A CASE CONTROL STUDY ON

RELATIONSHIP OF COLORECTAL CANCER AND SMOKING

EXPOSURE IN HOSPITAL UNIVERSITI SAINS MALAYSIA

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A CASE CONTROL STUDY ON RELATIONSHIP OF COLORECTAL CANCER AND SMOKING EXPOSURE IN HOSPITAL UNIVERSITI SAINS MALAYSIA

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Background: There have been inconsistent findings in the association between colorectal cancer and smoking exposure. Most reported data were from western population groups with only few involving Asian population while there're no available local data from Malaysia. As the causes of colorectal cancer are multifactorial, the genetic susceptibility, lifestyle and diet difference between Western and Asian population may be important in determining the overall individual risks across the world.

Methods: This study investigates such association in our local population at Hospital Universiti Sains Malaysia in Kelantan. Our case-control study involves patients diagnosed with colorectal cancer from 2005 till 2011 which is matched to a group of controls without the tumour. Data were collected from the patients file records and supplemented further by phone interviews or clinic follow up to complete the validated study proforma. We included a total of 92 cases matched with 92 controls.

Results: Current regular smokers have an overall significant association and increased risk of developing CRC (OR = 2.26: CI 95% 0.90-5.89). Increasing number of cigarettes smoked per day is related towards higher rectal cancer risk as compared to colon cancer (p value 0.009). There's statistically no significant association between dose-duration of cigarette smoking and the CRC risk however we find those who smoked over 30 years and had more than 20 cigarettes / day had higher OR of 1.92 compared to 1.42 of developing CRC in non-smokers. The cessation of smoking for 30

years could eventually reduce the OR to 1.13 closer to the baseline of non-smokers however again the data is statistically non significant.

Conclusion: We report a positive association of CRC risk in current smokers among our local population at Hospital Universiti Sains Malaysia in Kelantan with heavy smokers having a higher incidence of rectal cancer. The link between smoking and CRC is important in view of the high incidence of CRC in our country and the ever increasing number of smokers and in view of smoking as a modifiable risk. These findings may be use in educating the public on smoking cessation and also helping healthcare providers in screening patients in the high risk group for early detection of CRC. It also provides us with more local data on which is still very few and a role in future studies.

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LIST OF ABBREVIATIONS

HUSM – Hospital Universiti Sains Malaysia

CRC – Colorectal Cancer

APC – Adenomatous Polyposis Coli

KRAS – Kirsten rat sarcoma viral oncogene homolog

MSI - Microsatellite Instability

CIMP - CpG Island Methylator Phenotype

DNA – Deoxyribonucleic Acid

EGFR - Epidermal Growth Factor Receptor

COX – Cyclo-oxygenase

LOX – Lipo-oxygenase

VGEF - Vascular Endothelium Growth Factor

BMI – Basal Metabolic Index

ICD - International Classification of Disease

SD – Standard Deviation

OD – Odds Ratio

ASR – Age-Standardized Risk

ABSTRACT

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Keywords: Cigarette smoking, colorectal cancer, case-control study.

ABSTRAK

Latar Belakang: Terdapat penemuan yang tidak konsisten berkaitan hubungan antara kanser kolorektal dan pendedahan kepada merokok. Kebanyakan data yang diperolehi adalah daripada kumpulan penduduk barat dengan hanya sekumpulan kecil yang melibatkan penduduk Asia tetapi tiada lagi terbitan data dari Malaysia. Memandangkan punca kanser kolorektal adalah pelbagai perbezaan kerentanan genetik , gaya hidup dan diet antara penduduk barat dan asia mungkin memainkan peranan penting bagi menentukan risiko individu secara keseluruhan diseluruh dunia.

Kaedah: Kajian ini menyiasat hubungan risiko kanser kolorektal dengan cara merokok dalam kalungan penduduk tempatan di Hospital Universiti Sains Malaysia di Kelantan. Kajian kes kawalan kami melibatkan pesakit yang didiagnosa dengan kanser kolorektal dari 2005 hingga 2011 yang dipadankan kepada kumpulan kawalan tanpa kanser. Data dikumpul daripada rekod pesakit dan temubual telefon atau semasa rawatan susulan di klinik untuk melengkapkan Performa Kajian. Terdapat sejumlah 92 kes dan 92 kawalan dalam kajian kita.

