RESEARCH COMMUNICATION

Association of Colorectal Carcinoma with Metabolic Diseases; Experience with 138 Cases from Kelantan, Malaysia

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Abstract

Objective: Kelantan in Malaysia has a high prevalence of diabetes and colorectal cancer is also on the rise. This study is to determine the association of metabolic diseases, particularly diabetes type 2 [DM2] and hypertension, with colorectal cancer patients in our population. Methods: This retrospective study was conducted on all colorectal carcinomas in Hospital Universiti Sains Malaysia (HUSM) in Kelantan from ythe ears 2001-2006. The data were retrieved from the Registry in Pathology laboratory and the clinical details from the patients' clinical records and analyzed using SSPS Version 12.0, with a value of p<0.05 taken to be statistically significant. Results: 138 CRC cases with complete clinical records were included. The age ranged from 16.0 to 88.0 years, with a mean of 56.9 -/+ SD 15.4. The male 90(65%) to female 48(35%) ratio was 1.7:1.0 and 47.8% were suffering from metabolic diseases; 18(13.0%) with Diabetes Mellitus Type 2(DM2), and 48(34.8%) with hypertension (HT). Diabetes Type 2 and hypertension also demonstrated significant association [p<0.05] with the stage and the site of the cancer. Patients with diabetes type 2 88.8%(16/18) and Hypertension 85.4% (41/48) were strongly associated with cancers located in the distal to transverse colon [p<0.001]. Conclusion: There is a high proportion of metabolic diseases; hypertension and diabetes type 2 among colorectal carcinomas seen in Kelantan population. In this preliminary study we noted a strong association of metabolic diseases with the stage and site of the cancer. To reduce CRC incidence, the high prevalence of DM2 in Kelantan needs to be addressed.

Key Words: Colorectal carcinoma - metabolic diseases - diabetes type 2 - hypertension, Malaysia

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Introduction

Colorectal cancers have long been considered as cancers of the developed nations (Slattery et al., 1999; Popkin, 2007). Kelantan is essentially a rural state in Malaysia with per capita GDP of RM 6,134 [USD1918], far below the GDP for Malaysia, RM 14,582 of which 67.4% of the Kelantan state GDP is contributed by the services sector (Leete, 2004). Agriculture, fishing and forestry are the major industries in the state. In 1970, 75% of households in Kelantan was below poverty line, the figure dropped markedly to 12% in 2002 (Leete, 2004). With the change in socio-economic status, there is also a change in the pattern of life-style diseases. There is an increasing trend of obesity, hypertension and diabetes in the state.

The overall prevalence of diabetes mellitus in Kelantan in 1999 was 10.5% and impaired glucose tolerance was 16.5% (Mafauzy et al., 1999). Kelantan is ranked highest in prevalence of diabetes in Malaysia in which the overall national prevalence is 8.3% (Zaini, 2000). In 1960, the prevalence of diabetes in Malaysia was at 0.65% (Mustaffa et al., 1990). WHO has estimated that by 2030, there would be 2.48 million diabetics in Malaysia, a jump of 164% from 0.94 million in 2002 (Mafauzy, 2006). Since Kelantan has the highest prevalence of diabetes in Malaysia, it is expected that colorectal carcinoma would show an increasing trend. Diabetes has been shown to be strongly associated with colorectal adenomas (Santavirta, 2002) and carcinomas (Chang and Ulrich, 2003; Limburg et al., 2006; Berster and Goke, 2008)9,10,11.

The trend of prevalence of overweight/obesity is also rising in Kelantan. Diabetes and obesity has a parallel relationship. In one small rural village in a district of Kota Bharu, 49.1% of the populations were obese/ overweight (Nazri et al., 2008), much higher than the figure reported earlier in 1996 (Jackson et al., 1996). Excess body mass and abdominal obesity have been associated positively with CRC (Russo et al., 1998). In the Kelantan population, impaired glucose tolerance was found in 16.6% of the lean, 21.6% of the overweight and 32.0% of the obese subjects (Mohamad et al., 1996) and subjects with diabetes mellitus were more obese (38.4%) than normal subjects (24.1%) (Mafauzy et al., 1999). Obesity is associated as a risk factor in a number of cancers (Reeves et al., 2007; Rapp et al., 2008), particularly of

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the endometrium (Bjorge et al., 2007; McCourt., 2007), breast (Ahn et al., 2007; Dogan et al., 2007) and colorectal cancers (Moghaddam et al., 2007). Adipocytes have the ability to enhance the proliferation of colon cancer cells *in vitro* (Amemori et al., 2007).

