological Society

Figure 2.1: The Location of Colorectal Cancer

The symptoms of CRC usually cannot be detected at early stage and diagnosed when it becomes severe (American Cancer Society, 2011). The symptoms include a change in bowel habits such as diarrhea, constipation, or narrow stool that lasts for more than a few days; rectal bleeding, dark stools or blood in the stool; cramping or stomach pain; weakness and tiredness; and unexpected weight loss.

2.3 Pathogenesis of Colorectal Cancer

CRC is a consequence of the progressive accumulation of genetic and epigenetic alterations that developed from the transformation of normal colonic epithelium to colon adenocarcinoma which called polyps (Grady and Carethers, 2008). Gene mutations sequential process and epigenetic alterations lead to the development of malignant adenocarcinomas from benign adenomas because the signaling pathways effected by these mutation regulate characteristic behavior of cancer (Fearon and Vogelstein, 1990; Hanahan and Weinberg, 2000). This mutation acquisition arises as a consequence of loss genomic stability which appears to be a

key molecular in cancer formation (Lengauer *et al.*, 1998; Grady, 2004; Gollin, 2005). The categories of genomic instability include (1) subtle sequence changes as well as base substitution, deletions, or insertions; (2) aneuploidy– chromosome number alteration; (3) rearrangement of chromosome; and (4) amplification of gene (Lengauer *et al.*, 1998; Aguilera and Gómez-González, 2008; Grady and Carethers, 2008).

2.4 Staging of Colorectal Cancer

The first clinical staging system was created by Dukes who described the pathological classification according to the primary tumor extension; and emphasize the histologic grading of implication as a prognostic factor (Dukes, 1932; Dukes, 1937). Dukes highlighted on lymphatic spread, tumor local extension, and venous spread; and regarded the Dukes staging system for the rectal cancer is applicable for all intestinal cancers (Dukes, 1932).

Table 2.1: American Joint Committee on Cancer / Union for International Cancer Control Stage Groupings of Colorectal Cancer

	TNM			**Modified Astler-Coller**	**Dukes**
Stage 0	Tis	N0	M0	N/A	N/A
Stage I	T1	N0	M0	Stage A	A
	T2	N0	M0	Stage B1	A
Stage IIA	T3	N0	M0	Stage B2	B
Stage IIB	T4	N0	M0	Stage B3	B
Stage IIIA	T1, T2	N1	M0	Stage C1	C
Stage IIIB	T3, T4	N1	M0	Stage C2, C3	C
Stage IIIC	Any T	N2	M0	Stage C1, C2, C3	C
Stage IV	Any T	Any N	M1	Stage D	N/A

Source: Compton and Greene, 2004

As the staging system become known, the Dukes staging had been modified several time by other researchers and currently the cancer staging of TNM system has gained a wider acceptance globally as it fulfill all the criteria of the stage of locoregional disease, the presence or absence of metastases, specific prognostic and predictive factors (Obrocea *et al.*, 2011). Table 2.1 showed the staging that provided by the AJCC and UICC for cancer staging.

For the TNM system, the "T" refers to the extension of local untreated primary tumor at the time of initial diagnosis; the "N" refers to the status of metastatic of the regional lymph nodes; and "M" refers to the distant metastatic disease at that time (Obrocea *et al.*, 2011). The clinical determination prescribed by the symbol of "c" written before T, N, and/or M (e.g., cT3) is based on evidence acquired from physical examination, radiologic imaging, biopsy, endoscopy, and surgical exploration while the pathologic classification is based on gross and microscopic examination of the untreated primary tumor specimen which prescribed by the symbol of "p" of T or N (Compton and Greene, 2004; Compton, 2006; Edge *et al.*, 2009; Washington *et al.*, 2009).

i) T Category

For CRC, size is not a factor in staging and has no prognostic importance (Washington *et al.*, 2009). The designation of "pTis" refer to both intraepithelial malignancies and intramucosal carcinomas (cancers that invaded the mucosa stroma) because the colorectal mucosa is inimitable as contrast to mucosa elsewhere in the rest of human body; therefore, both may be preferred descriptive terms in the pTis

category for colorectal tumor (Compton and Greene, 2004). CRC that has invaded through the muscularis propria but not completely is designated as pT2, while the pT3 category characterized by all transmurally invasive tumor that penetrated the perimuscular soft tissues (Compton and Greene, 2004). pT4 is the highest category of local extension that involve both adherent to other organs or structure and, parietal peritoneum penetration with or without adjacent structure involvement (Wittikind *et al.*, 2003). Along with the feature of pT4, penetration of serosal is the most ominous as it was associated with worse outcome (Edge *et al.*, 2009). Table 2.2 showed the T category of CRC staging accordingly.

