Review

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The Epidemiology and Etiology of Right-Sided Colonic Diverticulosis: A Review

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Diverticulosis of the colon is a common condition in Western countries and most patients will remain asymptomatic, but some will present with symptoms of acute diverticulitis or bleeding. Our understanding of diverticulosis is evolving but is mostly derived from diverticulosis affecting the left-sided colon. In contrast, right-sided colonic diverticulosis (RCD) is more commonly seen in Asian countries but is much less common overall. Based on the marked differences in epidemiology, it is commonly thought that these are 2 distinct disease processes. A review of the literature describing the epidemiology and etiology of RCD was performed, with a comparison to the current understanding of left-sided diverticulosis. RCD is becoming increasingly common. The epidemiology of RCD shows it to be a mostly acquired condition, and not congenital as previously thought. Many factors in the etiology of RCD are similar to that seen in left-sided diverticulosis, with a few variations. It is therefore likely that most cases of RCD represent the same disease process that is seen in the left colon.

Keywords: *Diverticulum; Diverticulitis; Colon; Ascending colon; Cecum*

INTRODUCTION

Diverticulosis of the colon is a common finding in the Western world. Most patients will remain asymptomatic throughout their lifetime, with the diagnosis only being made as an incidental finding at endoscopy or on cross-sectional imaging. A proportion of patients will become symptomatic with complications of diverticulosis, such as acute diverticulitis (AD) or bleeding.

The distribution of diverticula throughout the colon shows marked geographic variation. The traditional belief is that in the West it is predominantly left-sided, affecting the sigmoid colon in older patients. In contrast, Asian countries show much lower rates overall, but when diverticula are present, they often affect the right side of the colon of younger patients. Our understanding of the pathogenesis of diverticula formation has moved from being centered around the fiber hypothesis proposed by Painter and Burkitt in the 1970s [1], to be a complex interaction of genetic predisposition, connective tissue degradation, and multiple lifestyle influences [2].

The aim of this article is to review the epidemiology of right-sided colonic diverticulosis (RCD), and discuss the etiology, with reference to what is presently understood for left-sided disease.

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EPIDEMIOLOGY OF RIGHT-SIDED COLONIC DIVERTICULOSIS

When considering the epidemiology of diverticulosis, 2 features dominate—geography and age [3]. The prevalence of RCD varies markedly.

As diverticulosis is asymptomatic in the majority, establishing the prevalence in a population remains challenging. The reported prevalence varies not only with the population being studied but also with the modality used for diagnosis. Cross-sectional imaging is generally considered to be more sensitive for the detection of diverticulosis than endoscopy [4]. However, such imaging is mostly performed in patients with abdominal symptoms of some description, resulting in selection bias. In contrast, colonoscopy is commonly used in asymptomatic patients for colorectal cancer screening, resulting in large datasets of asymptomatic patients, from which to estimate the prevalence. A limitation of colonos-

copy is the potential for missing diverticula obscured by haustral folds [5]. Perhaps more importantly, since diverticulosis can be such a common finding at colonoscopy, it may be considered "normal" by the endoscopists and omitted from the procedure report. This may result in underestimation of the true prevalence in large colonoscopy datasets [6]. Regardless of the method of diagnosis, there are clear geographic differences seen in the absolute prevalence of RCD, and what proportion of diverticulosis it comprises as demonstrated in Tables 1 and 2 respectively [3-26].

Western countries

Diverticulosis is reported to be present in more than 70% of the population by the 8th decade of life [4]; however, this is predominantly left-sided colonic diverticulosis (LCD), which accounts for over 90% of diverticulosis seen in Western countries [4, 27].

There is clearly increasing incidence with advancing age. A recent large study by Peery et al. [28] reviewed 271,181 screening colonoscopies in the United States. They found that the prevalence of diverticulosis increased with age in men and women of all ethnicities. In the 40- to 49-year age group, diverticulosis was identified in 27% of men and 21% of women. In the ≥80-year age group, this increased to 72% for both sexes. Interestingly, they found that the higher prevalence in males was consistent across all age groups until the age of 70 years when the sex difference evens out. Given the time taken for diverticulosis to develop, they postulate that endogenous ovarian steroid hormones may be protective for diverticulosis. This study also found ethnic variation in the colonic distribution of diverticulosis. Non-Hispanic Black patients were 1.53 times more likely than White patients to have any RCD, and 2.47 times more likely to have RCD only.