Smoking is associated with metabolic syndromes such as hypertension and cardio-vascular diseases which is also high in Kelantan (Mafauzy et al., 2003; Rahman et al., 2007). Smoking is also strongly associated with a number of cancers notably lung, larynx, bladder, breasts, esophagus and cervix. While in developed countries the prevalence of smoking is decreasing (Lando et al., 2005), the scenario is the opposite in developing countries. In Kelantan, the prevalence of smoking is 15.6% among primary school children (Norbanee et al., 2006), 33.2% among secondary school children (Shamsuddin and Haris, 2000) and 40.6% among secondary school teachers (Naing and Ahmad, 2001). The initiation and the influence to start smoking is similar as in many other countries (Warren et al., 2008). Diabetics who were either current or former cigarette smokers were at higher risk to develop CRC than never smokers (Limburg et al., 2006). Ever-smokers were associated with an 8.8-fold increased risk of colorectal cancers when fed on well-done red meat diet if they have NAT2 and CYP1A2 rapid phenotypes (Le Marchand et al., 2001), no similar association being found in never-smokers. Smoking is strongly associated with ischemic heart disease (Thun et al., 1999) and hypertension (Wenger, 2008).

The aim of this study is to determine the proportion of colorectal carcinomas in our population that is associated with metabolic diseases particularly diabetes type 2 and hypertension and to examine whether the presence of such diseases is associated with the stage and the site of the cancer. To our knowledge, no similar study on Malaysian population has been done previously.

Materials and Methods

This is a retrospective study on all colorectal carcinomas (CRC) consecutively diagnosed and managed in Hospital Universiti Sains Malaysia (HUSM) from year 2001-2006. The data was retrieved from the Registry of Pathology laboratory and the clinical details were obtained from the patients' clinical records at the Medical Record office of the hospital. The data retrieved were the hospital registration number, the histopathology (HPE) serial number, age, sex, stage at diagnosis and the presence/absence of metabolic diseases (Type 2 Diabetes Mellitus and hypertension). Colorectal carcinoma was classified according to the modified Duke's classification. The data was scrutinized to avoid duplicate or repeat entry of the same patient. The presence/absence of other metabolic syndromes was excluded due to incomplete data in some of the patients' records. Only those with complete data were included in the study. The cancer was classified as 'Proximal' when located proximal to the transverse colon and 'Distal' when located distal to it. The data was analyzed using SSPS Version 12.0. Value $p<0.05$ was taken to be statistically significant. For univariate analysis, Dukes A and B were grouped together as 'Local' disease and Dukes B and C as 'Metastatic' disease.

Table 1. Univariate Analysis of Risk Factors Associated With Stage of CRC in HUSM; 2001-2006

Factors		Stage 1 (Dukes A,B)	Stage 2 (Dukes C,D)	P value
DM 2	Positive	9	9	0.043
	Negative	32	88	
Hypertension	Positive	24	24	0.001
	Negative	17	73	
Gender	Male	32	58	0.040
	Female	9	39	
Ethnic	Malay	28	82	0.030
	Non Malay	13	15	
Site	Proximal	8	3	0.001
	Distal	33	94	
Age		64.1	53.9	*0.001

* T-test , others using chi-square test. DM2=Diabetes Type 2; 1= Local Disease; 2=Metastatic disease

