

Association between diverticular disease and prevalence of colorectal adenomatous polyps or adenocarcinomas

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Ethics Committee Approval

This study was approved by the clinical research ethics committee of Erzurum Regional Training and Research Hospital (IRB approval number: 2022/11-131).

All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest

No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Although the link between diverticular disease (DD) of the colon and colon polyp is known, the relationship between colon adenocarcinoma is not clear. This study evaluated the association between DD and adenomatous polyp or colon adenocarcinoma.

Methods: Patients who underwent colonoscopy for the first time in 2020-2021 were evaluated and included in this retrospective cohort study. Patients with a previous history of cancer diagnosis, colon surgery, DD, and inflammatory bowel disease were excluded from the study. Age, gender, colonoscopy indications, colonoscopy diagnoses, presence of DD, characteristics of polyps (pathology, diameter, number, localization), and presence of adenocarcinoma were recorded. Obtained data were analyzed between DD and non-DD groups.

Results: A total of 2633 patients were included in the study. The prevalence of DD was 16.4%. Colon adenocarcinoma was detected in 4.7%. The adenomatous polyp rate was 14.1%. A significantly higher rate of adenomatous polyps was detected in the DD group compared to the non-DD group (19.7% vs. 12.9%; $P = 0.001$). Higher rates of high-grade dysplasia (3.0 vs. 1.1%; $P = 0.002$) and colon adenocarcinoma (7.2% vs. 4.2%; $P = 0.008$) were observed in the DD group also. In logistic regression analyses, it was observed that the presence of concomitant DD increases the risk of adenomatous polyps (OR: 1.469, 95% CI: 1.158–1.865), the risk of adenomatous polyps with positive villous component (OR: 2.378, 95% CI: 1.437–3.934), the risk of adenomatous polyps with high-grade dysplasia (OR: 2.822, 95% CI: 1.426–5.582), and the risk of colon adenocarcinoma (OR: 2.953, 95% CI: 1.445–6.533).

Conclusion: DD is associated with precancerous lesions of the colon (adenomatous polyp, villous adenoma, high-grade dysplasia) and colon adenocarcinoma. Further studies are needed to investigate its association with colon carcinogenesis and its role and value in cancer screening.

Keywords: Adenomatous polyp, Colon adenocarcinoma, Diverticular disease, High-grade dysplasia, Villous adenomatous polyp

Introduction

Colon adenocarcinoma ranks third among all cancers in men and second in women. Its incidence among all cancers is 12%. Colon adenocarcinoma has significant mortality and is the third deadliest among all cancers [1, 2]. Adenomatous polyps are benign tumors of the colon with low-grade dysplasia. Sporadic colon adenocarcinoma progress from adenomatous polyps due to an increase in dysplasia with the effects of genetic and epigenetic changes [3]. Advanced age, increased number of polyps, larger polyp size (>10 mm), and high-grade dysplasia are risk factors for the development of malignancy from the polyp. In the presence of a diameter greater than 10 mm, the presence of a villous component, and severe dysplasia, conversion to adenocarcinoma is observed at an annual rate of 3%, 17%, and 37%, respectively [4, 5].

In the presence of typical symptoms and findings (including rectal bleeding, anemia, weight loss, defecation irregularity, and pain) for colon adenocarcinoma, further examination with colonoscopy is already required. The most important preventive method for colon adenocarcinoma is to include the cases in the colonoscopy screening program according to the risk factors. In cases with risk factors, such as a family history of polyps or colon adenocarcinoma, and the presence of ulcerative colitis, early screening can detect polyps before dysplasia progresses and adenocarcinoma transformation develops. Cure can be provided in cases with simple polypectomies. As a result of the increase in colonoscopies for screening purposes, the prevalence and incidence of colon adenocarcinoma have decreased in the last 20 years compared to previous years. [2, 6, 7].