A further important finding from the Peery study [28] was the incidence of RCD with advancing age. A common misconception is that RCDs are congenital. This study analyzed the finding of RCD into subgroups of "any RCD" (i.e., patients who had RCD but may or may not have concurrent LCD) and "only RCD" (those with no LCD). Patients with only RCD did not show an increasing incidence with age, being present in only 1% of individuals aged 40 to 49 years and those aged ≥80 years. In contrast, patients with any RCD had an increasing incidence with age rising from 5% in the 40- to 49-year age group to 16% in the over 80s (odds ratio, 4.34; 95% confidence interval, 3.80–4.95). These findings suggest that while a proportion of RCD is congenital, the majority are acquired and represent the same pathological process as LCD migrating proximally in the colon.

Other studies from Western populations report varying rates of diverticulosis. De Cecco et al. [18] reviewed 1,091 computed tomography (CT) colonography studies performed in Italy and found diverticulosis in 51.6% of patients overall. Diverticula were found in the cecum, ascending, and transverse colons of 9.6%, 13.1%, and 12.7% of patients, respectively. The prevalence of RCD again increased with age. A further Italian study reported a much lower rate of diverticulosis at 19% overall, with RCD in only 2% [19]. However, this study used colonoscopy rather than cross-sectional imaging as the diagnostic modality, and defined diverticulosis as the presence of 5 or more diverticula; and therefore, patients with few diverticula will have been underrepresented. In a study of 796 French patients undergoing colonoscopy, diverticulosis was found in 40%; and of patients with diverticulosis, a third had RCD [14]. The overall prevalence of RCD was 25% by 75 years of age. The authors suggest that, based on their findings, the prevalence of RCD in Western countries is likely underestimated.

A result reported in Table 2 worthy of discussion is that of Meh-

Table 1. Studies reporting population prevalence of right-sided diverticulosis

Study	Year	Country	Diagnostic Modality	Total	Total diverticulosis	Right-sided	Left-sided	Bilateral
Kubo et al. [7]	1983	Japan	DCBE	12,505	969 (7.7)	745 (6.0)	126 (1.0)	108 (0.9)
Lee [8]	1986	Singapore	Autopsy	1,014	194 (19.1)	141 (13.9)	34 (3.4)	19 (1.9)
Nakada et al. [9]	1995	Japan	DCBE	6,849	1,074 (15.7)	743 (10.8)	143 (2.1)	188 (2.7)
Song et al. [10]	2010	Korea	Colonoscopy	848	103 (12.1)	87 (10.3)	9 (1.1)	7 (0.8)
Fong et al. [11]	2011	Singapore	DCBE	1,663	751 (45.2)	597 (35.9)	297 (17.9)	169 (10.2)
Nagata et al. [12]	2013	Japan	Colonoscopy	2,164	542 (25.0)	271 (12.5)	112 (5.2)	159 (7.3)
Lohsiriwat and Suthikeeree [13]	2013	Thailand	DCBE	2,877	820 (28.5)	641 (22.3)	383 (13.3)	98 (3.4)
Faucheron et al. [14]	2013	France	Colonoscopy	796	318 (39.9)	103 (12.9)	215 (27.0)	63 (7.9)
Nagata et al. [15]	2014	Japan	Colonoscopy	28,192	6,150 (21.8)	2,861 (10.1)	1,470 (5.2)	1,631 (5.8)
Tanaka et al. [16]	2016	Japan	Colonoscopy	5,145	1,539 (29.9)	780 (15.2)	759 (14.8)	Not stated
Hong et al. [17]	2016	China	Colonoscopy	63,034	1248 (2.0)	1065 (1.7)	136 (0.2)	47 (0.1)
Bong et al. [3]	2020	Korea	Colonoscopy	1,316	115 (8.7)	105 (8.0)	24 (1.8)	14 (1.1)

Values are presented as number only or number (%).
DCBE, double-contrast barium enema.