Hasil: Kami mendapati peningkatan risiko sebanyak 2 kali ganda dalam golongan perokok dibandingkan dengan mereka yang tidak merokok (OR = 2.26 : CI 95% 0,90-5,89). Risiko mendapat kanser rektum meningkat dengan penambahan jumlah rokok yang dihisap sehari (*p value* 0.009). Didapati tiada hubungan statistik yang signifikan di antara dos atau tempoh merokok dengan risiko kanser kolorektal, bagaimanapun kamimendapati mereka yang merokok melebihi 30 tahun atau melebihi 20 batang rokok sehari mempunyai risiko kanser kolorektal yang lebih tinggi (OR of 1.92 dan 1.42) berbanding dengan mereka yang tidak merokok. Pemberhentian merokok selama 30 tahun didapati dapat mengurangkan risiko (OR 1.13) bagaimanapun data statistik adalah tidak signifikan.

Kesimpulan: Terdapat hubungan antara risiko kanser kolorektal dalam kalangan perokok tempatan di Hospital Universiti Sains Malaysia di Kelantan, dan seseorang perokok mempunyai risiko kanser rektum yang lebih tinggi dibandingkan dengan mereka yang tidak merokok. Kaitan antara perokok dan risiko kejadian kanser kolorektalyang tinggi adalah penting di negara kita, yang mana jumlah kes kanser kolorektal dan bilangan perokok yang semakin meningkat. Penemuan ini dapat membantu untuk mendidik orang ramai untuk berhenti merokok di samping itu dapat membantu pihak kesihatan dalam program saringan untuk mereka yang mempunyai risiko tinggi bagi pengesanan awal kanser kolorektal. Ia juga telah memberikan kita lebih banyak data tempatan yang dapat dibandingkan dengan laporan daripada negara lain dan juga dalam dalam kajian yang akan datang.
Kata Kunci : Merokok, Kanser Kolorektal, kajian kes-kawalan,

1. INTRODUCTION

1.1 General Overview

Colorectal cancer (CRC) is currently the 3rd most common cancer and 4th most common cause of death worldwide (Ferlay, Shin et al. 2010) .In Malaysia the incidence of CRC has been on the rising trend, and according to the latest Malaysian National Cancer Registry report 2007 it is now the 2ndmost common cancer for both men and women of all races in our country (Malaysia 2007).

It is known that genetic predisposition syndromes only accounts for less than 3% of CRC cases while the majority of the causes are multifactorial in combination with other environmental factors which includes dietary, alcohol intake and cigarette smoking (Cannon-Albright, Skolnick et al. 1988) .

The cigarette smoke contains over 3000 chemicals including a large numbers of carcinogenic compounds like polycyclic aromatic hydrocarbons, nitrosamines and aromatic amines (Manabe, Tohyama et al. 1991). Besides the cancerous effect in the cigarette smoke on the lungs, bladder, kidneys and pancreas, recent meta-analysis study have linked it to the increasing risk of causing colorectal adenomas which are a precursors of CRC (Giovannucci 2001). It is hypothesized that the carcinogens from the cigarette smoke travel either via the circulatory system or through direct ingestion in which on contact with the colonic mucosa, it further binds to the cellular DNA and forms adducts which potentially causes irreversible genetic damage to the normal mucosa and later progresses into malignant changes (Sarebo, Skjelbred et al. 2006).

Despite earlier studies connecting the link between smoking and the development of colorectal adenomas, the association between smoking and colon cancer has been inconsistent

findings. Large prospective studies done for a period of 28 years in Finland showed that smoking increased the risk of colorectal cancer after a relatively long period of induction of over 30-40 years exposure (Knekt, Hakama et al. 1998). This is further concluded by 2 meta-analysis studies that associate the risk of developing colorectal cancer to both the cumulative dose and a longer duration of over 30 years in smoking (Giovannucci 2001, Botteri, Iodice et al. 2008). One author estimated that 12% of all CRC deaths may be directly due to smoking cause and smokers has a 40% increase risk of dying from the disease (Chao, Thun et al. 2000)

A recent survey by the Global Adult Tobacco Survey(Malaysia) in 2011 showed that over 40% of Malaysian adult males are smokers and reported an ever increasing number of smokers in the younger population group where about 32% are between the ages of 15 – 24 years old (Health 2011).In view that both smoking and colon cancers are much common in our country, a link or even a weak association between them will have a major impact on the population health and the public health care system.