Colonic diverticula are outpouchings of the intestinal wall that occur due to defects in the muscle layer of the colon wall. The prevalence of diverticular disease has increased in recent years. Advanced age, obesity, low fiber diet, and low exercise are risk factors for the development of colon adenocarcinoma as well as for the development of diverticular disease. Studies are showing an increased incidence of colon polyps in diverticular disease. However, when the literature is examined, the relationships between colon adenocarcinoma and diverticular disease are conflicted. Although some studies did not find a significant relationship between diverticular disease and colon adenocarcinoma, some studies reported an increased incidence of colon adenocarcinoma in diverticular disease [8–10]. In the present study, we evaluated the association between diverticular disease and adenomatous polyps or colon adenocarcinoma.

Materials and methods

This study was carried out after the approval of Erzurum Training and Research Hospital's Clinical and Research Ethics Committee with decision number 2022/11-131. Patients who underwent colonoscopy for the first time in the gastroenterology department of Erzurum Training and Research Hospital in 2020–2021 were evaluated retrospectively and included in the study.

Colonoscopy indications were determined as abdominal pain, constipation, chronic diarrhea, rectal bleeding, weight loss,

family history of colon adenocarcinoma, family history of colorectal polyps, iron deficiency anemia, and occult blood positivity in stool. Patients with a previous history of cancer diagnosis, a history of colon surgery, and a history of inflammatory bowel disease were excluded from the study.

In all cases, intestinal preparation was provided with sennoside oral laxative and sodium dihydrogen phosphate + disodium hydrogen phosphate enema. Patients with adequate bowel preparation and colonic visibility were included in the study. The patients were sedated by the anesthesiologist with propofol, midazolam, and fentanyl throughout the procedure. In patients, full colonoscopy was accepted as ileum intubation and clear evaluation of all colon areas from the cecum backward. Patients who could not be evaluated clearly and whose all areas could not be evaluated due to early termination of the procedure for any reason were excluded from the study.

Age, gender, colonoscopy indications, and colonoscopy diagnoses were evaluated and recorded. The presence of diverticula in any location of the colon in the colonoscopy procedure was considered a diverticular disease. The diagnosis of polyp detected on the colonoscopy was confirmed by histopathological evaluation. All polyps were evaluated by a gastrointestinal pathologist. As a result of the histopathological evaluation, polyps were recorded as hyperplastic, serrated, and adenomatous. The degree of dysplasia (low-grade, high-grade) and pathological subtypes according to the villous component (tubular, tubulovillous, and villous) in adenomas were determined and recorded. Location, number, and size of polyps were recorded.

According to the presence of diverticula, the cases were divided into two groups: diverticular disease (DD) and non-diverticular disease (non-DD). Both groups were compared in terms of the variables mentioned above.

Statistical analysis

Parameters were analyzed by using the “SPSS 22 for Windows” statistics program. Categorical (nominal) values are expressed as a percentage (%) and compared with the chi-square test (2). Continuous numerical (quantitative) values were expressed as mean (SD). Quantitative variables were compared with the “Student t-test.” Univariate analyses were conducted using Fisher's exact test to identify candidate risk factors for colon polyps and colon adenocarcinoma. All factors which were significant in univariate analyses were entered into multivariate logistic regression models. Logistic regression analysis was used to evaluate the association of DD with the prevalence of adenomatous polyps and colon adenocarcinoma. The results are expressed as odds ratios (OR) with 95% CI. $P < 0.05$ was determined as statistically significant.

Results

A total of 2,633 patients were included in the study. The mean age of the patients was 53.66 (16.33). 55.8% (n = 1468) of the patients were male. The prevalence of DD was 16.4% (n = 431). Colon adenocarcinoma was detected in 4.7% (n = 124). The prevalence of polyps was 20.8% (n = 547). Among all patients, the rate of hyperplastic polyps was 6.2% (n = 164), the serrated polyp rate was 0.5% (n = 12), and the adenomatous polyp rate was 14.1% (n = 371). 11.3% (n = 298) tubular

adenoma, 1.4% (n = 38) tubulovillous adenoma, and 1.4% (n = 36) villous adenoma were detected in all patients. The prevalence of adenomatous polyps with high-grade dysplasia was 1.4% (n = 37) of all patients. The rate of patients with more than one polyp was 11.7% (n = 64). The rate of patients diagnosed with polyps with a diameter ≥ 10 mm was 27.5% (n = 150). Polyps were located 36.1% (n = 197) in the rectum, 21.5% (n = 18) in the sigmoid colon, 16.5% (n = 91) in the descending colon, 11.4% (n = 62) in the transverse colon, 9.7% (n = 53) in the ascending colon, and 4.8% (n = 26) in the cecum.