Table 2. Prevalence of right-sided diverticulosis expressed as a proportion of cases that had any diverticulosis identified

Study	Year	Country	Diagnostic modality	Total	Right-sided (%)	Left-sided (%)	Bilateral (%)
Kubo et al. [7]	1983	Japan	DCBE	969	76.1	12.9	11.0
Sugihara et al. [21]	1984	Japan	DCBE	615	69.8	15.9	14.3
Lee [8]	1986	Singapore	Autopsy	194	72.7	17.5	9.8
Nakada et al. [9]	1995	Japan	DCBE	1,074	69.2	13.3	17.5
Takano et al. [22]	2005	Japan	DCBE	82	47.6	6.1	46.3
Song et al. [10]	2010	Korea	Colonoscopy	103	84.5	8.7	6.8
Fong et al. [11]	2011	Singapore	DCBE	751	60.5	17.0	22.5
Nagata et al. [12]	2013	Japan	Colonoscopy	542	50.0	20.7	29.3
Lohsiriwat and Suthikeeree [13]	2013	Thailand	DCBE	820	53.3	20.1	26.1
Faucheron et al. [14]	2013	France	Colonoscopy	318	12.6	67.6	19.8
Nagata et al. [15]	2014	Japan	Colonoscopy	6,150	48.0	24.7	27.4
Mehrzad et al. [20]	2015	United States	Colonoscopy	506	14.6	70.1	14.6
Tarao et al. [23]	2015	Japan	DCBE	113[a]	44.3	30.7	25.0
Tanaka et al. [16]	2016	Japan	Colonoscopy	1,539	50.7	49.3	Not stated
Dore et al. [19]	2016	Italy	Colonoscopy	841	2.0	71.6	14.4
De Cecco et al. [18]	2016	Italy	CT Colonography	561	35.4	64.6	Not stated
Hong et al. [17]	2016	China	Colonoscopy	1,248	85.3	10.9	3.8
Wong et al. [24]	2016	Brunei	Colonoscopy	479	39.5	31.7	28.8
Peery et al. [6]	2016	United States	Colonoscopy	260	18.0	82.0	Not stated
Sharara et al. [25]	2018	Lebanon	Colonoscopy	224	5.8	67.4	22.8
Yang et al. [26]	2018	China	Colonoscopy	1,045	72.9	11.9	15.2

DCBE, double-contrast barium enema; CT, computed tomography.
[a]Distribution breakdown limited to 88 patients who had 4+ diverticula.

rzad et al. [20]. This study from American authors reviewed 207 Vietnamese patients residing in Boston having their first screening colonoscopy and compared the findings to those of 299 White patients during the same period. When limited to the 207 Vietnamese participants, the prevalence of RCD and bilateral diverticulosis was 31.1% and 18.4%, respectively. In the White patients forming a control group, nearly 97% of these patients had LCD or bilateral diverticulosis, compared to only 3.0% with RCD alone.

Asian countries

The overall prevalence of diverticulosis in Asian countries is much lower than that seen in the West; however, RCD predominates. Table 1 shows the rate of 2% to 45%, overall, with RCD being found in over 1/3 of patients in Singapore [11], although most Asian studies report RCD to be found in the range of 10% to 15% of individuals. When considered as a proportion of individuals with diverticulosis, the majority have right-sided or bilateral diverticula (Table 2). Similar to that seen in Western populations, the prevalence of diverticulosis has been increasing in recent years [3, 10, 12, 26, 29].

ETIOLOGY AND RISK FACTORS FOR RIGHT-COLONIC DIVERTICULOSIS

Right-sided diverticula: congenital or acquired?

A diverticulum of the cecum was first described by Potier in 1912 [30]. With the tendency of RCD to affect younger patients, they are frequently considered to be congenital, solitary, and true diverticula affecting the full thickness of the bowel wall, in contrast to the acquired false diverticula seen in the distal colon. Amounting evidence demonstrates an increasing prevalence with advancing age, which contradicts this hypothesis.