Most of the major studies that reported on the association between smoking and colon cancer were from countries in the North America and Europe with few from China and Japan. (Botteri, Iodice et al. 2008).There is still no such study on the association of colorectal cancer with cigarette smoking in our Malaysian population. The need to have our own local data is because there's a culture, lifestyle, smoking habits and genetic susceptibility difference between our local and the western population which may affect the outcome of the risk findings.

Genetic factors and related genetic syndromes, causes only a very small percentage of colorectal cancers, with the understanding that the majority of the causes are believed to be due to environmental and lifestyle cause. Hence the understanding of colorectal cancer and its relationship to smoking in our population is important in the effort to help educate the

community, development of guidelines in CRC screening in smokers and in the early detection and prevention of the disease.

2. LITERATURE REVIEW

2.1 Epidemiology

Colorectal cancer (CRC) is a common and lethal disease with high mortality rate worldwide. It is now the 3rd most commonly diagnosed cancer in males and 2nd most commonly diagnosed cancer in females with over 1.2 million new cases and 608,700 deaths recorded in 2008 globally. The distribution of the disease worldwide varies about 10 fold with the highest incidence in Australia and New Zealand followed by Europe and North America. However, South Africa and Asia had the lowest rates (Jemal, Bray et al. 2011). These Geographic differences seems to be related to industrialization and socioeconomic standards where one study estimates the risk of CRC increased 30 percent in the lowest socioeconomic standards as compared to the highest socioeconomic standards group (Doubeni, Laiyemo et al. 2012). Modifiable behaviors such as inactivity, unhealthy diet, smoking, obesity and other factors including poor screening and health care contributes to the socioeconomic difference in the CRC risks.

In Malaysia both incidence and mortality had been increasing over the year which now reaches the 2nd most common cancer for both men and women of all races in National Cancer Registry Report 2007. In 2008, Malaysia recorded an age standardized annual incidence of colon cancer at 19.6 per 100,000 and annual death at 13.0 per 100,000 (GLOBOCAN 2008 v2.0).The incidence was highest among Chinese where the Age-Standardized Risk (ASR) was 21.4 per 100,000 population and were lower in Indian and Malay where the ASR was 11.3 per 100,000 and 9.5 per 100,000 respectively (National Cancer Registry 2006).

Global Adult Tobacco Survey (GATS) in 2011 reported that 43.6% of Malaysian male aged 15 years and above were current smokers (Health 2011). A recent local epidemiology study among male adult smokers in Malaysia showed that the prevalence of smoking in Malaysia was among the highest in Asian countries only behind China (66.9%) and the Philippines (53,8%). It reported 60% of Malaysian males started smoking by the age of 18 years old with an average of 13 cigarettes smoked per day and the highest group of smokers identified from the survey comes from the younger, rural males from the lower income group with less formal education (Lim, Ghazali et al. 2013).

Smoking has been closely linked to the cause of lung cancer with about 80% of all primary cancers in the lung are due to inhaled tobacco smoke. Other cancers of organs with direct contact with cigarette smoke carcinogen (oropharynx, larynx, esophagus, stomach) or indirect contact with the tobacco degradation products (kidneys, bladder, lower urinary tract, pancreas) have also been linked to tobacco. Few epidemiological data have linked smoking to the development of Colonic adenomatous polyps (Botteri, Iodice et al. 2008)which is a precursor to the development of colon cancer over time, however direct link between smoking to the risk of colorectal cancer still remains controversial.

2.2 Pathophysiology

About 20% of patients with CRC have a family history of CRC, however well recognized genetic syndromes only accounts for less than 3% of these CRC patients (Cannon-Albright, Skolnick et al. 1988). This shows that besides genetic syndromes (Familial Adenoma Polyposis, Hereditary Non-Polyposis Colorectal Cancer), the combination of environmental factors and inherited genetic variation in genes encoding carcinogen-metabolizing enzymes were likely contribute to the CRC development.