Table 1 and Table 2 summarize the comparison of the variables between the DD and non-DD groups. The DD and non-DD groups were similar in age, gender, colonoscopy indications, and family history of polyps or colon adenocarcinoma. It was observed that polyps were detected at a significantly higher rate in the DD group than in the non-DD group (26.5% vs. 19.7%, [P = 0.002]). There was no difference between the DD group and non-DD groups in terms of serrated polyp and hyperplastic polyp rates. A significantly higher rate of adenomatous polyps (tubular adenoma, tubulovillous adenoma, villous adenoma) was detected in the DD group compared to the non-DD group (19.7% vs. 12.9%, [P = 0.001]). The high-grade dysplasia rate was found to be higher in the DD group than in the non-DD group (3.0% vs. 1.1%, [P = 0.002]). Colon adenocarcinoma was observed at a significantly higher rate in the DD group than in the non-DD group (7.2% vs. 4.2%, [P = 0.008]). There was no difference between DD and non-DD groups in terms of the distribution of polyps, polyp diameters, and multiple polyp ratio.

Table 1: Demographic characteristics of patients

	Non-DD	DD	P-value
Age	53.54 (16.35)	54.26 (16.25)	0.403
Gender (Male)	55.6%	56.4%	0.791
Colonoscopy indication			
Iron deficiency anemia	13.9%	14.8%	0.651
Occult blood positivity in stool	18.8%	19.3%	0.841
Chronic diarrhea	10.8%	10.7%	0.981
Constipation	16.9%	17.2%	0.871
Rectal bleeding	9.4%	9.0%	0.934
Abdominal pain	14.7%	14.6%	0.882
Weight loss	2.9%	2.8%	0.971
Polyp history in family	8.1%	7.7%	0.712
Colon cancer history in family	4.5%	3.9%	0.693

Table 2: Comparison of polyp and colon cancer rates between Non-DD and DD groups

	Non-DD	DD	P-value
Colon cancer	4.2%	7.2%	0.008
Polyp	19.7%	26.5%	0.002
Hyperplastic polyp	6.4%	6.0%	0.798
Serrated polyp	0.4%	0.7%	0.445
Adenoma	12.9%	19.7%	0.001
Tubular adenoma	10.5%	14.6%	0.018
Tubulovillous adenoma	1.2%	2.7%	0.011
Villous adenoma	1.2%	2.5%	0.021
Polyp with high-grade dysplasia	1.1%	3.0%	0.002
Number of polyps ≥ 1	11.4%	13.2%	0.625
Polyp diameter ≥ 10 mm	27.8%	26.3%	0.814

In logistic regression analyses, it was observed that the risk of adenomatous polyps increased with age (OR: 1010, 95% CI: 1.004–1.016), the presence of a family history of polyp (OR: 3.899, 95% CI: 2.653–5.730), the presence of a family history of colon adenocarcinoma (OR: 2.681, 95% CI: 1.993–3.606), and concomitant DD in the case (OR: 1.469, 95% CI: 1.158–1.865). Gender did not increase the risk of adenomatous polyp (Table 3).

In logistic regression analyses, it was observed that the risk of adenomatous polyps with a positive villous component increased with age (OR: 1.027, 95% CI: 1.011–1.042) and concomitant DD in the case (OR: 2.378, 95% CI: 1.437–3.934). Gender and a family history of polyps or colon adenocarcinoma

did not increase the risk of adenomatous polyps with a positive villous component (Table 4).