Table 2.2: T Category for Primary Tumor in Colorectal Cancer Staging

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ: intraepithelial or invasion of the lamina propria (intramucosal)
T1	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades pericolorectal tissues
T3a	Tumor invades through the muscularis propria into the subserosa or into non-peritonealized pericolonic or perirectal tissues
T3b	T1 or T2 tumor with satellite deposits in pericolorectal tissues
T4a	Tumor penetrates the visceral peritoneum
T4b	Tumor directly invades or is adherent to other organs or structures

Source: Cunningham *et al.*, 2010; Obrocea *et al.*, 2011

ii) N Category

Pathologic evaluation of the regional lymph nodes performed to recognize the lymph nodes involved using conventional histologic staining as in CRC shown many nodal metastases in small lymph nodes (less than 5mm in diameter) (Brown *et al.*, 2004). Minimum of 12 to 18 lymph nodes need to be examined to precisely calculate

regional nodes negativity in CRC which depend on factor of age and anatomic variation, surgical technique, and assiduousness of the pathologist in harvesting all existing nodes (Goldstein, 2002; Joseph *et al.*, 2003; Le Voyer *et al.*, 2003).

Regional lymph nodes need separate examination from lymph nodes outside of the anatomic site as metastasis in any lymph node in the regional nodal group measured as pN disease while all other nodal metastases classified as pM1 (Wittikind *et al.*, 2003). Table 2.3 showed the regional lymph node groups corresponding to the anatomic subsites (Compton and Greene, 2004). In occasional cases, regional nodes at the primary tumor site are malignancy free, but nodes in the drainage site of organ invaded by T4 consists of metastasis; then the lymph nodes considered as those of primary site and classified in N category (Wittikind *et al.*, 2003).

Table 2.3: Subclassification of N Category in Colorectal Cancer

NX	Regional lymph nodes cannot be assessed	
N0	No regional lymph node metastasis	
N1	Metastasis in 1 to 3 regional lymph nodes	
	N1a	Metastasis in 1 regional lymph node
	N1b	Metastasis in 2-3 regional lymph nodes
N2	Metastasis in 4 or more regional lymph nodes	
	N2a	Metastasis in 4 to 6 regional lymph nodes
	N2b	Metastasis in 7 or more regional lymph node

Source: Edge *et al.*, 2009

Table 2.4: Regional Lymph Node Group Definition in Anatomic Subsite of Colorectum

Colorectum Subsite	Definition
Cecum	Anterior cecal, posterior cecal, ileocolic, right colic
Ascending colon	Ileocolic, right colic, middle colic
Hepatic flexture	Middle colic, right colic
Transverse colon	Middle colic
Splenic flexure	Middle colic, left colic, inferior mesenteric
Descending colon	Left colic, inferior mesenteric, sigmoid
Sigmoid colon	Inferior mesenteric, superior rectal sigmoidal, sigmoid mesenteric
Rectosigmoid colon	Perirectal*, left colic, sigmoid mesenteric, sigmoidal, inferior mesenteric, superior rectal, middle rectal
Rectum	Perirectal*, sigmoid mesenteric, inferior mesenteric, lateral sacral, presacral, internal iliac, sacral promontory, superior rectal, middle rectal, inferior rectal

*Perirectal lymph nodes involve the mesorectal (paraproctal), lateral sacral, presacral, sacral promontory (gerota), middle rectal (hemorrhoidal), and inferior rectal (hemorrhoidal) nodes (Compton and Greene, 2004).

iii) M Category

The M category refers to the distant metastasis which modified to imitate the fact that distant metastasis confined to one organ and in CRC it is subclassified into several category (Edge *et al.*, 2009). According to the pathological review, this category has two unique caveats; (1) pM0 does not exist as it would imply whole body elimination of metastasis by autopsy and would be classified using autopsy-specific nomenclature of AJCC; (2) pMX is dejected by CAP and COC even it is strictly correct in connoting the unknown distant metastasis of pathological status (Edge *et al.*, 2009; Washington *et al.*, 2009). Therefore, in CRC, only pM1 is accepted when tumor from distant metastatic site is pathologically confirmed as pM1 recognized metastasis to any non-regional lymph node, the parenchyma of organ or tissue, and/or the peritoneum of any structure of abdomen (Compton and Greene,

2004). M1 has been subdivided into 2 category which are M1a and M1b (Table 2.5) (Obrocea *et al.*, 2011).