Most Colon cancer arises from mucosal colonic polyps depending on its natural histology, with the 2 most common histologic types being the hyperplastic and adenomatous polyps. Histologically the hyperplastic polyps contained an increased number of glandular cells with decreased cytoplasmic mucus, but lack of nuclear hyperchromatism stratification or atypia. Whereas adenomatous nuclei were hyperchromatic, enlarged, cigar shaped and crowded together in palisade pattern. Adenomas were further classified into tubular, villous and tubulo-villous. Tubular adenomas is composed of branched tubules and villous adenomas contained villi arranged in a frond. A tubullovillous adenoma contained both elements. Adenomas is considered neoplastic and is a precursor to develope adenocarcinoma (adenoma-carcinoma sequence), which represents up to 98% of colorectal tumours (Leslie, Carey et al. 2002). Hyperplastic polyps were considered non-neoplastic in nature.

Virtually all colon cancers arises from adenomas with a risk rate of 4% after 5 years and 14% after 10 years if untreated (Stryker, Wolff et al. 1987). A study on small polyps in Taiwan found that over 60% of small polyps of less than 8 mm found on colonoscopy were adenomas proving that more than half of the small polyps were neoplastic in nature which will eventually turn carcinomas (Tsai and Lu 1995). Earlier large prospective studies done by Giovannucci et al had manage to strongly linked the risk of developing adenomatous colonic polyps to cigarette smoking in both men and women, it showed that a long induction period was needed to the development of adenomas, less than 20 years for a small adenoma and over 20 years for a large adenomas. They also and concluded that the induction period for colorectal cancers in smokers is at least 35 years (Giovannucci, Rimm et al. 1994). The Colonic mucosal cells are exposed to the mutagenic compounds in cigarette smokes through either by direct ingestion or through the respiratory-circulatory-colon system.

There has been wide research in the association of cigarette smoking with the few genetic changes known to cause Colorectal Cancer development. The Adenomatous Polyposis Coli (APC) gene is known to have a “gatekeeper” function in the colonic mucosa. Mutations in the APC tumour suppressor genes are thought to be the initiating factor in the early stages of the adenoma-carcinoma sequence. A case-control study on cigarette smoking, APC mutation and sporadic colorectal adenoma-carcinoma in Norway by Sarebo et al showed that although there was statistically significant link between the duration of smoking to the development of adenoma-carcinoma however APC mutations was found in CRC cases with patients who smoked for more than 40 years duration OR 2.0 (Sarebo, Skjelbred et al. 2006). This signifies that a long period of time with exposure to the cigarette carcinogen will cause the APC gene mutation, which in turn leads to the development of adenoma-carcinoma.

The KRAS oncogene mutation is a known cause of early colorectal cancer development. A meta-analysis by Porta el al of seven studies to analyze the risk of KRAS gene mutations in smokers showed no association between smoking and KRAS mutation in both colorectal adenomas and adenocarcinomas Odds Ratio 0.96. This showed that colorectal cancer in smokers was not mediated through KRAS (Porta, Crous-Bou et al. 2009). Microsatellite Instability (MSI) is known to occur in about 15% of colon tumour and characterized by presence of mutations in the DNA sequence. Slattery et al found that subjects who started smoking at a young age, with more than 20 cigarettes per day and a history of over 35 years of smoking had a higher risk of developing MSI with about 21% of MSI in colon cancer are due to cigarette smoking (Slattery, Curtin et al. 2000).

A detailed case-control study by Curtin et al further analyzed a large group of genes known to cause rectal cancers was carried out in Utah, America evaluating the TP53, KRAS2, BRAF V600E mutations, Microsatellite Instability (MSI) and CpG Island Methylator

Phenotype (CIMP) genes from the Tumour DNA. The report shows that Cigarette smoking of more than 20 pack-years was associated with an increased risk of TP53 mutations (OR = 1.4), BRAF mutations(OR = 4.2) and MSI (OR = 5.7) in rectal tumours (Curtin, Samowitz et al. 2009).

Other studies have used nicotine and carcinogens in tobacco to explore the relationship between smoking and cancer development. Nicotine was found to stimulate colon cancer cell (SW1116) proliferation via Epidermal Growth Factor Receptor (EGFR), it also promotes colon cancer cell (HT29) proliferation through the alpha7-nAChR (nicotine acetylcholine receptor and induction of the adrenaline production and beta-adrenergic activation in a dose-dependent manner. Additionally nicotine induced COX-2 and fibronectin expression through nAChR and enhances the colon cancer cell (SW480 and DLD-1) migration. In vitro studies on cigarette smoke have shown to promote cancer cell growth by increasing the expression of 5-lipoxygenase (5-LOX), vascular endothelium growth factor (VEGF), matrix metalloproteinase (MMPs) 2 and 9 in SW116 cells and stimulated HUVEC proliferation (Ye, Wu et al. 2005). Among the many carcinogens in tobacco, NNK, which is formed by the nitrosation of nicotine,was found to stimulate colon cancer cell proliferation and metastasis through alpha7-nAChR receptor in vitro studies. Hence continuing smoking in CRC patients will actually promotes the tumour proliferation and metastases which was the leading cause of the cancer death(Ye, Liu et al. 2004), (Wei, Lin et al. 2011).