Table 3: Risk factors for adenomatous polyp

	Adenomatous Polyp (+/-)			
	OR	Lower	Upper	P-value
Age	1.010	1.004	1.016	0.002
Gender (Male)	0.808	0.669	0.975	0.058
Polyp history in family	3.899	2.653	5.730	0.001
Colon cancer history in family	2.681	1.993	3.606	0.001
Diverticular disease	1.469	1.158	1.865	0.001

CI: Confidence Interval, OR: Odds Ratio

Table 4: Risk factors for polyp with villous component (+)

	Villous component (+/-)			
	OR	Lower	Upper	P-value
Age	1.027	1.011	1.042	0.001
Gender	0.667	0.419	1.060	0.096
Polyp history in family	1.583	0.626	4.002	0.380
Colon cancer history in family	1.833	0.927	3.625	0.082
Diverticular disease	2.378	1.437	3.934	0.001

In logistic regression analyses, it was observed that the risk of adenomatous polyps with high-grade dysplasia increased with age (OR: 1035, 95% CI: 1.013–1.058), a family history of colon adenocarcinoma (OR: 3.809, 95% CI: 1.783–8.183), and concomitant DD in the case (OR: 2.822, 95% CI: 1.426–5.582). Gender and a family history of polyps did not increase the risk of adenomatous polyps with high-grade dysplasia (Table 5).

Table 5: Risk factors for polyp with high-grade dysplasia

	High-Grade Dysplasia (+/-)			
	OR	Lower	Upper	P-value
Age	1.035	1.013	1.058	0.002
Gender	0.836	0.437	1.599	0.620
Polyp history in family	1.921	0.581	6.348	0.225
Colon cancer history in family	3.809	1.773	8.183	0.002
Diverticular disease	2.822	1.426	5.588	0.005

In logistic regression analyses, it was observed that the risk of colon adenocarcinoma increased with age (OR: 1.017, 95% CI: 1.005–1.028), a family history of polyps (OR: 1.168, 95% CI: 1.083–1.259), a family history of colon adenocarcinoma (OR: 2.967, 95% CI: 1.553–5.597), and concomitant DD in the case (OR: 2.953, 95% CI: 1.445–6.533). Gender did not increase the risk of colon adenocarcinoma (Table 6).

Table 6: Risk factors for colon adenocarcinoma

	Colon Adenocarcinoma (+/-)			
	OR	Lower	Upper	P-value
Age	1.017	1.005	1.028	0.004
Gender	1.367	0.730	2.560	0.329
Polyp history in family	1.168	1.083	1.259	0.001
Colon cancer history in family	2.967	1.537	5.597	0.001
Diverticular disease	2.953	1.445	6.033	0.004

Discussion

Colonic pre-neoplastic/neoplastic lesions and diverticular disease have similar risk factors, including age, obesity, low physical activity, low fiber diet, excess red meat, and carbohydrate consumption [11, 12]. It is thought that the frequency of co-occurrence will increase because they have similar risk factors. Many studies have investigated the association of DD with colonic adenomatous polyps or adenocarcinoma. In most of these studies, it has been reported that adenomatous colon polyps are clearly significantly increased in the presence of diverticular disease [8, 13–15]. There are still conflicting results regarding the relationship between DD and colon adenocarcinoma. A few studies have reported a significant relationship between DD and colon adenocarcinoma. These studies even suggest a vigilant follow-up procedure for preventing colon adenocarcinoma for patients with DD [9, 15–

18]. On the other side, some studies determined that there is no relationship between DD and colon adenocarcinoma. These mentioned studies indicate that there is a bias between DD and increased incidence or prevalence of colon adenocarcinoma. These studies stated that it is not a correct decision to include patients with DD in the surveillance program for polyps or colon adenocarcinoma according to these data [10, 19–23].

