RESEARCH ARTICLE

Diverticular Disease and Colorectal Neoplasms: Association between Left Sided Diverticular Disease with Colorectal Cancers and Right Sided with Colonic Polyps

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Abstract

Background: Both colorectal cancer (CRC) and diverticular disease (DD) are common in the affluent West, and their prevalence is also increasing in the rest of the world with economic development. Both diseases have common epidemiologic characteristics; increasing incidence, more common with advancing age and related to specific dietary changes. However, studies of associations between the two have generated mixed results with some showing positive correlations, whilst others have shown no or negative links. Most of these studies have been from the West with study populations that were predominantly Caucasians. Here the focus was on DD and colorectal neoplasms, including CRC, in Brunei. Materials and Methods: All patients who had undergone complete colonoscopy between 2011 and 2014 were identified and retrospectively reviewed. Patients under the age of 18 years old or had previous colonic surgeries (including previous CRC resection) were excluded. Results: The total number of colonoscopies included in the study was 2,766 (mean age 53.2±14.8 years old, male 51.8%), of which DD, CRC and colonic polyps were detected in 17.3%, 4.7% and 28.2% respectively. The proportions of DD, polyps and CRC increased proportionally with age (<30 years, 30-49, 50-69 and ≥70). Overall, there was no association between the presence of DD and CRC (3.6% *vs*. 5.0%, p=0.179) but there was a significant association between CRC and left sided DD (p=0.034 by trend). There were also a significant association between presence of DD and polyps (36.1% *vs*. 28.2%, p=0.001), in particular with right-sided and pan-DD (p=0.001 for trend). Conclusions: Our study showed that the prevalence of DD, CRC and polyps increases with age. There were significant associations between presence of left-sided DD with CRC and right-sided or pan-DD with colonic polyps. This suggests shared risk factors. Further studies are required to assess links in other countries of the Asian Pacific region.

Keywords: Colorectal neoplasms - colon cancer - diverticular disease - polyps

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Introduction

As nations progress with developmental and economic changes, alterations in disease patterns have also been observed. With improvement in standard of living and improved healthcare infrastructure, populations are getting older and coupled with adoption of the modern lifestyle (sedentary lifestyle and refined diet rich in fat and low in fiber), there is progressive increase in diseases or disorders associated with such changes, namely obesity and the non-communicable diseases (i.e. cancers, diabetes, hypertension, hyperlipidemia, coronary and strokes). Both colorectal cancers (CRC) (Chong et al., 2009; GLOBOCAN 2012) and diverticular disease (DD) (Fong et al., 2011; Templeton et al., 2015) are also examples of the consequences of these changes. Worldwide, the incidence of CRC is increasing and this increase is primarily seen in developing nations. Interestingly, there has been a plateauing and even declining trend in developed countries, probably due to awareness and screening programs (GLOBOCAN 2012). Similarly, the incidence of DD has also been reported to be increasing (Fong et al., 2011; Templeton et al., 2015).

Between the East and the West, differences exist in spectra of diseases, including CRC and DD. In the East, the incidence of CRC is much lower than the West, but the incidence is progressively increasing with some developed nations in the East now reporting rates similar to those in the West (GLOBOCAN 2012). The proportion of young CRC is however higher in the East (Koh et al., 2014). For DD, right-sided disease are more common in the East (Rajendra and Ho., 2005; Hirata et al., 2008; Fong et al.,

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2011) whereas left-sided disease predominates in the West (Templeton et al., 2015). Interestingly, both CRC and DD share many similar characteristics from epidemiology to changes at the mucosal level (Morini et al., 2008; Ekbom 2012). Epidemiologically, the incidence of both conditions is increasing worldwide, more common in population that are older and have less dietary fiber (Templeton et al., 2015). At the mucosal levels, changes such as aberrant crypts and chronic inflammation, even at low levels are reported (Morini et al., 2008). Interestingly, associations of DD with other cancers have also been reported (Stefansson et al., 1995).

Despite the number of studies reporting on the associations between DD and CRC and polyps, controversies remain regarding the associations; some reporting increase risk in patients with DD, others have reported no or negative associations (Morini et al., 2008; Ekbom, 2012). Most of these studies however have been carried out on western or Caucasian populations with only few studies done in Eastern population (Rajendra and Ho, 2005; Choi et al., 2007; Hirata et al., 2008; Huang et al., 2015). Given the increase in the incidence of CRC in developing nations, including those in the Asia Pacific region, it is particularly important to learn more about the disease so that effective measures can be implemented to tackle this rising tide. This study assessed the associations between DD and CRC, including colonic polyps (precursors to CRC) in Brunei Darussalam.