2.3 Effects of Smoking on Tumour Characteristics.

A large database analyzed involving 166,172 CRC patients that looked into the association between tobacco use and the CRC tumour characteristics showed that the probability of a distal (left colon and rectum) CRC was higher (Odds Ratio 1.16) in current

smokers compared to former smokers (Odds Ratio 1.009). Among them, the histological diagnosis was made up of adenocarcinoma (89%) and mucinous adenocarcinoma (11%). The tumour grades were divided into undifferentiated 0.4%, poorly differentiated 18%, moderately differentiated 69.9% and well differentiated 11.8%. The mean age of patients with CRC whom did not smoke or drink was 71.3 years while the mean age for smokers and with CRC is younger 66.1 years(Zisman, Nickolov et al. 2006). There was very limited data and study available that compares the difference in the tumour grade and type to the smoking pattern.

An earlier Case-Control study of 715 patients in Melbourne found no significant association between smoking habits in both gender and the tumour location in the colon compared to the control subjects. However the study reported a significant increased risk of developing CRC in males who smoked pipes and cigars with a Relative Risk of 2.61 which attributes to the suspicion that ingested tobacco has a direct carcinogenic effect onto the colonic mucosa leading to malignant changes (Kune, Kune et al. 1992).

Another large prospective cohort study involving 89,835 women by Paul et al in USA reported that smoking does increases the risk of CRC by 2 to 3 fold in smokers who smoked over 40 years with a preponderance for developing rectal cancer. Those who smoked lesser than 40 years in all amount of cigarettes/day where found statistically non-significant in developing CRC risk. The Study concluded that tobacco is an initiator rather than a promoter of rectal cancer (Terry, Miller et al. 2002) . This finding was further supported by another study on women smokers that included 146,877 patients, reported that active current smokers have a 2 fold risk of developing rectal cancers. There was a slight increasing risk in relation to the years of exposure (Paskett, Reeves et al. 2007).

2.4 Association of Colorectal Cancer with other Risk Factors.

A recently published large scale cohort study by Shin et al in Korea involving 1,265,226 participants on the association of CRC with most known lifestyle risk factors revealed some positive findings. It reported that higher BMI was associated with higher risk in developing distal colon cancer in men and proximal colon cancer in women. Positive family history of CRC was also associated with increased risk for distal colon cancer in both genders. However it found no association between serum cholesterol and glucose level with increased risk for CRC. The published data was consistent with previous known prospective studies (Shin, Joo et al. 2011).

We also reviewed another published report by Strummer et al in 2006, which was conducted among a large group of physicians, where he found a significant association between diabetes to the risk of CRC with a hazard ratio (HR) of 1.5 but the analysis of hypertension and hyperlipidaemia found no change in the risk (Sturmer, Buring et al. 2006).

There had been a lot of studies regarding the association of dietary factors to the risk of CRC particularly in relation to the intake of red meat and alcohol consumption. A recent review of 35 prospective studies that focus on the intake of red meat and alcohol found only a weak association with most relative risks below 1.5 and not statistically significant (Alexander and Cushing 2011). The authors concluded that it was difficult to analytically isolate the independent effect of red meat and alcohol consumption and other risk or behavioral factors may influence the outcome.

2.5 Association of Smoking Characteristics with Colorectal Cancer Risks

An early case-control study by Slattery et al reported that smoking over 35 pack-years was associated with 40% increased risk and smoking over 20 cigarettes per day was

associated with 50% higher risk compared to never smokers. In former smokers who stopped smoking, the risk of CRC went higher up to 70% in the initial 14 years of quitting and only reduces after 15 years of quitting tobacco. The author suggested that cigarette smoking may have caused specific mutations in the colonic cells resulting in adenomas which eventually turned into carcinoma during the period smoking was stopped or smoking played a role in suppressing the progression of the disease and that the risk rises after quitting (Slattery, Potter et al. 1997).