Multiple studies have shown that, histologically, right-sided diverticula are a mix of true and false diverticula. Hughes [31] carried out an autopsy study in Australia where the colons from 24 patients with cecal diverticulosis had histopathological examinations. Five of these patients had primary cecal diverticula with no diverticulosis elsewhere in the colon. Microscopically, all cecal diverticula proved to be false diverticula. Similar findings were found in a Singaporean autopsy study, where 194 patients with diverticulosis had false diverticula when examined microscopically. This included 39 patients who had a solitary diverticulum [8].

Graham and Ballantyne [32] reported a large series of cecal di-

verticulitis. Of 128 cases with histology available, 59% of cecal diverticula were false diverticula. They also found that among 288 patients, 81% of cecal diverticula were solitary and 19% multiple. A Japanese study of over 12,000 barium enemas found the opposite, with 20% of right-sided diverticula being solitary [7].

Further evidence to support RCD being an acquired condition comes from a study of 84 patients who had consecutive barium enemas at least 10 years apart, assessing the number and distribution of diverticula within the colon. It found that, initially, diverticula were predominantly on the right side, and tended to strongly increase in number on the right side as well as become bilateral over time [22].

While many textbooks still convey the theory of RCD being congenital, solitary, true diverticula, there is significant direct and epidemiological evidence to counteract this. It is most likely that RCD represents 2 distinct processes. A proportion of RCD is congenital; however, it is increasingly evident that RCD is an extension of the same process that causes LCD. Comparisons of differences in epidemiology and various etiological factors are shown in Table 3.

Dietary fiber intake and the role of raised intraluminal pressure

In the 1970s, Painter and Burkitt [1] reported diverticulosis to be a disease of Western society, based on a study that found much lower rates of diverticulosis in African populations, compared to that of the United States. This was ascribed to differences in the intake of insoluble dietary fiber influencing the development of diverticulosis. Reduced dietary fiber in Western populations results in reduced stool bulk and firmer stools; and therefore, to propel the stool distally in the colon, higher intraluminal pressure must be generated. This higher pressure results in herniation of the mucosa/submucosa through points of weakness in the muscle coat, resulting in diverticula formation.

This theory remained surgical dogma for decades, but more recently has been challenged [33]. Current understanding of the pathophysiology of diverticulosis is that it is a multifactorial process, secondary to connective tissue degeneration in a genetically susceptible individual [34].

An important factor driving the fiber hypothesis was that diverticulosis is commonly seen in the sigmoid colon, where stool is firm and the lumen is narrow. In contrast, the right colon contents are more liquid and its lumen is larger; and therefore, according to the law of Laplace, the peak wall tension generated will be lower.

An early study by Sugihara et al. [35] in Japan measured the intraluminal pressure in 13 patients with RCD compared to 10 healthy controls. At resting state, the RCD patients had greater colonic motility than controls. After administration of intravenous neostigmine, higher pressure peristaltic contractions were generated and the increase in colonic motility was exaggerated compared to the control group. They concluded that high intraluminal pressure and abnormal motility do play a role in the pathogenesis of RCD. Similar conclusions were reached by a further study with similar methodology [36].

While the evidence is accumulating disproving the Painter and Burkitt's hypothesis [1] for diverticulosis in general, data specific to the influence of dietary fiber for RCD and/or Asian populations is lacking. Bong et al. [3] from Korea performed a case-control study evaluating the influence of a vegetarian diet on the likelihood of diverticulosis at screening colonoscopy. The vegetarian group was comprised of Buddhist monks, who are obligatory lifelong vegetarians for spiritual reasons (thus avoiding recall bias or previous exposure to nonvegetarian diet), compared to a nonvegetarian control group. They found that 6.1% of Buddhist monks had RCD, which was significantly lower than the 9.9% seen in the control group. On multivariate analysis, a nonvegetarian diet remained associated with a significantly increased risk of RCD.