Results

In the 5 year period, a total of 138 CRC cases with complete data were included in the study. The patients age ranged from 16.0 to 88.0 years old (Figure 1), with the mean age of 56.9 -/+ SD 15.4. The male 90(65%) to female 48 (35%) ratio was 1.7:1.0. There were 2.0% Indian, 18.0% Chinese and the rest were Malay patients. Most patients were diagnosed at advanced stage [beyond Dukes B] and the majority of the cancers were from the rectum, with the least from the descending colon. Some 47.8% of cases had metabolic diseases; 18(13.0%) had diabetes mellitus type 2(DM2), and 48(34.8%) had hypertension (HPT). Patients with diabetes type 2 88.8%(16/18) and hypertension 85.4% (41/48) were more prone to have distal cancer. Univariate analysis of risk factors showed diabetes type 2 and hypertension were

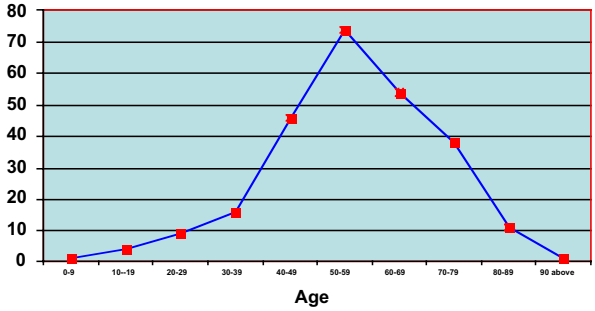

Figure 1. The Age Distribution of the Colorectal Cancer Cases

Table 2. Multivariate Analysis of Risk Factors Associated With CRC in HUSM; 2001-2006

Factor	P value	Odds ratio	95% CI
DM 2	NS	0.724	0.226-2.321
Hypertension	NS	0.500	0.202-1.234
Gender	NS	0.475	0.180-1.254
Ethnic	NS	1.276	0.463-3.518
Site	0.005	0.099	0.020-0.501
Age	0.011	0.955	0.922-0.990

NS= non significant. 95% CI= 95% confidence interval. DM2+, Diabetes Type 2. Analyses was adjusted for all factors using multivariate logistic regression, with SPSS version 12.0

Table 3. Univariate Analysis of Metabolic Diseases and the Site of the CRC in HUSM; 2001-2006

Disease	Proximal	Distal		*P value
DM 2	Positive	2	16	<0.001
	Negative	9	111	
Hypertension	Positive	7	41	<0.001
	Negative	4	86	

*Chi-square test. Proximal= cancers located proximal to transverse colon; Distal= cancers located distal to transverse colon. DM2=Diabetes type 2

significantly associated with the stage of the CRC. Other clinical parameters such as age, ethnic and the site of the cancer were also strongly associated (Table 1). However multivariate analysis showed only the site of the cancer and the age of the patients to be significantly associated with the stage of the disease (Table 2). Diabetes type2 and hypertension were strongly associated with cancers located distal to transverse colon; p<0.001 (Table 3).

Discussion

We found a high proportion (47.8%) of patients with colorectal cancers in our study had had concomitant metabolic diseases; hypertension and diabetes type 2. Hypertension was seen in more than a third of the cases, diabetes in about 13% of the population. These metabolic diseases were already present when the patients were diagnosed to have colorectal carcinoma. Most of our patients were diagnosed in advanced stage [beyond Duke B]. Those with diabetes and hypertension were more prone to develop cancers located distal to transverse colon; 88.8% among diabetics type 2 and 85.4% among hypertensive patients. However the presence of such diseases did not influence whether the patients would have local or metastatic disease at the time of diagnosis. There have been many studies linking metabolic diseases and colorectal cancer (Yang et al., 2005; Ahmed et al., 2006; Seow et al 2006). Most common researched thus far is association of diabetes with colorectal carcinomas (Schiel et al., 2005; Ehrmann-Josko et al., 2006; Sturmer et al., 2006) and a few on colorectal adenoma (Santavirta, 2002; Morita et al., 2005; Elwing et al., 2006).