The cancer risk due to smoking was also supported by Lindsay and colleagues in a prospective study from 1992 till 2005 involving 184,187 subjects in Georgia USA. They found finds that the incidence of colorectal cancer was about 30% higher in active smokers compared to non-smokers. They also reported a higher incidence in colon cancers than to rectal cancers in smokers. The author stressed that the risk is related to the smoking duration with the link strongest in those who has smoked over 50 years or more. The risk was found to be high in the first 10 years of quitting smoking in former smokers at a risk ratio of 1.48 and the risk decreases with time after (Hannan, Jacobs et al. 2009).

Both studies supported the hypothesis by Giovanucci et al in 2001 findings that the risk of colorectal cancer in smokers is dose-duration dependent and significant after 30-40 years of exposure (Giovannucci 2001). Which in turn explains the possibility that earlier studies, which found no association between colorectal cancer and smoking, may be due to the shorter smoking duration that was analyzed.

3 OBJECTIVES

3.1 Study Objectives

Specific Objectives are:

1. To determine the association of smoking in colorectal cancer patients in Hospital Universiti Sains Malaysia.
2. To describe the socio-demographic data and smoking pattern associated to colorectal cancer patients in Hospital Universiti Sains Malaysia.
3. To determine the association between smoking status and the CRC tumour characteristics among cases in Hospital Universiti Sains Malaysia.

Hypothesis

The hypothesis of this study states that:

1. There's significant association of smoking in CRC patients
2. The dose and duration of smoking increases the risk of developing CRC compared to non-smokers
3. Smoking affects the clinical characteristics of CRC compared to non-smokers

The null hypothesis states that:

1. There's no association of smoking in CRC patients
2. The dose and duration of smoking does not increase the risk of developing CRC compared to non-smokers
3. Smoking does not affect the clinical characteristics of CRC compared to non-smoker.

4. METHODOLOGY

4.1 Study design

This is a case-control study where the case notes of all patients diagnosed with colorectal cancer (Cases) and those with normal colonoscopy findings (Controls) in Hospital Universiti Sains Malaysia between 2005 – 2011 will be reviewed.

4.2 Setting of the study

This study is performed in Hospital Universiti Sains Malaysia, a tertiary referral center in the East Coast of Peninsular Malaysian on a population of patients both diagnosed with and without Colorectal Cancers between the years 2005 to 2011.

4.3 Sample Size Determination

The PS Power and Sample Size Software version 2009 was used to calculate the study sample size. The corresponding values are spelled out:

$\alpha = 0.05$, $\phi = 0.5$, $\Psi = 3$, $m = 1$, $P_o = 0.13$, power = 0.8

The calculated sample size for this study is 92 patients (refer to appendices)

4.4 Inclusion Criteria

1. For case group, all patients diagnosed with Colorectal Cancer within the study period in Hospital Universiti Sains Malaysia from 2005 to 2011
2. For control group. all patients with normal colonoscopy findings within the study period in Hospital Universiti Sains Malaysia from 2005 to 2011

4.5 Exclusion Criteria

4.5.1 Case group

1. Patients with familial polyposis or history of inflammatory bowel disease have been shown to have a higher risk of developing colorectal cancer from the above disease itself, hence will be excluded
2. Patients with insufficient required data in their case notes and whom are unable to participate in interviews to provide further relevant information will be excluded

4.5.2 Control group

1. Patients with history of CRC, familial polyposis or inflammatory bowel disease
2. Patients with insufficient required data in their case notes and whom are unable to participate in interviews to provide further relevant information

4.6 Instrument tools

This study is performed via a structured, proforma based data collection form, which is the main instrument tool in this dissertation (refer to appendices).

Apart from containing the basic information regarding the patient's demographic details, data regarding patient medical history, Body Mass Index, smoking status and pattern, complete information regarding the colorectal tumour type and characteristics will also be documented. The study proforma contains 15 sections labeled from A till O in alphabetical order. Patients from Case group will fill up section A till O while patients from Control group will fill up only section A till L excluding section M,N and O which describes the tumour characteristics.

After filtering the patients in line with the inclusion and exclusion criteria as set out in the proforma, all further relevant data was obtained from the patient's case notes via the