In contrast, Song et al. [10] found no association between dietary fiber intake and the presence of diverticulosis on screening colonoscopy in a Korean population. Likewise, Nagata et al. [37] found no association with the presence of RCD and constipation/

Table 3. Summary of epidemiological changes and various etiological factors and their relative importance in the development of right-sided colonic diverticulosis

Variable	Right-sided diverticulosis	Left-sided diverticulosis
Epidemiology		
Prevalence	Relatively low	Common
Incidence over time	Increasing	Increasing
Congenital vs. acquired	Mostly acquired, some congenital	Acquired
Etiology		
Role of intraluminal pressure	Uncertain	Increasingly challenged of late
Genetics	+++	++
Colonic wall structural change	+	++
Obesity	Insufficient evidence	++

firm stool. Interestingly, for LCD they found a negative association between firm stool and presence of diverticulosis.

Gas production by intestinal bacteria as a cause of raised intraluminal pressure

Methane gas has been reported to delay small intestinal transit and increase intraluminal pressure, and intraluminal pressure has been hypothesized to lead to diverticulosis as described above. Methanogenic bacteria and archaea convert lactulose into methane gas, and Jang et al. [38] tested the hypothesis that methane gas production increases intraluminal pressure in the right colon, which may predispose to the development of RCD. The study performed lactulose breath testing on 30 patients with RCD, compared to 30 healthy controls. They did not find a significant difference in the rate of methane or hydrogen gas production between the 2 groups, concluding that colonic gas is unlikely to be implicated in the pathogenesis of RCD.

Genetic influences are likely to be particularly important in the development of right-sided diverticulosis

For diverticulosis in general, evidence for a genetic influence is accumulating [39]. Based on twin studies, genetic variation is thought to account for 40% to 50% of an individual's risk of diverticulosis [40, 41]. As well as information gathered from twin studies, connective tissue disorders, such as Marfan and Ehlers-Danlos syndromes, with well-defined genetic mutations, have predisposition to diverticulosis [39, 42].

The role of genetic influences is likely to be even greater for RCD. Such marked variation in the prevalence of RCD between Asian and Western countries will undoubtedly be attributable to variations in lifestyle. However, even within a given geographic area, there are ethnic differences in prevalence observed, which suggests lifestyle factors do not explain all of the variations.

The Peery study described above [28] found that Asians or Pacific Islanders were more than 3 times more likely to have only RCD, with a smaller but still significantly increased risk of RCD in Black individuals, when compared to the non-Hispanic White reference population. Similarly, in a study of barium enemas performed in Singapore, all ethnicities appeared to have a similar risk of LCD, whereas ethnic Chinese patients appeared particularly susceptible to RCD [11].

Perhaps the greatest support for the genetic influence in RCD comes from the fact that Japanese people, who immigrate to Hawaii and adopt a Western lifestyle, maintain a similar pattern of RCD to those who remain in mainland Japan [43]. Song et al. [10] hypothesize that the higher rate of RCD seen in Asians is due to a structurally weaker right colon, possibly explained by genetic factors. Other authors support the hypothesis that genetics have a greater influence on the development of diverticulosis in Asian compared to Western populations [44].

In general, highly prevalent conditions are due to complex interactions of multiple genes, rather than a single causative mutation. Therefore, it is unlikely that diverticulosis is attributable to a single genetic fault. Progress has, however, been made in identifying gene(s) implicated in its development. Choe et al. [45] performed a genome-wide association study of RCD in a Korean population. They performed genomic analysis on patients having comprehensive health checks, who were also undergoing screening colonoscopy, and compared genomic aberrations with the presence or absence of RCD at colonoscopy. They identified 9 single nucleotide polymorphisms, within or adjacent to 3 potential candidate genes (*WNT4*, *RHOU*, and *OAS1/3* genes). These 3 genes could conceivably play a role in the development of RCD based on their known functions. *WNT4* is involved in vascular smooth-muscle cell proliferation, while the *RHOU* gene plays a role in mediating *WNT* signaling pathways. The *OAS* gene products are induced by interferon and may play a role in the mucosal response to gut bacteria and low-grade inflammation.

Alterations in the enteric nervous system and structural changes within the colonic wall

An *in vitro* study examining functional differences of the enteric nervous system of both right and left colons, with and without diverticulosis, subjected to selective receptor blockade, found that colons with diverticulosis showed significantly stronger cholinergic contractions compared to normal controls, regardless of laterality [46]. This suggests that cholinergic (stimulatory) nerves dominate in colons with diverticulosis, in contrast to nonadrenergic, noncholinergic nerves dominating in normal colons. These findings lend support to higher intraluminal pressure caused by colonic segmentation being present in diverticular colons. This functional result of high intraluminal pressure in colons with RCD agrees with *in vivo* findings originally reported in the 1980s [35].