Table 2.5: Colorectal Cancer Subclassified of M Category

MX	Distant metastasis cannot be assessed	
cM0	No distant metastasis (the category pM0 does not exist)	
M1	Distant metastasis	
	M1a	Metastasis confined to one organ or site (e. g., liver, lung, ovary, non-regional node)
	M1b	Metastasis in more than one organ/site or the peritoneum

Source: Edge *et al.*, 2009; Obrocea *et al.*, 2011

2.5 Factors Associated with Colorectal Cancer

There are various factors that can contribute to the occurrence of CRC. The factors can be associated to the individual itself and also the environment. Some factors can increase the risk of developing CRC (risk factors) and some factors may protect from CRC occurrence (protective factors). The risk factors of CRC are divided into several part which are socio-demography, dietary, obesity, lifestyle and medical history. There are several parts of protective factors that associate with decreased risk of CRC such as dietary, medical supplements, hormone and others.

2.5.1 Risk factors of Colorectal cancer

The risk factors can be divided into modifiable and non-modifiable factors. The modifiable risk factors are the factors that can be modified by individual such as lifestyle such as smoking, alcohol consumption, physical activity and diet. Knowledge and attitude about risk factors of CRC are also modifiable by health promotions, campaigns and screening behaviors which to detect the early stage of CRC. In addition, the non-modifiable risk factors are the factors that beyond individual control such as age, gender, and ethnicity.

Non-modifiable Risk Factors

i) Socio-demography

Age was reported to be one of the risk factor of CRC. The CRC mostly occurred in patients who aged above 50 years and rarely occurred in patient younger than 40 years old (Ozsoy *et al.*, 2007). In Malaysia, the incidence of CRC increased with age in males and females, with people aged more than 45 years old tend to diagnosed with CRC (Zainal Ariffin and Nor Saleha, 2011). The data from SEER also reported that the frequency of CRC patients was increasing as the age increased until >70 years old (Howlader *et al.*, 2013)

Gender may play important role in CRC developing. In 2007, the incidence of CRC was slightly higher among males (Aged Standardized Rates (ASR) 13.4 per 100,000) compared to females (ASR 10.2 per 100,000) (Zainal Ariffin and Nor Saleha, 2011). The CRC risk of diet-related regarding gender may differ due to

hormonal variation between males and females and also the female has tendency to develop proximal tumor while male develop rectal and distal tumor (Jacobs *et al.*, 2007).

Every ethnic has their own lifestyles and cultures which result in difference impact on the chronic diseases occurrence. Different races have differences in the CRC risk due to own lifestyle and cultural factors. The hypothesis from previous study stated that racial and ethnic differences in CRC incidence and mortality could potentially be effected by the factors such as age, education, health insurance status, and health system-level such as medical care utilization and screening (Simon *et al.*, 2011). In Malaysia, a report in 2007 showed that Chinese had the higher incidence of CRC among male and female with the ASR 19.4 and 14.6 per 100,000 population respectively (Zainal Ariffin and Nor Saleha, 2011).

Modifiable Risk Factors

i) Dietary Factors

Red Meat

Previous studies showed that the risk of CRC was strongly associated with dietary intake (Muñoz *et al.*, 1998; Navarro *et al.*, 1998; Navarro *et al.*, 2004). Red meat has been thought to promote CRC through the effects of fat, iron, protein, and in the case of processed meat, *N*-nitroso compounds (Bingham, 1999; Sesink *et al.*, 1999). Higher intake of some meats rich in fat content, such as cold cuts, sausages, and bovine viscera, were linked to increased risk for colorectal cancer (Navarro *et al.*, 2004).