We aimed to investigate the relationship between diverticular disease and both premalignant (adenomatous polyp) and malignant (adenocarcinoma) lesions of the colon by retrospectively evaluating the data in our clinic. In the present study, the incidence of DD, adenomatous polyps, and colon adenocarcinoma was 16.4%, 20.8%, and 4.7%, respectively. In the present study, colon adenomatous polyps and adenocarcinomas were found at a significantly higher rate in the DD group, similar to some cross-sectional, case-control, and cohort studies in the literature (19.7% vs. 12.9% and 7.2% vs. 4.2%). In logistic regression analysis, it was determined that the presence of DD increased the relative risk for both adenomatous polyps and colon adenocarcinoma (OR: 1.469 and OR: 2.953). Colonoscopy indications of the DD and non-DD groups were similar. There was also no difference in risk factors such as advanced age, family history of colon cancer or polyps between DD and non-DD groups. According to the higher incidence of both premalignant and malignant lesions of the same carcinogenesis pathway in DD, we can strongly suggest that DD is associated with colon adenocarcinoma.

Most colon adenocarcinomas (sporadic 90%) develop from adenomatous polyps. It is known that the risk of malignant transformation is low in hyperplastic polyps. The risk of malignant transformation of serrated polyps and tubular adenoma is similar. There are certain risk factors for the transformation of adenomatous polyp into adenocarcinoma. The risk of cancer development from adenomatous polyps increases in the presence of polyps larger than 10 mm, multiple polyps, high villous components, and a high degree of dysplasia [3–5, 24]. It was observed that DD especially increased the frequency of adenomatous polyps, similar to the studies in literature, while no change was observed in the incidence of serrated and hyperplastic polyps with DD. Studies in the literature mostly investigated the relationship between DD and colon adenomatous polyps or adenocarcinoma [8, 9, 13–18]. Different from the studies in the literature investigating the relationship between DD and adenomatous polyps, it was observed in our study that the presence of DD increased the risk of adenomatous polyps with a villous component or high degree of dysplasia. We think that DD is associated with all phases of the adenoma-cancer sequence.

It is unclear what kind of pathogenesis the relationship between the presence of DD and pre-neoplastic or neoplastic lesions of the colon can be based on. In fact, the pathogenesis of the two diseases is actually completely different. In diverticular disease, diverticula are formed due to the weakening of the muscular layer of the colon [25]. In colorectal carcinogenesis, malignant transformation is observed in polyps as a result of the adenomatous polyp/adenocarcinoma sequence triggered by genetic and epigenetic changes in cells of the mucosal area [26]. It is accepted that both genetic and environmental factors have a

role in diverticular disease and adenomatous colon polyps or adenocarcinoma development [25, 26]. The fact that age and similar environmental factors increase the risk for both diseases suggests that there is a possible involvement in similar genetic pathways. A positive family history is a risk factor for both DD and adenomatous colon polyps or adenocarcinoma. When all these findings are evaluated, it would be appropriate to support the relationship between DD and adenomatous polyp/colon adenocarcinoma, especially with genetic and epigenetic studies.

Limitations

The disadvantage of the study is that it is a retrospective study like the studies in the literature. In particular, it may be insufficient to show the cause-effect relationship between DD and adenomatous polyps or colon adenocarcinoma. However, the analyses showed that more adenomatous polyps and colon adenocarcinomas were encountered in patients with DD, which have risk factors similar to patients with non-DD. The high rate of adenomatous polyps with villous components or high degree of dysplasia, similar to adenocarcinoma, may suggest that there is a relationship between DD and both precancerous (adenomatous polyp) and cancerous (adenocarcinoma) lesions of the colon.

Conclusion

Age and family history of colon polyps or adenocarcinoma increase the risk of both adenomatous colon polyps and colon adenocarcinoma. DD is associated with adenomatous polyps and colon adenocarcinoma. A significant association is observed between DD and adenomatous polyps with villous component or high-grade dysplasia, which have malignant potential. Our results suggest that DD increases both pre-neoplastic (adenomatous polyp) and neoplastic lesions (adenocarcinoma) of the colon. There is a need for further genetic/epigenetic and prospective studies to investigate the relationship between DD and adenomatous polyps and adenocarcinoma.

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