Additional support for enteric nervous system changes comes from Hildebrand et al. [47]. They reviewed 16 ascending colons resected for diverticular disease, 7 of which had hypo- or aganglionosis, suggestive of intestinal neuronal dysplasia, which is sometimes seen in patients with chronic constipation. It was unclear, however, whether these observed changes were a primary cause or a secondary phenomenon of RCD.

Colonic wall thickening is common in LCD [2], but evidence is conflicting in RCD. Autopsy findings from a Singaporean study found that thickening of the muscular wall was not grossly apparent in RCD, but was often obvious and marked in LCD [8]. In contrast, Murayama et al. [48] examined surgical specimens with RCD, measuring the muscular wall thickness. Over half had thickening of the taenia and almost 2/3 had hypertrophy of the circular muscle layer, suggesting that changes in connective tissue composition may be less important in RCD as they are in LCD.

Obesity as a risk factor for right-sided diverticulosis

Obesity is a well-defined risk factor for the development of LCD; however, data specific to RCD are few and conflicting. A Japanese

study of 215 patients undergoing colonoscopy found patients with RCD to be significantly less likely to be obese than those who had LCD [49]. However, this study was focusing on obesity as a risk factor for developing AD in patients with RCD versus LCD, and, therefore, it lacked a control group of individuals with normal colons.

Song et al. [10] found no association between BMI and RCD in 848 patients undergoing colonoscopy. In contrast, Nagata et al. [50] assessed visceral adiposity on CT for 1,445 Japanese patients undergoing colonoscopy and found that increasing abdominal adiposity area was associated with RCD, even in normal bodyweight individuals (note that this finding was also true for LCD). With the limitations in describing the prevalence of RCD, it is unsurprising that defining its association with obesity has proved challenging.

More thoroughly investigated is the influence of obesity on developing AD in patients with RCD. A recent meta-analysis addressed this, finding no association between obesity and the development of right-sided AD among 1,252 patients across 4 studies [51].

Other lifestyle factors and their risk of right-sided diverticulosis

Like obesity, robust evidence for the influence of various lifestyle factors on the development of RCD is lacking. The role of such factors in the development of AD in patients with RCD is often better defined.

Smoking

In Western countries, with predominantly left-sided disease, smoking increases the risk of both diverticulosis and AD [52]. Smoking does not appear to significantly increase the risk of developing RCD [3, 53]. However, the likelihood of developing right-sided AD is elevated in smokers [51] and may also increase the likelihood of complicated diverticulitis [54].

Alcohol

Alcohol consumption has been shown to be a risk factor for RCD in studies from Korea and Japan [10, 12], with the Japanese study [12] reporting alcohol consumption to be a risk factor for RCD, but having no association with LCD. Similarly, Sharara et al. [55] found an association with diverticulosis overall but did not perform specific analysis for the RCD subgroup.

Perhaps the best evidence for the association of alcohol intake with the development of any diverticulosis comes from the United States, where Aldoori et al. [56] examined lifestyle factors in 47,678 men. Alcohol intake showed a nonsignificant trend toward an association with diverticulosis.

Dietary factors other than fiber intake

Dietary contributors other than insoluble fiber intake have been also been considered. When adjusting for the confounding effects of obesity or fiber intake, a diet rich in red meat or fat may increase the likelihood of RCD [10, 53].

CONCLUSION

Diverticulosis affecting the right colon is becoming increasingly common. Historical teaching explained RCD as an uncommon congenital finding in Asian populations. Our understanding of this condition has improved, and there is increasing evidence showing it to be an extension of the more common LCD, with a few variations in its etiology. The increasing prevalence of RCD parallels that observed for LCD in recent decades. While the changes in RCD are not entirely explained by the etiological factors discussed above, it is likely the trend will continue. As the prevalence of RCD increases, its clinical manifestations such as AD are likely to be encountered more frequently in the coming decades.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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