A case-control study of colorectal cancer cases (1997-2000) aged 20-74 years old, identified through the population-based Ontario Cancer Registry and recruited by the Ontario Family Colorectal Cancer Registry, reported results of 1,095 cases and 1,890 controls who were involved in answering food questionnaires. It was reported that red meat intake such as beef, pork, veal, lamb and venison was associated with the increased CRC risk (OR: 1.67; 95% CI: 1.36-2.05) (Cotterchio *et al.*, 2008) (Table 2.6).

Another study on the association of red meat risk towards CRC was studied in the U.S. population. A prospective cohort study reported 2,719 CRC cases from cohort of 300,948 men and women during 7 years of follow-up. The detail questionnaire asked about details on meat cooking methods and meat type used in estimating intake of mutagens formed in the meats cooked. The result from the study showed that red meat (beef, pork, and lamb, including bacon, cold cuts, ham, hamburger, hog dogs, liver, sausage and steak) and process meat (bacon, red meat sausage, poultry sausage, luncheon meat, cold cuts, ham and regular hotdogs) had an elevated risk for CRC (HR: 1.24; 95% CI: 1.09-1.42) and (HR: 1.16; 95% CI: 1.01-1.32) respectively (Cross *et al.*, 2010) (Table 2.6).

The World Cancer Research Fund/American Institute of Cancer Research reported in 2007 that the evidence of red meat and processed meat on the colorectal carcinogenesis was very convincing. A meta-analysis of prospective study had been carried out to explore whether there is a non-linear association of red and processed meats towards colorectal cancer risk. The result showed that red meat (beef, veal, pork, mutton and lamb) and processed meat (ham, bacon, sausages, cured or

preserved meat) was associated with CRC risk (RR: 1.22; 95% CI: 1.11-1.34) (Chan *et al.*, 2011) (Table 2.6).

A study was done in Malaysia to evaluate the role of food in association with the risk of CRC in Malaysian subjects. A pre-tested quantitative food frequency questionnaire (FFQ) was used on 59 cases and 59 controls at the Hospital Kuala Lumpur (HKL). The result showed that red meat intake was significantly increased the risk of CRC (OR: 2.51; 95% CI: 1.02-6.28) (Ramadas and Kandiah, 2009).

Table 2.6: Summary of Evidence on Association Between Dietary Types and Colorectal Cancer from Different Study Designs

Study	Design and description	Risk factor	Result
Cotterchio *et al*. (2008) Ontario, Canada	Case-control study: 1,095 cases and 1,890 controls.	Red meat (beef, pork, veal, lamb and venison)	Increased red meat intake associated with increased CRC risk OR: 1.67; 95% CI: 1.36-2.05
Cross *et al*. (2010) USA	Prospective cohort study: 2,719 CRC from cohort of 300,948 men and women.	Red meat (beef, pork, and lamb, including bacon, beef, cold cuts, ham, hamburger, hot dogs, liver, pork, sausage, and steak) White meat (chicken, turkey, and fish) Process meat (bacon, red meat sausage, poultry sausage, luncheon meat, cold cuts, ham and regular hotdogs.	Red and process meat indicated ad elevated risk for CRC. Red meat (HR: 1.24; 95% CI: 1.09-1.42) and process meat (HR: 1.16; 95% CI: 1.01-1.32)
Chan *et al*. (2011)	Meta-analysis of prospective study	Red meat (beef, veal, pork, mutton and lamb) and process meat (ham, bacon, sausages, cured or preserved meats)	Increased red and process meat was associated with CRC risk. RR: 1.22; 95% CI: 1.11-1.34

Table 2.6 continued.