Materials and Methods

Study Design, Population and Samples: This study was a retrospective cohort study on all colonoscopies done in a major tertiary referral center in Brunei Darussalam (RIPAS Hospital) between 2011 and 2014. The reference population of this study were patients who had been referred for colonoscopy and who had a complete colonoscopy. The study was approved by the Medical and Health Research Ethics Committee (MHREC) of Ministry of Health in Brunei Darussalam, and Ethics Committee of PAPRSB Institute of Health Sciences (IHSREC).

Exclusion criteria; patients younger than 18 years old and those who had colonic surgeries (especially colonic resections for CRC or other reasons) were excluded from the study. Patients with previous resections were excluded as these patients may have DD affecting resected portion. However, patients who had polyp surveillance were included as these patients did not have any colonic resections.

Data collection and Research Instruments:

Data collected included the colonoscopy endoscripts, demographic data (age, gender and ethnic group), the indications of the colonoscopy and the endoscopic findings with specific references (CRC and DD). Patient's identifier were kept confidential to maintain anonymity. The details on the locations of the colorectal tumors and DD; left, right or pan-colonic involvements were collected. Left sided involvement was taken as involvement up till the splenic flexure (rectum, sigmoid and descending colon) whereas involvement from splenic flexure to the cecum (transverse colon, ascending colon and cecum) was taken as right sided involvement. Pan-colonic involvement was taken as involvement of both sides. Presence of any polyps or diverticula would fulfil the definition of polyps and diverticular disease in this study.

Statistical analysis

Data were collected on patient demographics, indication and detailed findings. No data that may identify the patient's identity were collected to maintain anonymity. Data collection form had been pretested for at least 10 case notes to ensure reliability and validity. For analyses, subjects were categorized into three age groups; <30 years, 30-49 years, 50-69 and 70 and above. The collected data were recorded in computer (Microsoft Excel 2013) and analyzed with the IBM Statistical Package for Social Sciences 21.0 (SPSS 21.0) for Windows. Independent t-test was used to compare the mean age value of the patients of DD and non-DD. Hypothesis testing to find out the association between DD and CRC and polyps were assessed. Two-sided Chi-Square or Fisher's Exact test was used to find out the association between DD and CRC and polyps. A P value of <0.050 was considered statistically significant.

Results

The total number of colonoscopies done between 2011 and 2014 were 2,817 with 51 cases excluded (age<18 years old or previously had colonic resections) leaving 2,766 cases for the study. There was slightly more men (n=1,434 51.8%) than women (n=1,332, 48.2%) with a mean age of 53.2±14.8 years old.

The most common indications for colonoscopy were assessment of bleeding per rectum (21.5%), abdominal pain (17.7%) and evaluation of anemia (11.4%).

Over the four age groups, the incidence of polyps, CRC and DD increase progressively with age (Figure 1) with significant difference between the three disorders with each age groups (all p values <0.005). The proportion of patients in each age groups with both DD and CRC only started to increase in the older age group.

Overall, there 479 (17.3%) patients diagnosed with DD, CRC in 131 (4.7%) and polyps in 781 (28.2%). The

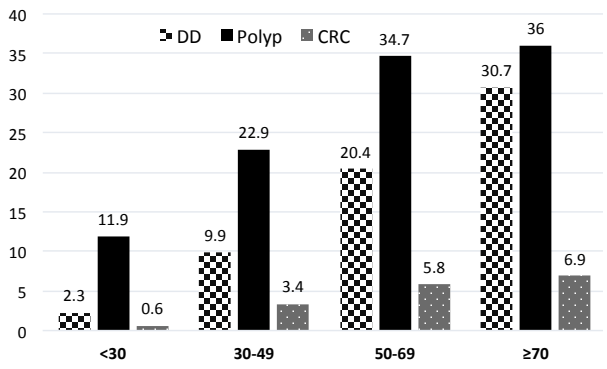

Figure 1. Incidence of Polyps, CRC and DD among the Different Age Groups. X axis age groups and y-axis percentages (%)

Table 1. Locations of DD, CRC and Polyps

	Left side	Right side	Involvement of both sides	Total
	n (%)	n (%)	n (%)	n (%)
DD	152 (31.7)	189 (39.5)	138 (28.8)	479 (100)
CRC	104 (79.4)	26 (19.8)	1 (0.8)	131 (100)
Polyps	530 (67.9)	134 (17.2%)	117 (14.9)	781 (100)