In this retrospective study, we found only 13.0% of the CRC cases had had diabetes. Based on the association of diabetes with CRC in other studies, we expect to see a higher proportion of CRC having the disease because the trend of CRC in Kelantan is on the rise (Othman et al., 2008). The prevalence of diabetes in Kelantan at 10.5% is ranked highest in Malaysia in which the overall national prevalence is 8.3%. According to National Cancer Registry issued by Ministry of Health Malaysia in 2002 (Lim et al., 2002) and 2003 (Lim et al., 2003) colon and rectal cancers combined ranked first and third in males and females, respectively. Colorectal cancer is increasing rapidly in Asia (Sung et al., 2005; Goh, 2007). This change is parallel with the rise of obesity and diabetes in the region.

Why do diabetics have risks to develop colorectalcarcinoma? The mechanism is complex and there are several models proposed (Sandhu et al., 2002). Like many epithelial cancers, there are multiple factors and multiple steps occurring randomly or in stages. It involves interaction between insulin and other factors. There is increasing evidence that insulin promotes growth (Gupta et al., 2002). Other factors involved are growth hormone (GH), insulin-like growth factor-1 (IGF-1), and insulin-like growth factor receptor (IGFR) and IGF binding protein (IGFBP). IGF-1 being a mitogen, promotes cancer development by direct and indirect effects. IGF-1 also induces an angiogenic hormone; vascular endothelial growth factor (VEGF); a factor which supports the growth of many types of malignancies (Warren et al., 1996). Hyperinsulinaemia and hyperglycemia are the initial risk factors (Chang and Ulrich, 2003). The mechanism of CRC in obese individuals is through hyperinsulinaemia. Increasing adiposity is associated with insulin hypersecretion (Peiris et al., 1986). Shao et al (2004) found mRNA level of insulin growth factor binding protein related protein-1 (IGFBP-rP1) highest in colorectal carcinoma, moderate in colorectal adenoma and tissue adjacent to the cancer site and lowest in normal tissue (P<0.05) suggesting IGFBP-rP1 might play an important role in the initiation and promotion of colorectal cancer.

Diabetic patients have 9.9 fold increased risk to develop CRC than non-diabetics 38. Sturmer et al (2006) studied 22,071 male physicians over 19 year follow-up, of whom 494 developed colorectal cancer. There was an increased risk for colorectal cancer when they had two or more metabolic abnormalities; overweight (RR, 1.4; 95% CI, 1.1-1.7) and diabetes (RR, 1.5; 95% CI, 1.1-2.0). The low number of diabetics among our CRC cases is probably due to incomplete detailing of the medical history as this is a retrospective study.

There is also a proposal, it is the CRC that predisposes to diabetes and not the other way round since there is a higher incidence of impaired glucose metabolisms among CRC patients than the health control populations (Ehrmann-Josko et al., 2006). Glucose metabolism is abnormal in non-diabetic CRC patients (Kokal et al., 1983). Such conclusion could be achieved in long-term prospective study of normal subjects in our population.

Hypertension is another metabolic disease often associated with colorectal carcinoma. The association is an indirect relationship through obesity and diabetes. An earlier study on Kelantan population showed hypertensive patients had a higher prevalence of diabetes mellitus (19.0%), obesity (39.4%) and hypercholesterolemia (70.7%) than non-hypertensive subjects (Mafauzy et al., 2003). In another study on the same community, 23.3% of obese individuals were hypertensive (Mohamad et al., 1996). 34.8% of the patients in our series had hypertension. The presence of metabolic diseases such as diabetes and hypertension had significant association with the stage of colorectal cancer in our series.

Majority of CRC cases in our series is distal to transverse colon. Only about 17% are from the right colon. In the study by Limburg et al (2006), patients with diabetes mellitus type 2 are more at risk to develop proximal than distal CRC. We do not share similar findings. In our series, diabetics were more prone to get cancers distal to

transverse colon than non-diabetics.

In conclusion, there are a high proportion of metabolic diseases; hypertension and diabetes type 2 among colorectal carcinomas seen in patients attending Hospital University Sains Malaysia. In this preliminary study we noted a strong association of such diseases with the stage and the site of the cancer. Patients who had had diabetics and hypertension were more prone to get cancers distal to the transverse colon. This is the first data on such in our population. Reduction in the prevalence of diabetes and other metabolic diseases would reduce the incidence of CRC in our population.

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