Bingham *et al*. (2003) Europe	Observational study: 1,065 cases from 1,939,011 data.	Fiber: cereal, fruits, legume, and vegetables.	Dietary fiber decreased incidence of CRC (RR: 0.75; 95% CI: 0.59-0.95)
Nomura *et al*. (2007)	Cohort study: 1,138 men 972 women of CRC from cohort of 85,903 men and 105,108 women.	Fiber: fruits, vegetables, grains, and legumes.	Fiber was inversely associated with CRC in men (RR: 0.49; 95% CI: 0.41-0.60) and women (RR: 0.75; 95% CI: 0.61-0.92)
Dahm *et al*. (2010) United Kingdom	Nested case-cotrol study: 579 cases and 1,996 controls.	Fiber: cereal; vegetables including potatoes; fruits and legumes; and, seed and nuts	Dietary fiber inversely associated with CRC risk. OR: 0.66; 95% CI: 0.45-0.96
Norat *et al*. (2005) Europe	Cohort study: 1,329 CRC from cohort of 478,040 men and women.	Fish: fresh, canned, salted, and smoked fish	Fish was inversely associated with CRC risk (HR: 0.69; 95% CI: 0.54-0.88)
Hall *et al*. (2008)	Prospective study: 500 male of CRC.	Fish intake: canned tuna fish, dark meat fish (mackerel, salmon, sardines, bluefish, and sword fish), other fish, and shrimp, lobster, or scallops	Fish intake inversely associated with CRC risk. mRR: 0.60; 95% CI: 0.40-0.91
Spencer *et al*. (2010) United Kingdom	Case-control study: 579 cases and 1,996 controls.	Fatty fish: salmon, herring, fresh tuna, and other oily fish	30g or more fatty fish associated with decreased CRC risk (OR: 0.73; 95% CI: 0.54-0.98)
Mizoue *et al*. (2008) Japan	Case-control study: 840 cases and 1,500 controls.	Milk	200g versus 50g milk intake per day reduced CRC risk (OR: 0.60; 95% CI: 0.40-0.91)

Table 2.6 continued.

Larsson *et al*. (2006)	Cohort study: 449 CRC from cohort of 45,306 men.	Dairy product: low-fat (0.1% and 0.5% fat) milk, medium fat (1.5%) milk, whole (3%) milk, low-fat cultured milk (sour milk and yogurt), full-fat cultured milk (sour milk and yogurt), low-fat hard cheese, hard cheese, cottage or cream cheese, reduced-fat sour cream, full-fat sour cream, ice cream, and butter.	High consumption of dairy products associate with low CRC risk (RR: 0.46; 95% CI: 0.30-0.71)
Murphy *et al*. (2013) Sweden	Prospective cohort study: 4,513 CRC from 477,122 subject.	Total milk: whole-fat, skimmed, semi-skimmed and other types of milk.	Total milk consumption inversely associated with CRC risk (HR:0.93; 95% CI: 0.89-0.98)
Ramadas and Kandiah (2009) Malaysia	Case-control study: 59 cases and 59 controls	Red meat	Red meat significantly increased the CRC risk (OR: 2.51; 95% CI: 1.02-6.28)
		Fiber: fruits (citrus, local, imported, dried and preserved fruits) and vegetables (green, cruciferous, herbs/spices/fungi, colored vegetables, tubers and leguminous vegetables).	Fruits and vegetables were significantly decrease risk of CRC (OR: 0.47; 95% CI: 0.30-0.74) and (OR: 0.49; 95% CI: 0.29-0.80) respectively.
		Fish: fresh fish, fresh seafood and preserved seafood.	Intakes more than 3 times a week of fresh fish (OR: 1.10; 95% CI: 0.42-2.90), fresh seafood (OR: 1.64; 95% CI: 0.68-3.93) and preserved seafood (OR: 2.43; 95% CI: 0.79-7.53) were non-significantly associated with the risk of CRC.

	Dairy products: fresh milk and canned milk.	Intakes more than 3 times a week of fresh milk (OR: 0.77; 95% CI: 0.26-2.29) and canned milk (OR: 0.76; 95% CI: 0.22-2.62) were reduced risk of CRC.

ii) Obesity

Overweight and obesity are linked with many chronic diseases, including CRC. Data from a large population based case-control study suggested that adiposity and adult weight gain in men were positively associated with CRC risk (Campbell *et al.*, 2007). A meta-analysis study on obesity and risk of CRC reported that obese had higher risk to get CRC compared to normal weight people (RR: 1.19; 95% CI: 1.11-1.29) (Moghaddam *et al.*, 2007).

iii) Smoking and Alcohol Consumption

Lifestyle factors included smoking and alcohol consumption were associated with CRC. Among current smokers, increased smoking duration was associated with increased risk of CRC, with the greatest relative risk among current smokers with at least 50 years of smoking (HR: 1.38; 95% CI: 1.04-1.84) (Hannan *et al.*, 2009). Ever-smokers were also at moderately increased risk for incident CRC (RR: 1.19; 95% CI: 1.05 to 1.35) compared with never-smokers (Limsui *et al.*, 2010).