Table 2. Associations between DD, CRC and Polyps

	CRC	Polyps	Overall polyps
	n (%)	n (%)	n (%)
DD			
Yes	17 (3.6)	173 (36.1)	183 (20.8)
No	114 (5.0)	645 (28.2)	718 (79.2)
P value	0.179	0.001	
Locations of DD			
Left	11 (7.3)	45 (29.8)	51 (33.6)
Right	3 (1.6)	73 (38.6)	78 (41.3)
Pan-diverticular	3 (2.2)	55 (39.9)	60 (43.5)
p value	0.034 (for trend)	0.001 (for trend)	0.002 (for trend)

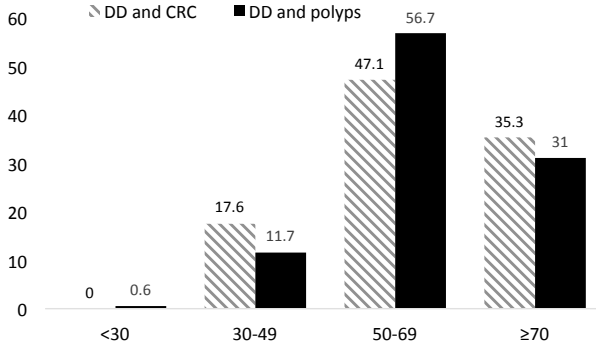

Figure 2. Proportions of Patients with DD and CRC and DD and Polyps among the Different Age Groups. X axis age groups and y-axis percentages (%)

breakdowns of the locations are shown in Table 1.

Even when patients who previously had polypectomies (but not colonic resections) were taken into account, the association remained (p=0.002 for trend) (Table 2).

Between the three disorders studied, there was no significant difference between the presence of DD and CRC but significant association between DD and polyps (Table 2). By locations of DD however, there was a significance association for left-sided DD with CRC. The association remained for polyps, mainly with right-sided DD and Pan-DD.

The proportion of patients with both DD and CRC and DD and polyps increased with age. However, in the youngest age group (<30 years), there was no case of DD and CRC.

Discussion

Our study showed that 17.3% of our patients referred for colonoscopy had DD and 4.7% and 28.2% had CRC and polyps respectively. Compared to our previous study, these has been an increment over the last decade from 12.1% for DD, 3.8% for CRC and 17.6% for colonic polyps (Chong et al., 2012). These increases are likely the results of ageing population and change in lifestyle, following the trends reported in other developing nations.

The proportion of patients with DD, CRC and polyps increased with age. This is not unexpected given that age is an important risk factor for all the three disorders. However, unlike what have been reported in Caucasian or western population, the proportion of young CRC is much higher in the East including Brunei Darussalam (Koh et al., 2015). In this study, we also showed that polyps were common, in fact more common than DD and following the pattern of DD, the proportion increased with age. CRC accounted for smaller fraction but the pattern mirrored the other two conditions. Finding of increased in prevalence of bowel pathologies with increasing age is well known.

Association between DD and CRC has been studied but to date, the findings have been conflicting with some showing a positive association whilst others have not or shown negative associations. The differences in the result reported are likely due to differences in; study designs (population database and modalities for diagnosis with some using surgical specimen, others using barium study and others colonoscopy). Two database studies from Sweden showed that presence of DD (Stefansson et al., 1993) or diverticulitis (Stefansson et al., 2004) were associated with left-sided CRC. A Taiwan study based on discharge database found increased risk of subsequent diagnosis of CRC within the first 12 months after diagnosis of DD but not subsequently (Huang et al., 2014). Another population based study from Sweden also reported similar findings; increased risk of diagnosis of CRC within six months of diagnosis of DD but not after 12 months onwards (Granlund et al., 2011). Both studies attributed the findings to likely diagnosis misclassification rather than actual association. On the other hand, another database study from the United States found positive associations between diagnoses of DD with CRC; proximal, distal and rectal cancers (Cooper et al., 2014). Meurs-Szojda et al. did not find any association between DD or diverticulitis with CRC or polyps (Meurs-Szojda et al., 2008).

Our study showed that overall, there was association between DD and CRC. In fact, numerically, there were fewer CRC cases in patients with DD compared to those without DD. However when the location of DD was taken into account, we showed that left-sided DD was strongly associated with presence of CRC. When the locations of CRC was also taken into account, presence of left sided DD was still associated with more CRC cases (Table 2). However, this was not significant but approaching significance (p=0.059 for trend). Our findings are in agreement with several studies (Stefansson et al., 1993; Cooper et al., 2014). In our study, the rate for pan-DD was slightly higher suggesting that presence of DD in the distal colon may be an important factor whilst right-sided DD may have negative association (Table 2). Previous studies from Asia had been based on smaller sample sizes and may not have detected this association (Rajendra and Ho., 2005; Hirata et al., 2008; Lee et al., 2010; Choi et al.,

2011). This deserve further study to assess whether right and left-sided DD have different pathogenesis and their association with CRC.

Associations between DD and polyps, either overall or advanced adenoma (defined as either large polyp of >10mm, presence of 25% venous component) have been reported. Similar to what have been reported with CRC, the findings of associations of DD with polyps have also been mixed. However, most studies have reported positive associations.

One study done in Malaysia which share almost similar population ethnic breakdown to our population showed positive association between DD and colorectal adenoma (Rajendra and Ho., 2005). Two Korean studies also found similar associations (Lee et al., 2010; Choi et al., 2011). Lee et al., found polyps to be associated with both right- and left-sided DD (Lee et al., 2010). A Japanese study also showed similar association (Hirata et al., 2008). A study on African American also found association with polyps and adenoma (Ashktorab et al., 2015). Rondagh et al. interestingly found that colorectal polyps was association with DD in patients aged 60 years or younger. This suggest perhaps slightly difference pathogenic pathways with age (Rondagh et al., 2011). A study based on Middle Eastern population also found association with adenomatous polyps (Azzam et al., 2013). We also showed that polyps were significantly associated with DD. However unlike association with CRC, the association was the opposite. Presence of polyps was more associated with the presence of right-sided DD or pan-DD. However in our study, the prevalence of left-sided polyps was also high. On the other hands several studies have not found any association (Kieff et al., 2004; Peery et al., 2015). Kieff et al. did not find any association between DD and distal advanced adenoma (Kieff et al., 2011). However, this study had specifically looked at advanced adenoma and defined DD as either extensive or none (a few or no diverticula). Several other studies had also defined the presence of diverticular disease as present of several or more diverticular disease, hence excluding those with milder disease or at the early stage of DD.

Of note, there was no patient diagnosed with both DD and CRC in the youngest age group (<30 years) and peaked in the 50-69 years group. Importantly, the 30-49 age group, an age group which is not part of the recommended CRC screening category accounted for a fifth of cases with both DD and CRC. We also previously showed that young cancer (defined as <45 year old) is common accounting for 15.1% of our CRC patients (Koh et al., 2014) and that the increase start to increase in the younger age group; younger for rectal cancer compared to colon cancer (Chong et al., 2015). A similar trend was seen in the DD and polyps groups. This suggest that when younger patients are suspected or found to have left-sided DD especially if sigmoidoscopy is routinely utilized for younger patients, it is important to consider evaluating the whole colon.

With improvements in the standard of living and adoption of modern 'Westernized lifestyle', developing nations will be deluged with the epidemic of non-communicable diseases. In this context, DD should also perhaps be included as non-communicable disease. Given that DD shares many similarities from the epidemiologic stand points (increasing incidence) and risk factors, findings of associations between DD and colorectal neoplasm (CRC and polyps) are important and needs further evaluations. In the Asia Pacific region, this issue is particularly important given that the incidences of CRC (Chong et al., 2009; GLOBOCAN 2012; Xie et al., 2012; Baniasadi et al., 2015) and DD are increasing (Fong et al., 2011). Whether presence of DD requires special consideration such as shorter interval or age of screening in any CRC screening programs is still uncertain. However, it is well accepted that any patients who have been treated for diverticulitis requires a colonoscopy to exclude an underlying CRC manifested as DD.

In conclusion, our study showed that DD is common in our setting with almost a fifth of our patients who had colonoscopy affected. CRC accounted for 4.7% and polyps 29.6%. The prevalence of each condition increased with age. Although overall, there was no significant association between the presences of DD with CRC, left-sided DD was significantly associated with CRC. Interestingly, presence of proximal DD was associated with colonic polyps. Given the epidemiological and disease patterns between the East and the West it is paramount that more studies based on population in the region be conducted to better understand the natural history and changing trends. Such changing trends have major implication on the delivery of health service such as whether patients with DD should be screened differently for CRC compared to the general public or patients without DD.

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