For the alcohol consumption, the pathological effects of alcohol consumption on the colorectal tract have been extensively investigated but still remain largely

unclear; A daily alcohol consumption of ≥30g was positively associated with an increase in risk of CRC (Bongaerts *et al.*, 2007). The individual who consumed more than 12 drinks per week compared with non-drinkers (OR: 1.21; 95% CI: 1.03-1.44) had increase the risk of CRC (Poynter *et al.*, 2009).

iv) Family History

The medical history of patient's family contributed to the increased of CRC risk. The risk was higher when first degree of family which included parents, siblings and children had a history of CRC. A person who reported having at least first degree relative (parents, siblings, or children) with CRC is classified as having a family history of CRC (Zlot *et al.*, 2012). A retrospective study indicated that family history of polyps was linked with an increased risk of adenomas development (OR: 2.8; 95% CI: 1.4-5.5) (Gupta *et al.*, 2012).

2.5.2 Protective Factors of Colorectal Cancer

i)Dietary

The intake of large amount of dairy food, fiber, and unsaturated fatty acid positively result in decreased risk of CRC (Table 2.6). The mechanism of each of them may reduce the development of CRC.

Fiber

Dietary fiber is believed acting as protective factors against colorectal cancer. Kojima study stated that the possible mechanism of risk-reducing effect of fiber start when entering the large bowel, fiber will increase stool bulk and fecal carcinogen will be diluted. Fiber can shorten fecal transit time, thus reduce the contact of the carcinogen to colon epithelium (Kojima *et al.*, 2004).

An observational study was done to examine the association of dietary fiber intake and the colorectal cancer risk. The participants were recruited from ten European countries who were 25-70 years old. They completed a dietary questionnaire in 1992-1998 and were followed up for cancer incidence. The result showed that 1,065 CRC cases were reported from 1,939,011 data; the dietary fiber such as cereal, fruits, legume, and vegetables decreased the incidence of CRC (RR: 0.75; 95% CI: 0.59-0.95) (Bingham *et al.*, 2003) (Table 2.6).

The association of dietary fiber and colorectal cancer was further investigate using cohort study. 1,138 from 85,903 males and 972 from 105,108 females were diagnosed with adenocarcinoma of the large bowel after completing a quantitative food frequency questionnaire in 1993-1996. The result showed that fiber such as fruits, vegetables, grains, and legumes was inversely associated with CRC in males and females (RR: 0.49; 95% CI: 0.41-0.60) and (RR: 0.75; 95% CI: 0.61-0.92) respectively (Nomura *et al.*, 2007) (Table 2.6).

Due to the inconsistent findings of association of dietary fiber and colorectal cancer, a case-control study nested within seven UK cohort studies was conducted by Dahm and the associates. The study involved 579 patients diagnosed with CRC and 1,996 matched control subjects. The standardized dietary data obtained from 4- to 7-day food diaries were used. The result from the study reported that dietary fiber such as cereal, vegetables including potatoes, fruits, legumes, seed, and nuts inversely associated with CRC risk (OR: 0.66; 95% CI: 0.45-0.96) (Dahm *et al.*, 2010) (Table 2.6).

Comparing with the local study, dietary fiber did negatively associated with CRC risk. A previous study done in Malaysia reported that higher servings of fruits (citrus, local, imported, dried and preserved fruits) and vegetables (green, cruciferous, herbs/spices/fungi, colored vegetables, tubers and leguminous vegetables) were significantly decrease the risk of CRC (OR: 0.47; 95% CI: 0.30-0.74) and (OR: 0.49; 95% CI: 0.29-0.80) respectively (Ramadas and Kandiah, 2009).

Fish Intake

Fish is the main source of long chain n-3 fatty acids, which have been suggested act as protective role in development of CRC in laboratory and animal studies (Hall *et al.*, 2008). Many mechanisms had suggested the role of fatty acids in carcinogenesis which are modulation of immunity, inflammation, and cell signaling (Larsson *et al.*, 2004; Chapkin *et al.*, 2007). Polyunsaturated fatty acids (PUFAs) fatty acids reduce risk of CRC by inhibiting the cyclooxygenase-2 (COX-2) enzyme; *n*-3 fatty acids produce eicosanoids known as anti-inflammatory, and arachidonic